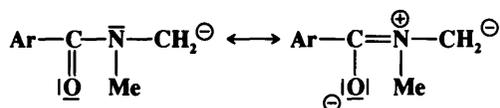


However, there is evidence against *d*-orbital overlap; and the stabilizing effects have been attributed to other causes.⁸⁸ An α silicon atom also stabilizes carbanions.⁸⁹

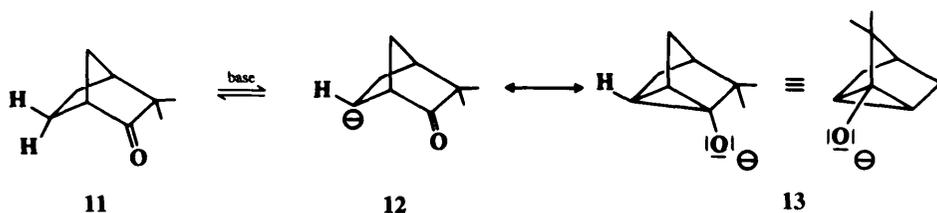
4. *Field effects.* Most of the groups that stabilize carbanions by resonance effects (either the kind discussed in paragraph 1 above or the kind discussed in paragraph 3) have electron-withdrawing field effects and thereby stabilize the carbanion further by spreading the negative charge, though it is difficult to separate the field effect from the resonance effect.

However, in a nitrogen ylide $R_3\overset{\oplus}{N}-\overset{\ominus}{C}R_2$ (see p. 39), where a positive nitrogen is adjacent to the negatively charged carbon, only the field effect operates. Ylides are more stable than the corresponding simple carbanions. Carbanions are stabilized by a field effect if there is any hetero atom (O, N, or S) connected to the carbanionic carbon, provided that the hetero atom bears a positive charge in at least one important canonical form,⁹⁰ e.g.,



5. Certain carbanions are stable because they are aromatic (see the cyclopentadienyl anion p. 46, and other aromatic anions in Chapter 2).

6. *Stabilization by a nonadjacent π bond.*⁹¹ In contrast to the situation with carbocations (see pp. 314-316), there have been fewer reports of carbanions stabilized by interaction with a nonadjacent π bond. One that may be mentioned is **13**, formed when optically active camphenilone (**11**) was treated with a strong base (potassium *t*-butoxide).⁹² That **13** was



truly formed was shown by the following facts: (1) A proton was abstracted: ordinary CH_2 groups are not acidic enough for this base; (2) recovered **11** was racemized: **13** is symmetrical and can be attacked equally well from either side; (3) when the experiment was performed in deuterated solvent, the rate of deuterium uptake was equal to the rate of racemization; and (4) recovered **11** contained up to three atoms of deuterium per molecule, though if **12** were the only ion, no more than two could be taken up. Ions of this type, in which a

⁸⁸Bernardi; Csizmadia; Mangini; Schlegel; Whangbo; Wolfe *J. Am. Chem. Soc.* **1975**, *97*, 2209; Epiotis; Yates; Bernardi; Wolfe *J. Am. Chem. Soc.* **1976**, *98*, 5435; Lehn; Wipff *J. Am. Chem. Soc.* **1976**, *98*, 7498; Borden; Davidson; Andersen; Denniston; Epiotis *J. Am. Chem. Soc.* **1978**, *100*, 1604; Bernardi; Bottoni; Venturini; Mangini *J. Am. Chem. Soc.* **1986**, *108*, 8171.

⁸⁹Wetzel; Brauman *J. Am. Chem. Soc.* **1968**, *110*, 8333.

⁹⁰For a review of such carbanions, see Beak; Reitz *Chem. Rev.* **1978**, *78*, 275-316. See also Rondan; Houk; Beak; Zajdel; Chandrasekhar; Schleyer *J. Org. Chem.* **1981**, *46*, 4108.

⁹¹For reviews, see Werstiuk *Tetrahedron* **1983**, *39*, 205-268; Hunter; Stothers; Warnhoff, in de Mayo *Rearrangements in Ground and Excited States*, vol. 1; Academic Press: New York, 1980, pp. 410-437.

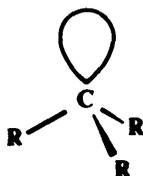
⁹²Nickon; Lambert *J. Am. Chem. Soc.* **1966**, *88*, 1905. Also see Brown; Occolowitz *Chem. Commun.* **1965**, 376; Grutzner; Winstein *J. Am. Chem. Soc.* **1968**, *90*, 6562; Staley; Reichard *J. Am. Chem. Soc.* **1969**, *91*, 3998; Hunter; Johnson; Stothers; Nickon; Lambert; Covey *J. Am. Chem. Soc.* **1972**, *94*, 8582; Miller *J. Am. Chem. Soc.* **1969**, *91*, 751; Werstiuk; Yeroushalmi; Timmins *Can. J. Chem.* **1983**, *61*, 1945; Lee; Squires *J. Am. Chem. Soc.* **1986**, *108*, 5078; Peiris; Ragauskas; Stothers *Can. J. Chem.* **1987**, *65*, 789; Shiner; Berks; Fisher *J. Am. Chem. Soc.* **1988**, *110*, 957.

negatively charged carbon is stabilized by a carbonyl group two carbons away, are called *homoenolate ions*.

Overall, functional groups in the α position stabilize carbanions in the following order: $\text{NO}_2 > \text{RCO} > \text{COOR} > \text{SO}_2 > \text{CN} \approx \text{CONH}_2 > \text{Hal} > \text{H} > \text{R}$.

It is unlikely that free carbanions exist in solution. Like carbocations, they are usually in ion pairs or else solvated.⁹³ Among experiments which demonstrated this was the treatment of $\text{PhCO}\bar{\text{C}}\text{HMe}^- \text{M}^+$ with ethyl iodide, where M^+ was Li^+ , Na^+ , or K^+ . The half-lives of the reaction were⁹⁴ for Li, 31×10^{-6} ; Na, 0.39×10^{-6} ; and K, 0.0045×10^{-6} , demonstrating that the species involved were not identical. Similar results⁹⁵ were obtained with Li, Na, and Cs triphenylmethides $\text{Ph}_3\text{C}^- \text{M}^+$.⁹⁶ Where ion pairs are unimportant, carbanions are solvated. Cram⁷⁰ has demonstrated solvation of carbanions in many solvents. There may be a difference in the structure of a carbanion depending on whether it is free (e.g., in the gas phase) or in solution. The negative charge may be more localized in solution in order to maximize the electrostatic attraction to the counterion.⁹⁷

The structure of simple unsubstituted carbanions is not known with certainty since they have not been isolated, but it seems likely that the central carbon is sp^3 -hybridized, with the unshared pair occupying one apex of the tetrahedron. Carbanions would thus have pyramidal structures similar to those of amines.



The methyl anion CH_3^- has been observed in the gas phase and reported to have a pyramidal structure.⁹⁸ If this is a general structure for carbanions, then any carbanion in which the three R groups are different should be chiral and reactions in which it is an intermediate should give retention of configuration. Attempts have been made to demonstrate this but without success.⁹⁹ A possible explanation is that pyramidal inversion takes place here, as in amines, so that the unshared pair and the central carbon rapidly oscillate from one side of the plane to the other. There is, however, other evidence for the sp^3 nature of the central carbon and for its tetrahedral structure. Carbons at bridgeheads, though extremely reluctant to undergo reactions in which they must be converted to carbocations, undergo with ease reactions in which they must be carbanions and stable bridgehead carbanions are known.¹⁰⁰

⁹³For reviews of carbanion pairs, see Hogen-Esch *Adv. Phys. Org. Chem.* **1977**, *15*, 153-266; Jackman; Lange *Tetrahedron* **1977**, *33*, 2737-2769. See also Ref 7.

⁹⁴Zook; Gumby *J. Am. Chem. Soc.* **1960**, *82*, 1386.

⁹⁵Solov'yanov; Karpyuk; Beletskaya; Reutov *J. Org. Chem. USSR* **1981**, *17*, 381. See also Solov'yanov; Beletskaya; Reutov *J. Org. Chem. USSR* **1983**, *19*, 1964.

⁹⁶For other evidence for the existence of carbanionic pairs, see Hogen-Esch; Smid *J. Am. Chem. Soc.* **1966**, *88*, 307, 318; **1969**, *91*, 4580; Abatjoglou; Eliel; Kuyper *J. Am. Chem. Soc.* **1977**, *99*, 8262; Solov'yanov; Karpyuk; Beletskaya; Reutov *Doklad. Chem.* **1977**, *237*, 668; DePalma; Arnett *J. Am. Chem. Soc.* **1978**, *100*, 3514; Buncel; Menon *J. Org. Chem.* **1979**, *44*, 317; O'Brien; Russell; Hart *J. Am. Chem. Soc.* **1979**, *101*, 633; Streitwieser; Shen *Tetrahedron Lett.* **1979**, 327; Streitwieser *Acc. Chem. Res.* **1984**, *17*, 353.

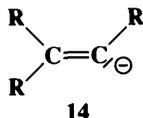
⁹⁷See Schade; Schleyer; Geissler; Weiss *Angew. Chem. Int. Ed. Engl.* **1986**, *21*, 902 [*Angew. Chem.* **98**, 922].

⁹⁸Ellison; Engelking; Lineberger *J. Am. Chem. Soc.* **1978**, *100*, 2556.

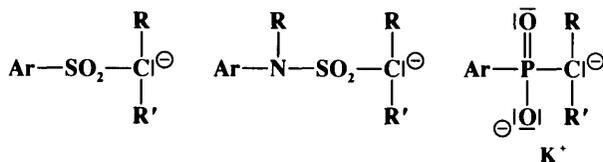
⁹⁹Retention of configuration has never been observed with simple carbanions. Cram has obtained retention with carbanions stabilized by resonance. However, these carbanions are known to be planar or nearly planar, and retention was caused by asymmetric solvation of the planar carbanions (see p. 574).

¹⁰⁰For other evidence that carbanions are pyramidal, see Streitwieser; Young *J. Am. Chem. Soc.* **1969**, *91*, 529; Peoples; Grutzner *J. Am. Chem. Soc.* **1980**, *102*, 4709.

Also, reactions at vinylic carbons proceed with retention,¹⁰¹ indicating that the intermediate **14** has sp^2 hybridization and not the sp hybridization that would be expected in the analogous carbocation. A cyclopropyl anion can also hold its configuration.¹⁰²



Carbanions in which the negative charge is stabilized by resonance involving overlap of the unshared-pair orbital with the π electrons of a multiple bond are essentially planar, as would be expected by the necessity for planarity in resonance, though unsymmetrical solvation or ion-pairing effects may cause the structure to deviate somewhat from true planarity.¹⁰³ Cram and co-workers have shown that where chiral carbanions possessing this type of resonance are generated, retention, inversion, or racemization can result, depending on the solvent (see p. 574). This result is explained by unsymmetrical solvation of planar or near-planar carbanions. However, some carbanions that are stabilized by adjacent sulfur or phosphorus, e.g.,



are inherently chiral, since retention of configuration is observed where they are generated, even in solvents that cause racemization or inversion with other carbanions.¹⁰⁴ The configuration about the carbanionic carbon, at least for some of the α -sulfonyl carbanions, seems to be planar,¹⁰⁵ and the inherent chirality is caused by lack of rotation about the C—S bond.¹⁰⁶

¹⁰¹Curtin; Harris *J. Am. Chem. Soc.* **1951**, *73*, 2716, 4519; Braude; Coles *J. Chem. Soc.* **1951**, 2078; Nesmeyanov; Borisov *Tetrahedron* **1957**, *1*, 158. Also see Miller; Lee *J. Am. Chem. Soc.* **1959**, *81*, 6313; Hunter; Cram *J. Am. Chem. Soc.* **1964**, *86*, 5478; Walborsky; Turner *J. Am. Chem. Soc.* **1972**, *94*, 2273; Arnett; Walborsky *J. Org. Chem.* **1972**, *37*, 3678; Feit; Melamed; Speer; Schmidt *J. Chem. Soc., Perkin Trans. 1* **1984**, 775; Chou; Kass *J. Am. Chem. Soc.* **1991**, *113*, 4357.

¹⁰²Walborsky; Motes *J. Am. Chem. Soc.* **1970**, *92*, 2445; Motes; Walborsky *J. Am. Chem. Soc.* **1970**, *92*, 3697; Boche; Harms; Marsch *J. Am. Chem. Soc.* **1988**, *110*, 6925. For a monograph on cyclopropyl anions, cations, and radicals, see Boche; Walborsky *Cyclopropane Derived Reactive Intermediates*; Wiley: New York, 1990. For a review, see Boche; Walborsky, in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley: New York, 1987, pp. 701-808 (the monograph includes and updates the review).

¹⁰³See the discussion in Cram *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965, pp. 85-105.

¹⁰⁴Cram; Nielsen; Rickborn *J. Am. Chem. Soc.* **1960**, *82*, 6415; Cram; Wingrove *J. Am. Chem. Soc.* **1962**, *84*, 1496; Corey; Kaiser *J. Am. Chem. Soc.* **1961**, *83*, 490; Goering; Towns; Dittmer *J. Org. Chem.* **1962**, *27*, 736; Corey; Lowry *Tetrahedron Lett.* **1965**, 803; Bordwell; Phillips; Williams *J. Am. Chem. Soc.* **1968**, *90*, 426; Annunziata; Cinquini; Colonna; Cozzi *J. Chem. Soc., Chem. Commun.* **1981**, 1005; Chassaing; Marquet; Corset; Froment *J. Organomet. Chem.* **1982**, *232*, 293. For a discussion, see Ref. 103, pp. 105-113.

¹⁰⁵Boche; Marsch; Harms; Sheldrick *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 573 [*Angew. Chem.* **97**, 577]; Gais; Vollhardt; Hellmann; Paulus; Lindner *Tetrahedron Lett.* **1988**, *29*, 1259; Gais; Müller; Vollhardt; Lindner *J. Am. Chem. Soc.* **1991**, *113*, 4002. For a contrary view, see Trost; Schmuft *J. Am. Chem. Soc.* **1985**, *107*, 396.

¹⁰⁶Grossert; Hoyle; Cameron; Roe; Vincent *Can. J. Chem.* **1987**, *65*, 1407.

The Structure of Organometallic Compounds¹⁰⁷

Whether a carbon-metal bond is ionic or polar-covalent is determined chiefly by the electronegativity of the metal and the structure of the organic part of the molecule. Ionic bonds become more likely as the negative charge on the metal-bearing carbon is decreased by resonance or field effects. Thus the sodium salt of acetoacetic ester has a more ionic carbon-sodium bond than methylsodium.

Most organometallic bonds are polar-covalent. Only the alkali metals have electronegativities low enough to form ionic bonds with carbon, and even here the behavior of lithium alkyls shows considerable covalent character. The simple alkyls and aryls of sodium, potassium, rubidium, and cesium¹⁰⁸ are nonvolatile solids¹⁰⁹ insoluble in benzene or other organic solvents, while alkyllithiums are soluble, although they too are generally nonvolatile solids. Alkyllithiums do not exist as monomeric species in hydrocarbon solvents or ether.¹¹⁰ In benzene and cyclohexane, freezing-point-depression studies have shown that alkyllithiums are normally hexameric unless steric interactions favor tetrameric aggregates.¹¹¹ Nmr studies, especially measurements of ¹³C-⁶Li coupling, have also shown aggregation in hydrocarbon solvents.¹¹² Boiling-point-elevation studies have been performed in ether solutions, where alkyllithiums exist in two- to fivefold aggregates.¹¹³ Even in the gas phase¹¹⁴ and in the solid state,¹¹⁵ alkyllithiums exist as aggregates. X-ray crystallography has shown that methylolithium has the same tetrahedral structure in the solid state as in ether solution.¹¹⁵ However, *t*-butyllithium is monomeric in THF, though dimeric in ether and tetrameric in hydrocarbon solvents.¹¹⁶ Neopentyllithium exists as a mixture of monomers and dimers in THF.¹¹⁷

The C-Mg bond in Grignard reagents is covalent and not ionic. The actual structure of Grignard reagents in solution has been a matter of much controversy over the years.¹¹⁸ In 1929 it was discovered¹¹⁹ that the addition of dioxane to an ethereal Grignard solution precipitates all the magnesium halide and leaves a solution of R₂Mg in ether; i.e., there can

¹⁰⁷For a monograph, see Elschenbroich; Salzer *Organometallics*; VCH: New York, 1989. For reviews, see Oliver, in Hartley; Patai *The Chemistry of the Metal-Carbon Bond*, vol. 2; Wiley: New York, 1985, pp. 789-826; Coates; Green; Wade *Organometallic Compounds*, 3rd ed., vol. 1; Methuen: London, 1967. For a review of the structures of organodialkali compounds, see Grovenstein, in Bunzel; Durst, Ref. 70, pt. C, pp. 175-221.

¹⁰⁸For a review of x-ray crystallographic studies of organic compounds of the alkali metals, see Schade; Schleyer *Adv. Organomet. Chem.* **1987**, *27*, 169-278.

¹⁰⁹X-ray crystallography of potassium, rubidium, and cesium methyls shows completely ionic crystal lattices; Weiss; Sauermann *Chem. Ber.* **1970**, *103*, 265; Weiss; Köster *Chem. Ber.* **1977**, *110*, 717.

¹¹⁰For reviews of the structure of alkyllithium compounds, see Setzer; Schleyer *Adv. Organomet. Chem.* **1985**, *24*, 353-451; Schleyer *Pure Appl. Chem.* **1984**, *56*, 151-162; Brown *Pure Appl. Chem.* **1970**, *23*, 447-462, *Adv. Organomet. Chem.* **1965**, *3*, 365-395; Kovrizhnykh; Shatenshtein *Russ. Chem. Rev.* **1969**, *38*, 840-849. For reviews of the structures of lithium enolates and related compounds, see Boche *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 277-297 [*Angew. Chem.* *101*, 286-306]; Seebach *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624-1654 [*Angew. Chem.* *100*, 1685-1715]. For a review of the use of nmr to study these structures, see Günther; Moskau; Bast; Schmalz *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1212-1220 [*Angew. Chem.* *99*, 1242-1250]. For monographs on organolithium compounds, see Wakefield *Organolithium Methods*; Academic Press: New York, 1988, *The Chemistry of Organolithium Compounds*; Pergamon: Elmsford, NY, 1974.

¹¹¹Lewis; Brown *J. Am. Chem. Soc.* **1970**, *92*, 4664; Brown; Rogers *J. Am. Chem. Soc.* **1957**, *79*, 1859; Weiner; Vogel; West *Inorg. Chem.* **1962**, *1*, 654.

¹¹²Fraenkel; Henrichs; Hewitt; Su *J. Am. Chem. Soc.* **1984**, *106*, 255; Thomas; Jensen; Young *Organometallics* **1987**, *6*, 565. See also Kaufman; Gronert; Streitwieser *J. Am. Chem. Soc.* **1988**, *110*, 2829.

¹¹³Wittig; Meyer; Lange *Liebigs Ann. Chem.* **1951**, *571*, 167. See also McGarrity; Ogle *J. Am. Chem. Soc.* **1985**, *107*, 1805; Bates; Clarke; Thomas *J. Am. Chem. Soc.* **1988**, *110*, 5109.

¹¹⁴Berkowitz; Bafus; Brown *J. Phys. Chem.* **1961**, *65*, 1380; Brown; Dickerhoof; Bafus *J. Am. Chem. Soc.* **1962**, *84*, 1371; Chinn; Lagow *Organometallics* **1984**, *3*, 75; Plavšić; Srzić; Klasinc *J. Phys. Chem.* **1986**, *90*, 2075.

¹¹⁵Dietrich *Acta Crystallogr.* **1963**, *16*, 681; Weiss; Lucken *J. Organomet. Chem.* **1964**, *2*, 197; Weiss; Sauermann; Thirase *Chem. Ber.* **1983**, *116*, 74.

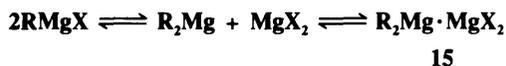
¹¹⁶Bauer; Winchester; Schleyer *Organometallics* **1987**, *6*, 2371.

¹¹⁷Fraenkel; Chow; Winchester *J. Am. Chem. Soc.* **1990**, *112*, 6190.

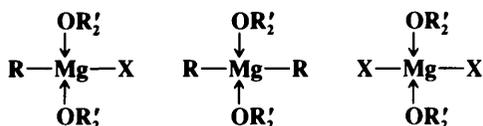
¹¹⁸For reviews, see Ashby *Bull. Soc. Chim. Fr.* **1972**, 2133-2142, *Q. Rev., Chem. Soc.* **1967**, *21*, 259-285; Wakefield *Organomet. Chem. Rev.* **1966**, *1*, 131-156; Bell *Educ. Chem.* **1973**, 143-145.

¹¹⁹Schlenk; Schlenk *Ber.* **1929**, *62B*, 920.

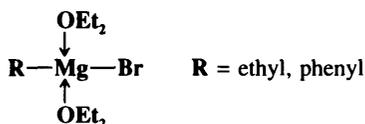
be no RMgX in the solution since there is no halide. The following equilibrium, now called the *Schlenk equilibrium*, was proposed as the composition of the Grignard solution:



in which 15 is a complex of some type. Much work has demonstrated that the Schlenk equilibrium actually exists and that the position of the equilibrium is dependent on the identity of R, X, the solvent, the concentration, and the temperature.¹²⁰ It has been known for many years that the magnesium in a Grignard solution, no matter whether it is RMgX , R_2Mg , or MgX_2 , can coordinate with two molecules of ether in addition to the two covalent bonds:

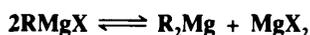


Rundle and co-workers performed x-ray-diffraction studies on solid phenylmagnesium bromide dietherate and on ethylmagnesium bromide dietherate, which they obtained by cooling ordinary ethereal Grignard solutions until the solids crystallized.¹²¹ They found that the structures were monomeric:



These solids still contained ether. When ordinary ethereal Grignard solutions prepared from bromomethane, chloromethane, bromoethane, and chloroethane were evaporated at about 100°C under vacuum so that the solid remaining contained no ether, x-ray diffraction showed *no* RMgX but a mixture of R_2Mg and MgX_2 .¹²² These results indicate that in the presence of ether $\text{RMgX} \cdot 2\text{Et}_2\text{O}$ is the preferred structure, while the loss of ether drives the Schlenk equilibrium to $\text{R}_2\text{Mg} + \text{MgX}_2$. However, conclusions drawn from a study of the solid materials do not necessarily apply to the structures in solution.

Boiling-point-elevation and freezing-point-depression measurements have demonstrated that in tetrahydrofuran at all concentrations and in ether at low concentrations (up to about 0.1 M) Grignard reagents prepared from alkyl bromides and iodides are monomeric, i.e., there are few or no molecules with two magnesium atoms.¹²³ Thus, part of the Schlenk equilibrium is operating



¹²⁰See Parris; Ashby *J. Am. Chem. Soc.* **1971**, *93*, 1206; Salinger; Mosher *J. Am. Chem. Soc.* **1964**, *86*, 1782; Kirmann; Hamelin; Hayes *Bull. Soc. Chim. Fr.* **1963**, 1395.

¹²¹Guggenberger; Rundle *J. Am. Chem. Soc.* **1968**, *90*, 5375; Stucky; Rundle *J. Am. Chem. Soc.* **1964**, *86*, 4825.

¹²²Weiss *Chem. Ber.* **1965**, *98*, 2805.

¹²³Ashby; Becker *J. Am. Chem. Soc.* **1963**, *85*, 118; Ashby; Smith *J. Am. Chem. Soc.* **1964**, *86*, 4363; Vreugdenhil; Blomberg *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 453, 461.

but not the other part; i.e., **15** is not present in measurable amounts. This was substantiated by ^{25}Mg nmr spectra of the ethyl Grignard reagent in THF, which showed the presence of three peaks, corresponding to EtMgBr , Et_2Mg , and MgBr_2 .¹²⁴ That the equilibrium between RMgX and R_2Mg lies far to the left for "ethylmagnesium bromide" in ether was shown by Smith and Becker, who mixed 0.1 *M* ethereal solutions of Et_2Mg and MgBr_2 and found that a reaction occurred with a heat evolution of 3.6 kcal/mol (15 kJ/mol) of Et_2Mg , and that the product was *monomeric* (by boiling-point-elevation measurements).¹²⁵ When either solution was added little by little to the other, there was a linear output of heat until almost a 1:1 molar ratio was reached. Addition of an excess of either reagent gave no further heat output. These results show that at least under some conditions the Grignard reagent is largely RMgX (coordinated with solvent) but that the equilibrium can be driven to R_2Mg by evaporation of all the ether or by addition of dioxane.

For some aryl Grignard reagents it has proved possible to distinguish separate nmr chemical shifts for ArMgX and Ar_2Mg .¹²⁶ From the area under the peaks it is possible to calculate the concentrations of the two species, and from them, equilibrium constants for the Schlenk equilibrium. These data show¹²⁶ that the position of the equilibrium depends very markedly on the aryl group and the solvent but that conventional aryl Grignard reagents in ether are largely ArMgX , while in THF the predominance of ArMgX is less, and with some aryl groups there is actually more Ar_2Mg present. Separate nmr chemical shifts have also been found for alkyl RMgBr and R_2Mg in HMPA¹²⁷ and in ether at low temperatures.¹²⁸ When Grignard reagents from alkyl bromides or chlorides are prepared in triethylamine the predominant species is RMgX .¹²⁹ Thus the most important factor determining the position of the Schlenk equilibrium is the solvent. For primary alkyl groups the equilibrium constant for the reaction as written above is lowest in Et_3N , higher in ether, and still higher in THF.¹³⁰

However, Grignard reagents prepared from alkyl bromides or iodides in ether at higher concentrations (0.5 to 1 *M*) contain dimers, trimers, and higher polymers, and those prepared from alkyl chlorides in ether at all concentrations are dimeric,¹³¹ so that **15** is in solution, probably in equilibrium with RMgX and R_2Mg ; i.e., the complete Schlenk equilibrium seems to be present.

The Grignard reagent prepared from 1-chloro-3,3-dimethylpentane in ether undergoes rapid inversion of configuration at the magnesium-containing carbon (demonstrated by nmr; this compound is not chiral).¹³² The mechanism of this inversion is not completely known.

It might be mentioned that matters are much simpler for organometallic compounds with less-polar bonds. Thus Et_2Hg and EtHgCl are both definite compounds, the former a liquid and the latter a solid.

The Generation and Fate of Carbanions

The two principal ways in which carbanions are generated are parallel with the ways of generating carbocations.

¹²⁴Benn; Lehmkuhl; Mehler; Ruffinska *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 534 [*Angew. Chem.* 96, 521].

¹²⁵Smith; Becker *Tetrahedron* **1966**, 22, 3027.

¹²⁶Evans; Khan *J. Chem. Soc. A* **1967**, 1643; Evans; Fazakerley *Chem. Commun.* **1968**, 974.

¹²⁷Ducom *Bull. Chem. Soc. Fr.* **1971**, 3518, 3523, 3529.

¹²⁸Ashby; Parris; Walker *Chem. Commun.* **1969**, 1464; Parris; Ashby, Ref. 120.

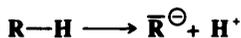
¹²⁹Ashby; Walker *J. Org. Chem.* **1968**, 33, 3821.

¹³⁰Parris; Ashby, Ref. 120.

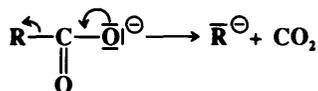
¹³¹Ashby; Smith, Ref. 123.

¹³²Whitesides; Witanowski; Roberts *J. Am. Chem. Soc.* **1965**, 87, 2854; Whitesides; Roberts *J. Am. Chem. Soc.* **1965**, 87, 4878. Also see Witanowski; Roberts *J. Am. Chem. Soc.* **1966**, 88, 737; Fraenkel; Cottrell; Dix *J. Am. Chem. Soc.* **1971**, 93, 1704; Pechhold; Adams; Fraenkel *J. Org. Chem.* **1971**, 36, 1368; Maercker; Geuss *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 270 [*Angew. Chem.* 83, 288].

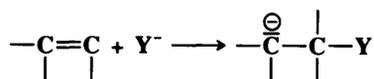
1. A group attached to a carbon leaves without its electron pair:



The leaving group is most often a proton. This is a simple acid–base reaction, and a base is required to remove the proton.¹³³ However, other leaving groups are known (see Chapter 12):



2. A negative ion adds to a carbon–carbon double or triple bond (see Chapter 15):

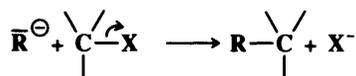


The addition of a negative ion to a carbon–oxygen double bond does not give a carbanion, since the negative charge resides on the oxygen.

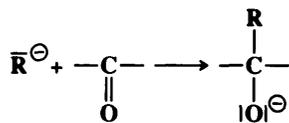
The most common reaction of carbanions is combination with a positive species, usually a proton, or with another species that has an empty orbital in its outer shell (a Lewis acid–base reaction):



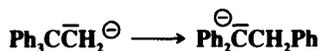
Carbanions may also form a bond with a carbon that already has four bonds, by displacing one of the four groups (S_N2 reaction, see Chapter 10):



Like carbocations, carbanions can also react in ways in which they are converted to species that are still not neutral molecules. They can add to double bonds (usually C=O double bonds; see Chapters 10 and 16),



or rearrange, though this is rare (see Chapter 18),



¹³³For a review of such reactions, see Durst, in Buncl; Durst, Ref. 70, pt. B, pp. 239-291.

or be oxidized to free radicals.¹³⁴ A system in which a carbocation [$\text{Ph}(p\text{-Me}_2\text{NC}_6\text{H}_4)_2\text{C}^+$] oxidizes a carbanion [$(p\text{-NO}_2\text{C}_6\text{H}_4)_3\text{C}^-$] to give two free radicals, reversibly, so that all four species are present in equilibrium, has been demonstrated.¹³⁵

Organometallic compounds that are not ionic but polar-covalent behave very much as if they were ionic and give similar reactions.

FREE RADICALS

Stability and Structure¹³⁶

A *free radical* (often simply called a *radical*) may be defined as a species that contains one or more unpaired electrons. Note that this definition includes certain stable inorganic molecules such as NO and NO₂, as well as many individual atoms, such as Na and Cl. As with carbocations and carbanions, simple alkyl radicals are very reactive. Their lifetimes are extremely short in solution, but they can be kept for relatively long periods frozen within the crystal lattices of other molecules.¹³⁷ Many spectral¹³⁸ measurements have been made on radicals trapped in this manner. Even under these conditions the methyl radical decomposes with a half-life of 10 to 15 min in a methanol lattice at 77 K.¹³⁹ Since the lifetime of a radical depends not only on its inherent stability, but also on the conditions under which it is generated, the terms *persistent* and *stable* are usually used for the different senses. A stable radical is inherently stable; a persistent radical has a relatively long lifetime under the conditions at which it is generated, though it may not be very stable.

Associated with the spin of an electron is a magnetic moment, which can be expressed by a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$. According to the Pauli principle, any two electrons occupying the same orbital must have opposite spins, so the total magnetic moment is zero for any species in which all the electrons are paired. In radicals, however, one or more electrons are unpaired, so there is a net magnetic moment and the species is paramagnetic. Radicals can therefore be detected by magnetic-susceptibility measurements, but for this technique a relatively high concentration of radicals is required. A much more important technique is *electron spin resonance* (esr), also called *electron paramagnetic resonance* (epr).¹⁴⁰ The principle of esr is similar to that of nmr, except that electron spin is involved

¹³⁴For a review, see Guthrie, in Buncler; Durst, Ref. 70, pt. A, pp. 197-269.

¹³⁵Arnett; Molter; Marchot; Donovan; Smith *J. Am. Chem. Soc.* **1987**, *109*, 3788. See also Ref. 84.

¹³⁶For monographs, see Alfassi *Chemical Kinetics of Small Organic Radicals*, 4 vols.; CRC Press: Boca Raton, FL, 1988; Nonhebel; Tedder; Walton *Radicals*; Cambridge University Press: Cambridge, 1979; Nonhebel; Walton *Free-Radical Chemistry*; Cambridge University Press: Cambridge, 1974; Kochi *Free Radicals*, 2 vols.; Wiley: New York, 1973; Hay *Reactive Free Radicals*; Academic Press: New York, 1974; Pryor *Free Radicals*; McGraw-Hill: New York, 1966. For reviews, see Kaplan *React. Intermed. (Wiley)* **1985**, *3*, 227-303; **1981**, *2*, 251-314; **1978**, *1*, 163-196; Griller; Ingold *Acc. Chem. Res.* **1976**, *9*, 13-19; Huyser, in McManus, Ref. 1, pp. 1-59; Isaacs, Ref. 1, pp. 294-374.

¹³⁷For a review of the use of matrices to study radicals and other unstable species, see Dunkin *Chem. Soc. Rev.* **1980**, *9*, 1-23; Jacox *Rev. Chem. Intermed.* **1978**, *2*, 1-36. For a review of the study of radicals at low temperatures, see Mile *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 507-519 [*Angew. Chem.* **80**, 519-531].

¹³⁸For a review of infrared spectra of radicals trapped in matrices, see Andrews *Annu. Rev. Phys. Chem.* **1971**, *22*, 109-132.

¹³⁹Sullivan; Koski *J. Am. Chem. Soc.* **1963**, *85*, 384.

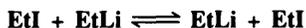
¹⁴⁰For monographs, see Wertz; Bolton *Electron Spin Resonance*; McGraw-Hill: New York, 1972 [reprinted by Chapman and Hall: New York, and Methuen: London, 1986]; Assenheim *Introduction to Electron Spin Resonance*; Plenum: New York, 1967; Bersohn; Baird *An Introduction to Electron Paramagnetic Resonance*; W. A. Benjamin: New York, 1966. For reviews, see Bunce *J. Chem. Educ.* **1987**, *64*, 907-914; Hirota; Ohya-Nishiguchi, in Bernasconi *Investigation of Rates and Mechanisms of Reactions*, 4th ed., pt. 2; Wiley: New York, 1986, pp. 605-655; Griller; Ingold *Acc. Chem. Res.* **1980**, *13*, 193-200; Norman *Chem. Soc. Rev.* **1980**, *8*, 1-27; Fischer, in Kochi, Ref. 136, vol. 2, pp. 435-491; Russell, in Nachod; Zuckerman *Determination of Organic Structures by Physical Methods*, vol. 3; Academic Press: New York, 1971, pp. 293-341; Rassat *Pure Appl. Chem.* **1971**, *25*, 623-634; Kevan *Methods Free-Radical Chem.* **1969**, *1*, 1-33; Geske *Prog. Phys. Org. Chem.* **1967**, *4*, 125-211; Norman; Gilbert *Adv. Phys. Org. Chem.* **1967**, *5*, 53-119; Schneider; Möbius; Plato *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 856-867 [*Angew. Chem.* **77**, 888-900]. For a review on the application of esr to photochemistry, see Wan *Adv. Photochem.* **1974**, *9*, 1-145. For a review of the related ENDOR method, see Kurreck; Kirste; Lubitz *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 173-194 [*Angew. Chem.* **96**, 171-193]. See also Poole *Electron Spin Resonance. A Comprehensive Treatise on Experimental Techniques*, 2nd ed.; Wiley: New York, 1983.

rather than nuclear spin. The two electron spin states ($m_s = \frac{1}{2}$ and $m_s = -\frac{1}{2}$) are ordinarily of equal energy, but in a magnetic field the energies are different. As in nmr, a strong external field is applied and electrons are caused to flip from the lower state to the higher by the application of an appropriate radio-frequency signal. Inasmuch as two electrons paired in one orbital must have opposite spins which cancel, an esr spectrum arises only from species that have one or more unpaired electrons, i.e., free radicals.

Since only free radicals give an esr spectrum, the method can be used to detect the presence of radicals and to determine their concentration. Furthermore, information concerning the electron distribution (and hence the structure) of free radicals can be obtained from the splitting pattern of the esr spectrum (esr peaks are split by nearby protons).¹⁴¹ Fortunately (for the existence of most free radicals is very short), it is not necessary for a radical to be persistent for an esr spectrum to be obtained. Esr spectra have been observed for radicals with lifetimes considerably less than 1 sec. Failure to observe an esr spectrum does not prove that radicals are not involved, since the concentration may be too low for direct observation. In such cases the *spin trapping* technique can be used.¹⁴² In this technique a compound is added that is able to combine with very reactive radicals to produce more persistent radicals; the new radicals can be observed by esr. The most important spin-trapping compounds are nitroso compounds, which react with radicals to give fairly stable nitroxide radicals:¹⁴³ $RN=O + R'\cdot \rightarrow RR'N-O\cdot$.

Because there is an equal probability that a given unpaired electron will have a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$, radicals cause two lines or groups of lines to appear on an electronic spectrum, and are sometimes referred to as *doublets*.

Another magnetic technique for the detection of free radicals uses an ordinary nmr instrument. It was discovered¹⁴⁴ that if an nmr spectrum is taken during the course of a reaction, certain signals may be enhanced, either in a positive or negative direction; others may be reduced. When this type of behavior, called *chemically induced dynamic nuclear polarization*¹⁴⁵ (CIDNP), is found in the nmr spectrum of the product of a reaction, it means that *at least a portion of that product was formed via the intermediacy of a free radical*.¹⁴⁶ For example, the question was raised whether radicals were intermediates in the exchange reaction between ethyl iodide and ethyllithium (2-39):



Curve *a* in Figure 5.1¹⁴⁷ shows an nmr spectrum taken during the course of the reaction. Curve *b* is a reference spectrum of ethyl iodide (CH₃ protons at $\delta = 1.85$; CH₂ protons at

¹⁴¹For reviews of the use of esr spectra to determine structures, see Walton *Rev. Chem. Intermed.* **1984**, *5*, 249-291; Kochi *Adv. Free-Radical Chem.* **1975**, *5*, 189-317. For esr spectra of a large number of free radicals, see Bielski; Gebicki *Atlas of Electron Spin Resonance Spectra*; Academic Press: New York, 1967.

¹⁴²For reviews, see Janzen; Haire *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, *1*, 253-295; Gasanov; Freidlina *Russ. Chem. Rev.* **1987**, *56*, 264-274; Perkins *Adv. Phys. Org. Chem.* **1980**, *17*, 1-64; Zubarev; Belevskii; Bugaenko *Russ. Chem. Rev.* **1979**, *48*, 729-745; Evans *Aldrichimica Acta* **1979**, *12*, 23-29; Janzen *Acc. Chem. Res.* **1971**, *4*, 31-40. See also the collection of papers on this subject in *Can. J. Chem.* **1982**, *60*, 1379-1636.

¹⁴³For a series of papers on nitroxide radicals, see *Pure Appl. Chem.* **1990**, *62*, 177-316.

¹⁴⁴Ward; Lawler *J. Am. Chem. Soc.* **1967**, *89*, 5518; Ward; Lawler; Cooper *J. Am. Chem. Soc.* **1969**, *91*, 746; Bargon; Fischer; Johnsen *Z. Naturforsch., Teil A* **1967**, *22*, 1551; Bargon; Fischer *Z. Naturforsch., Teil A* **1967**, *22*, 1556; Lepley *J. Am. Chem. Soc.* **1968**, *90*, 2710. **1969**, *91*, 749; Lepley; Landau *J. Am. Chem. Soc.* **1969**, *91*, 748.

¹⁴⁵For a monograph on CIDNP, see Lepley; Closs *Chemically Induced Magnetic Polarization*; Wiley: New York, 1973. For reviews, see Adrian *Rev. Chem. Intermed.* **1986**, *7*, 173-194; Closs; Miller; Redwine *Acc. Chem. Res.* **1985**, *18*, 196-202; Lawler; Ward; in Nachod; Zuckerman, Ref. 140, vol. 5, 1973, pp. 99-150; Ward, in Kochi, Ref. 136, vol. 1, pp. 239-273; *Acc. Chem. Res.* **1972**, *5*, 18-24; Closs *Adv. Magn. Reson.* **1974**, *7*, 157-229; Lawler *Acc. Chem. Res.* **1972**, *5*, 25-32; Kaptein *Adv. Free-Radical Chem.* **1975**, *5*, 319-380; Bethell; Brinkman *Adv. Phys. Org. Chem.* **1973**, *10*, 53-128.

¹⁴⁶A related technique is called chemically induced dynamic electron polarization (CIDEP). For a review, see Hore; Joslin; McLauchlan *Chem. Soc. Rev.* **1979**, *8*, 29-61.

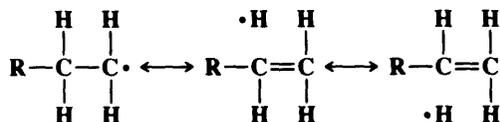
¹⁴⁷Ward; Lawler; Cooper, Ref. 144.



FIGURE 5.1¹⁴⁷ (a) Nmr spectrum taken during reaction between EtI and EtLi in benzene (the region between 2.5 and 3.5 δ was scanned with an amplitude twice that of the remainder of the spectrum). The signals at 1.0 to 1.6 δ are due to butane, some of which is also formed in the reaction. (b) Reference spectrum of EtI.

$\delta = 3.2$). Note that in curve *a* some of the ethyl iodide signals are enhanced; others go below the base line (*negative enhancement*; also called *emission*). Thus the ethyl iodide formed in the exchange shows CIDNP and hence was formed via a free-radical intermediate. CIDNP results when protons in a reacting molecule become dynamically coupled to an unpaired electron while traversing the path from reactants to products. Although the presence of CIDNP almost always means that a free radical is involved,¹⁴⁸ its absence does not prove that a free-radical intermediate is necessarily absent, since reactions involving free-radical intermediates can also take place without observable CIDNP. Also, the presence of CIDNP does not prove that *all* of a product was formed via a free-radical intermediate, only that some of it was.

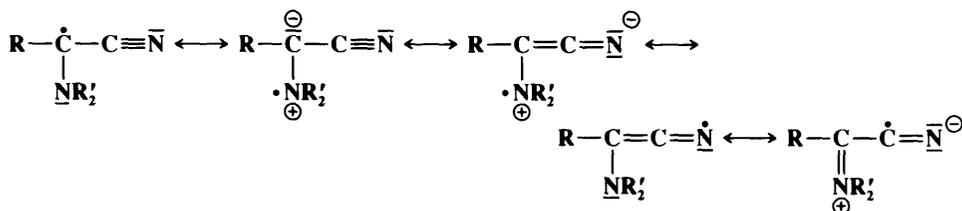
As with carbocations, the stability order of free radicals is tertiary > secondary > primary, explainable by hyperconjugation, analogous to that in carbocations (p. 167):



¹⁴⁸It has been shown that CIDNP can also arise in cases where *para* hydrogen (H_2 in which the nuclear spins are opposite) is present: Eisenschmid; Kirss; Deutsch; Hommeltoft; Eisenberg; Bargon; Lawler; Balch *J. Am. Chem. Soc.* **1987**, *109*, 8089.

radicals are electronically very similar, but **17**, being planar, has much less steric hindrance to dimerization than $\text{Ph}_3\text{C}^\bullet$, while **18**, with six groups in ortho positions, has much more. On the other hand, the planarity of **17** means that it has a maximum amount of resonance stabilization, while **18** must have much less, since its degree of planarity should be even less than $\text{Ph}_3\text{C}^\bullet$, which itself is propeller-shaped and not planar. Thus if resonance is the chief cause of the stability of $\text{Ph}_3\text{C}^\bullet$, **18** should dimerize and **17** should not, but if steric hindrance is the major cause, the reverse should happen. In the event, it was found¹⁵⁷ that **18** gave no evidence of dimerization, even in the solid state, while **17** existed primarily in the dimeric form, which is dissociated to only a small extent in solution,¹⁵⁸ indicating that steric hindrance to dimerization is the major cause for the stability of triarylmethyl radicals. A similar conclusion was reached in the case of $(\text{NC})_3\text{C}^\bullet$, which dimerizes readily though considerably stabilized by resonance.¹⁵⁹ Nevertheless, that resonance is still an important contributing factor to the stability of radicals is shown by the facts that (1) the radical $t\text{-Bu}(\text{Ph})_2\text{C}^\bullet$ dimerizes more than $\text{Ph}_3\text{C}^\bullet$, while $p\text{-PhCOC}_6\text{H}_4(\text{Ph}_2)\text{C}^\bullet$ dimerizes less.¹⁶⁰ The latter has more canonical forms than $\text{Ph}_3\text{C}^\bullet$, but steric hindrance should be about the same (for attack at one of the two rings). (2) A number of radicals ($p\text{-XCOC}_6\text{H}_4)_3\text{C}^\bullet$, with $\text{X} = \text{F}, \text{Cl}, \text{O}_2\text{N}, \text{CN}$, etc. do not dimerize, but are kinetically stable.¹⁶¹ Completely chlorinated triarylmethyl radicals are more stable than the unsubstituted kind, probably for steric reasons, and many are quite inert in solution and in the solid state.¹⁶²

It has been postulated that the stability of free radicals is enhanced by the presence at the radical center of both an electron-donating and an electron-withdrawing group.¹⁶³ This is called the *push-pull* or *captodative effect* (see also pp. 129). The effect arises from increased resonance, e.g.:



There is some evidence in favor¹⁶⁴ of the captodative effect, some of it from esr studies.¹⁶⁵ However, there is also experimental¹⁶⁶ and theoretical¹⁶⁷ evidence against it. There is evidence that while FCH_2^\bullet and $\text{F}_2\text{CH}^\bullet$ are more stable than CH_3^\bullet , the radical CF_3^\bullet is less stable; that is, the presence of the third F destabilizes the radical.¹⁶⁸

¹⁵⁸Müller; Moosmayer; Ricker; Scheffler *Tetrahedron Lett.* **1967**, 3877. See also Neugebauer; Hellwinkel; Aulmich *Tetrahedron Lett.* **1978**, 4871.

¹⁵⁹Kaba; Ingold *J. Am. Chem. Soc.* **1976**, *98*, 523.

¹⁶⁰Zarkadis; Neumann; Marx; Uzick *Chem. Ber.* **1985**, *118*, 450; Zarkadis; Neumann; Uzick *Chem. Ber.* **1985**, *118*, 1183.

¹⁶¹Dünnebacke; Neumann; Penenory; Stewen *Chem. Ber.* **1989**, *122*, 533.

¹⁶²For reviews, see Ballester *Adv. Phys. Org. Chem.* **1989**, *25*, 267-445, pp. 354-405, *Acc. Chem. Res.* **1985**, *18*, 380-387. See also Hegarty; O'Neill *Tetrahedron Lett.* **1987**, *28*, 901.

¹⁶³For reviews, see Sustmann; Korth *Adv. Phys. Org. Chem.* **1990**, *26*, 131-178; Viehe; Janousek; Merényi; Stella *Acc. Chem. Res.* **1985**, *18*, 148-154.

¹⁶⁴For a summary of the evidence, see Pasto *J. Am. Chem. Soc.* **1988**, *110*, 8164. See also Ref. 163.

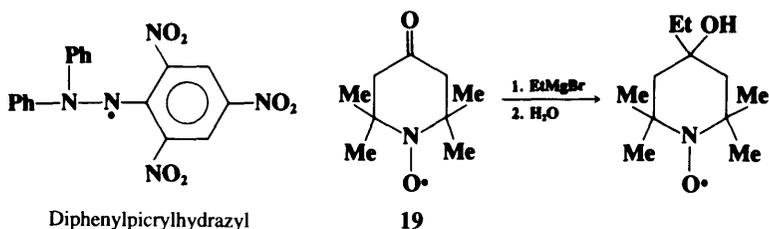
¹⁶⁵See, for example Korth; Lommes; Sustmann; Sylvander; Stella *New J. Chem.* **1987**, *11*, 365; Sakurai; Kyushin; Nakadaira; Kira *J. Phys. Org. Chem.* **1988**, *1*, 197; Rhodes; Roduner *Tetrahedron Lett.* **1988**, *29*, 1437; Viehe; Merényi; Janousek *Pure Appl. Chem.* **1988**, *60*, 1635; Creary; Sky; Mehrsheikh-Mohammadi *Tetrahedron Lett.* **1988**, *29*, 6839; Bordwell; Lynch *J. Am. Chem. Soc.* **1989**, *111*, 7558.

¹⁶⁶See, for example Beckhaus; Rüchardt *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 770 [*Angew. Chem.* *99*, 807]; Neumann; Penenory; Stewen; Lehnig *J. Am. Chem. Soc.* **1989**, *111*, 5845; Bordwell; Bausch; Cheng; Cripe; Lynch; Mueller *J. Org. Chem.* **1990**, *55*, 58; Bordwell; Harrelson *Can. J. Chem.* **1990**, *68*, 1714.

¹⁶⁷See Pasto. Ref. 164.

¹⁶⁸Jiang; Li; Wang *J. Org. Chem.* **1989**, *54*, 5648.

Certain radicals with the unpaired electron not on a carbon are also very stable.¹⁶⁹ Diphenylpicrylhydrazyl is a solid that can be kept for years. We have already mentioned nitroxide radicals. **19** is a nitroxide radical so stable that reactions can be performed on it



without affecting the unpaired electron¹⁷⁰ (the same is true for some of the chlorinated triarylmethyl radicals mentioned above¹⁷¹).

Dissociation energies (D values) of R—H bonds provide a measure of the relative inherent stability of free radicals R.¹⁷² Table 5.3 lists such values.¹⁷³ The higher the D value, the less stable the radical.

TABLE 5.3 D_{298} values for some R—H bonds¹⁷³
Free-radical stability is in the reverse order

R	D	
	kcal/mol	kJ/mol
Ph•	111	464
CF ₃ •	107	446
CH ₂ =CH•	106	444
cyclopropyl ¹⁷⁴	106	444
Me•	105	438
Et•	100	419
Me ₃ CCH ₂ •	100	418
Pr•	100	417
Cl ₃ C•	96	401
Me ₂ CH•	96	401
Me ₃ C ¹⁷⁵	95.8	401
cyclohexyl	95.5	400
PhCH ₂ •	88	368
HCO•	87	364
CH ₂ =CH—CH ₂ •	86	361

¹⁶⁹For reviews of radicals with the unpaired electron on atoms other than carbon, see, in Kochi, Ref. 136, vol. 2, the reviews by Nelson, pp. 527-593 (N-centered); Bentrude, pp. 595-663 (P-centered); Kochi, pp. 665-710 (O-centered); Kice, pp. 711-740 (S-centered); Sakurai, pp. 741-807 (Si, Ge, Sn, and Pb-centered).

¹⁷⁰Neiman; Rozantsev; Mamedova *Nature* **1963**, *200*, 256. For reviews of such radicals, see Aurich, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley: New York, 1982, pp. 565-622 [This review has been reprinted, and new material added, in Breuer; Aurich; Nielsen *Nitrones, Nitronates, and Nitroxides*; Wiley: New York, 1989, pp. 313-399]; Rozantsev; Sholle *Synthesis* **1971**, 190-202, 401-414.

¹⁷¹See Ballester; Veciana; Riera; Castañer; Armet; Rovira *Chem. Soc., Chem. Commun.* **1983**, 982.

¹⁷²It has been claimed that relative D values do not provide such a measure: Nicholas; Arnold *Can. J. Chem.* **1984**, *62*, 1850, 1860.

¹⁷³Except where noted, these values are from Kerr, in Weast *Handbook of Chemistry and Physics*, 69th ed.; CRC Press: Boca Raton, FL, 1988, p. F-183. For another list of D values, see McMillen; Golden *Annu. Rev. Phys. Chem.* **1982**, *33*, 493. See also Tsang *J. Am. Chem. Soc.* **1985**, *107*, 2872; Holmes; Lossing; Maccoll *J. Am. Chem. Soc.* **1988**, *110*, 7339; Holmes; Lossing *J. Am. Chem. Soc.* **1988**, *110*, 7343; Roginskii *J. Org. Chem. USSR* **1989**, *25*, 403.

¹⁷⁴For a review of cyclopropyl radicals, see Walborsky *Tetrahedron* **1981**, *37*, 1625-1651. See also Boche; Walborsky, Ref. 102.

¹⁷⁵This value is from Gutman *Acc. Chem. Res.* **1990**, *23*, 375-380.

There are two possible structures for simple alkyl radicals.¹⁷⁶ They might have sp^2 bonding, in which case the structure would be planar, with the odd electron in a p orbital, or the bonding might be sp^3 , which would make the structure pyramidal and place the odd electron in an sp^3 orbital. ESR spectra of CH_3^\bullet and other simple alkyl radicals as well as other evidence indicate that these radicals have planar structures.¹⁷⁷ This is in accord with the known loss of optical activity when a free radical is generated at a chiral carbon.¹⁷⁸ In addition, electronic spectra of the CH_3 and CD_3 radicals (generated by flash photolysis) in the gas phase have definitely established that under these conditions the radicals are planar or near-planar.¹⁷⁹ IR spectra of CH_3^\bullet trapped in solid argon led to a similar conclusion.¹⁸⁰

Evidence from studies on bridgehead compounds shows that though a planar configuration is more stable, pyramidal structures are not impossible. In contrast to the situation with carbocations, free radicals have often been generated at bridgeheads, although studies have shown that bridgehead free radicals are less rapidly formed than the corresponding open-chain radicals.¹⁸¹ In sum, the available evidence indicates that though simple alkyl free radicals prefer a planar, or near-planar shape, the energy difference between a planar and a pyramidal free radical is not great. However, free radicals in which the carbon is connected to atoms of high electronegativity, e.g., CF_3^\bullet , prefer a pyramidal shape;¹⁸² increasing the electronegativity increases the deviation from planarity.¹⁸³ Cyclopropyl radicals are also pyramidal.¹⁸⁴

Free radicals with resonance are definitely planar, though triphenylmethyl-type radicals are propeller-shaped,¹⁸⁵ like the analogous carbocations (p. 172).

A number of diradicals (also called biradicals) are known.¹⁸⁶ When the unpaired electrons of a diradical are widely separated, e.g., as in $\bullet\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2^\bullet$, the species behaves spectrally like two doublets. When they are close enough for interaction or can interact through an unsaturated system (as in trimethylenemethane,¹⁸⁷ they can have total spin numbers of $+1$, 0 , or -1 , since each electron could be either $+\frac{1}{2}$ or $-\frac{1}{2}$. Spectroscopically

¹⁷⁶For a review, see Kaplan, in Kochi, Ref. 136, vol. 2, pp. 361-434.

¹⁷⁷See, for example, Cole; Pritchard; Davidson; McConnell *Mol. Phys.* **1958**, *1*, 406; Fessenden; Schuler *J. Chem. Phys.* **1963**, *39*, 2147; Symons *Nature* **1969**, 222, 1123, *Tetrahedron Lett.* **1973**, 207; Bonazzola; Leray; Roncin *J. Am. Chem. Soc.* **1977**, *99*, 8348; Giese; Beckhaus *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 594 [*Angew. Chem.* **90**, 635]; Ref. 98. See, however, Paddon-Row; Houk *J. Am. Chem. Soc.* **1981**, *103*, 5047.

¹⁷⁸There are a few exceptions. See p. 682.

¹⁷⁹Herzberg; Shoosmith *Can. J. Phys.* **1956**, *34*, 523; Herzberg *Proc. R. Soc. London, Ser. A* **1961**, 262, 291. See also Tan; Winer; Pimentel *J. Chem. Phys.* **1972**, *57*, 4028; Yamada; Hirota; Kawaguchi *J. Chem. Phys.* **1981**, *75*, 5256.

¹⁸⁰Andrews; Pimentel *J. Chem. Phys.* **1967**, *47*, 3637; Milligan; Jacox *J. Chem. Phys.* **1967**, *47*, 5146.

¹⁸¹Lorand; Chodroff; Wallace *J. Am. Chem. Soc.* **1968**, *90*, 5266; Fort; Franklin *J. Am. Chem. Soc.* **1968**, *90*, 5267; Humphrey; Hodgson; Pincock *Can. J. Chem.* **1968**, *46*, 3099; Oberlinner; Rüchardt *Tetrahedron Lett.* **1969**, 4685; Danen; Tipton; Saunders *J. Am. Chem. Soc.* **1971**, *93*, 5186; Fort; Hiti *J. Org. Chem.* **1977**, *42*, 3968; Lomas *J. Org. Chem.* **1987**, *52*, 2627.

¹⁸²Fessenden; Schuler *J. Chem. Phys.* **1965**, *43*, 2704; Rogers; Kispert *J. Chem. Phys.* **1967**, *46*, 3193; Pauling *J. Chem. Phys.* **1969**, *51*, 2767.

¹⁸³For example, 1,1-dichloroalkyl radicals are closer to planarity than the corresponding 1,1-difluoro radicals, though still not planar: Chen; Tang; Montgomery; Kochi *J. Am. Chem. Soc.* **1974**, *96*, 2201. For a discussion, see Krusic; Bingham *J. Am. Chem. Soc.* **1976**, *98*, 230.

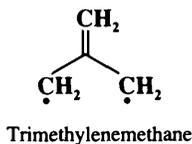
¹⁸⁴See Deycard; Hughes; Luszyk; Ingold *J. Am. Chem. Soc.* **1987**, *109*, 4954.

¹⁸⁵Adrian *J. Chem. Phys.* **1958**, *28*, 608; Andersen *Acta Chem. Scand.* **1965**, *19*, 629.

¹⁸⁶For a monograph, see Borden *Diradicals*; Wiley, New York, 1982. For reviews, see Johnston; Scaiano *Chem. Rev.* **1989**, *89*, 521-547; Doubleday; Turro; Wang *Acc. Chem. Res.* **1989**, *22*, 199-205; Scheffer; Trotter *Rev. Chem. Intermed.* **1988**, *9*, 271-305; Wilson *Org. Photochem.* **1985**, *7*, 339-466; Borden *React. Intermed. (Wiley)* **1985**, *3*, 151-188, **1981**, *2*, 175-209; Borden; Davidson *Acc. Chem. Res.* **1981**, *14*, 69-76; Salem; Rowland *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 92-111 [*Angew. Chem.* **84**, 86-106]; Salem *Pure Appl. Chem.* **1973**, *33*, 317-328; Jones *J. Chem. Educ.* **1974**, *51*, 175-181; Morozova; Dyatkina *Russ. Chem. Rev.* **1968**, *37*, 376-391. See also Döhnert; Koutecký *J. Am. Chem. Soc.* **1980**, *102*, 1789. For a series of papers on diradicals, see *Tetrahedron* **1982**, *38*, 735-867.

¹⁸⁷For reviews of trimethylenemethane, see Borden; Davidson *Ann. Rev. Phys. Chem.* **1979**, *30*, 125-153; Bergman; in Kochi, Ref. 136, vol. 1, pp. 141-149.

they are called *triplets*,¹⁸⁸ since each of the three possibilities is represented among the molecules and gives rise to its own spectral peak. In triplet *molecules* the two unpaired

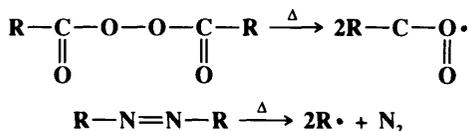


electrons have the same spin. Radicals with both unpaired electrons on the same carbon are discussed under carbenes.

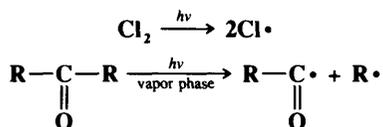
The Generation and Fate of Free Radicals¹⁸⁹

Free radicals are formed from molecules by breaking a bond so that each fragment keeps one electron.¹⁹⁰ The energy necessary to break the bond is supplied in one of two ways.

1. *Thermal cleavage.* Subjection of any organic molecule to a high enough temperature in the gas phase results in the formation of free radicals. When the molecule contains bonds with *D* values of 20 to 40 kcal/mol (80 to 170 kJ/mol), cleavage can be caused in the liquid phase. Two common examples are cleavage of diacyl peroxides¹⁹² and of azo compounds;¹⁹³



2. *Photochemical cleavage* (see p. 236). The energy of light of 600 to 300 nm is 48 to 96 kcal/mol (200 to 400 kJ/mol), which is of the order of magnitude of covalent-bond energies. Typical examples are photochemical cleavage of chlorine and of ketones;



¹⁸⁸For discussions of the triplet state, see Wagner; Hammond *Adv. Photochem.* **1968**, *5*, 21-156; Turro *J. Chem. Educ.* **1969**, *46*, 2-6. For a discussion of esr spectra of triplet states, see Wasserman; Hutton *Acc. Chem. Res.* **1977**, *10*, 27-32.

¹⁸⁹For a summary of methods of radical formation, see Giese *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Elmsford, NY, 1986, pp. 267-281. For a review on formation of free radicals by thermal cleavage, see Brown *Pyrolytic Methods in Organic Chemistry*; Academic Press: New York, 1980, pp. 44-61.

¹⁹⁰It is also possible for free radicals to be formed by the collision of two nonradical species. For a review, see Harmony *Methods Free-Radical Chem.* **1974**, *5*, 101-176.

¹⁹¹For a review of homolytic cleavage of carbon-metal bonds, see Barker; Winter, in Hartley; Patai, Ref. 107, pp. 151-218.

¹⁹²For a review of free radical mechanisms involving peroxides in solution, see Howard, in Patai *The Chemistry of Peroxides*; Wiley: New York, 1983, pp. 235-258. For a review of pyrolysis of peroxides in the gas phase, see Batt; Liu, in the same volume, pp. 685-710. See also Chateaucneuf; Luszyk; Ingold *J. Am. Chem. Soc.* **1988**, *110*, 2877, 2886.

¹⁹³For a review of the cleavage of azoalkanes, see Engel *Chem. Rev.* **1980**, *80*, 99-150. For summaries of later work, see Adams; Burton; Andrews; Weisman; Engel *J. Am. Chem. Soc.* **1986**, *108*, 7935; Schmittel; Ruchardt *J. Am. Chem. Soc.* **1987**, *109*, 2750.

Radicals are also formed from other radicals, either by the reaction between a radical and a molecule (which *must* give another radical, since the total number of electrons is odd) or by cleavage of a radical to give another radical, e.g.,



Radicals can also be formed by oxidation or reduction, including electrolytic methods.

Reactions of free radicals either give stable products (termination reactions) or lead to other radicals, which themselves must usually react further (propagation reactions). The most common termination reactions are simple combinations of similar or different radicals:

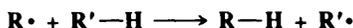


Another termination process is disproportionation:¹⁹⁴

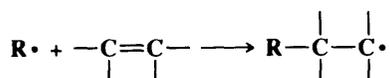


There are four principal propagation reactions, of which the first two are most common:

1. *Abstraction of another atom or group, usually a hydrogen atom* (see Chapter 14):



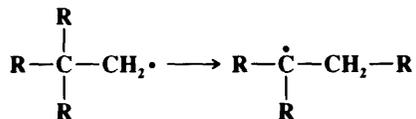
2. *Addition to a multiple bond* (see Chapter 15):



The radical formed here may add to another double bond, etc. This is one of the chief mechanisms for vinyl polymerization.

3. *Decomposition*. This can be illustrated by the decomposition of the benzyloxy radical (above).

4. *Rearrangement*:



This is less common than rearrangement of carbocations, but it does occur (though not when R = alkyl or hydrogen; see Chapter 18).

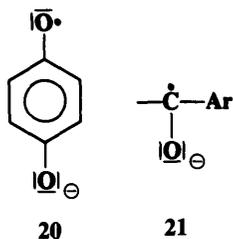
Besides these reactions, free radicals can be oxidized to carbocations or reduced to carbanions.¹⁹⁵

¹⁹⁴For reviews of termination reactions, see Pilling *Int. J. Chem. Kinet.* **1989**, *21*, 267-291; Khudyakov; Levin; Kuz'min *Russ. Chem. Rev.* **1980**, *49*, 982-1002; Gibian; Corley *Chem. Rev.* **1973**, *73*, 441-464.

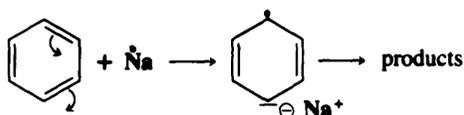
¹⁹⁵For a review of the oxidation and reduction of free radicals, see Khudyakov and Kuz'min *Russ. Chem. Rev.* **1978**, *47*, 22-42.

Radical Ions¹⁹⁶

Several types of radical anions are known with the unpaired electron or the charge or both on atoms other than carbon. Important examples are semiquinones¹⁹⁷ (20) and ketyls¹⁹⁸



(21). Reactions in which alkali metals are reducing agents often involve radical anion intermediates, e.g., reaction 5-10:



Several types of radical cation are also known.¹⁹⁹

CARBENES

Stability and Structure²⁰⁰

Carbenes are highly reactive species, practically all having lifetimes considerably under 1 sec. With exceptions noted below (p. 200), carbenes have been isolated only by entrapment in matrices at low temperatures (77 K or less).²⁰¹ The parent species CH_2 is usually called

¹⁹⁶For a monograph, see Kaiser; Kevan *Radical Ions*; Wiley: New York, 1968. For reviews, see Gerson; Huber *Acc. Chem. Res.* **1967**, *20*, 85-90; Todres *Tetrahedron* **1985**, *41*, 2771-2823; Russell; Norris, in McManus, Ref. 1, pp. 423-448; Holy; Marcum *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 115-124 [*Angew. Chem.* **83**, 132-142]; Bilevich; Okhlobystin *Russ. Chem. Rev.* **1968**, *37*, 954-968; Szwarc *Prog. Phys. Org. Chem.* **1968**, *6*, 322-438. For a related review, see Chanon; Rajzmann; Chanon *Tetrahedron* **1990**, *46*, 6193-6299. For a series of papers on this subject, see *Tetrahedron* **1986**, *42*, 6097-6349.

¹⁹⁷For a review of semiquinones, see Depew; Wan, in Patai; Rappoport *The Chemistry of the Quinonoid Compounds*, vol. 2, pt. 2; Wiley: New York, 1988, pp. 963-1018.

¹⁹⁸For a review of ketyls, see Russell, in Patai; Rappoport *The Chemistry of Enones*, pt. 1; Wiley: New York, 1989, pp. 471-512.

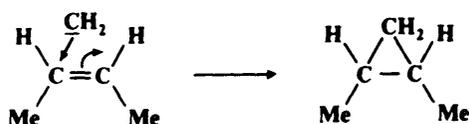
¹⁹⁹For reviews, see Roth *Acc. Chem. Res.* **1987**, *20*, 343-350; Courtneidge; Davies *Acc. Chem. Res.* **1987**, *20*, 90-97; Hammerich; Parker *Adv. Phys. Org. Chem.* **1984**, *20*, 55-189; Symons *Chem. Soc. Rev.* **1984**, *13*, 393-439; Bard; Ledwith; Shine *Adv. Phys. Org. Chem.* **1976**, *13*, 155-278.

²⁰⁰For monographs, see Jones; Moss *Carbenes*, 2 vols.; Wiley: New York, 1973-1975; Kirmse *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971; Rees; Gilchrist *Carbenes, Nitrenes, and Arynes*; Nelson: London, 1969. For reviews, see Minkin; Simkin; Glukhovtsev *Russ. Chem. Rev.* **1989**, *58*, 622-635; Moss; Jones *React. Intermed. (Wiley)* **1985**, *3*, 45-108, **1981**, *2*, 59-133, **1978**, *1*, 69-115; Isaacs, Ref. 1, pp. 375-407; Bethell *Adv. Phys. Org. Chem.* **1969**, *7*, 153-209; Bethell, in McManus, Ref. 1, pp. 61-126; Closs *Top. Stereochem.* **1968**, *3*, 193-235; Herold; Gaspar *Fortschr. Chem. Forsch.* **1966**, *5*, 89-146; Rozantsev; Fainzil'berg; Novikov *Russ. Chem. Rev.* **1965**, *34*, 69-88. For a theoretical study, see Liebman; Simons *Mol. Struct. Energ.* **1986**, *1*, 51-99.

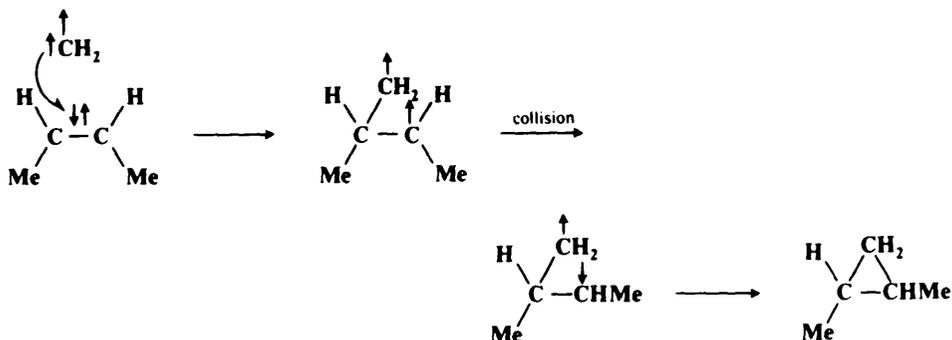
²⁰¹For example, see Murray; Trozzolo; Wasserman; Yager *J. Am. Chem. Soc.* **1962**, *84*, 3213; Brandon; Closs; Hutchison *J. Chem. Phys.* **1962**, *37*, 1878; Milligan; Mann; Jacox; Mitsch *J. Chem. Phys.* **1964**, *41*, 1199; Nefedov; Maltsev; Mikaelyan *Tetrahedron Lett.* **1971**, 4125; Wright *Tetrahedron* **1985**, *41*, 1517. For reviews, see Zuev; Nefedov *Russ. Chem. Rev.* **1989**, *58*, 636-643; Sheridan *Org. Photochem.* **1987**, *8*, 159-248, pp. 196-216; Trozzolo *Acc. Chem. Res.* **1968**, *1*, 329-335.

methylene, though derivatives are more often named by the carbene nomenclature. Thus CCl_2 is generally known as dichlorocarbene, though it can also be called dichloromethylene.

The two nonbonded electrons of a carbene can be either paired or unpaired. If they are paired, the species is spectrally a *singlet*, while, as we have seen (p. 193), two unpaired electrons appear as a *triplet*. An ingenious method of distinguishing between the two possibilities was developed by Skell,²⁰² based on the common reaction of addition of carbenes to double bonds to form cyclopropane derivatives (5-50). If the singlet species adds to *cis*-2-butene, the resulting cyclopropane should be the *cis* isomer since the movements of



the two pairs of electrons should occur either simultaneously or with one rapidly succeeding another. However, if the attack is by a triplet species, the two unpaired electrons cannot both go into a new covalent bond, since by Hund's rule they have parallel spins. So one of the unpaired electrons will form a bond with the electron from the double bond that has the opposite spin, leaving two unpaired electrons that have the same spin and therefore cannot form a bond at once but must wait until, by some collision process, one of the



electrons can reverse its spin. During this time, there is free rotation about the C—C bond and a mixture of *cis*- and *trans*-1,2-dimethylcyclopanes should result.²⁰³

The results of this type of experiment show that CH_2 itself is usually formed as a singlet species, which can decay to the triplet state, which consequently has a lower energy (molecular-orbital calculations and experimental determinations show that the difference in energy between singlet and triplet CH_2 is about 8 to 10 kcal/mol or 33 to 42 kJ/mol²⁰⁴). However, it is possible to prepare triplet CH_2 directly by a photosensitized decomposition of diazomethane.²⁰⁵ CH_2 is so reactive²⁰⁶ that it generally reacts as the singlet before it has

²⁰²Skell; Woodworth *J. Am. Chem. Soc.* **1956**, *78*, 4496; Skell *Tetrahedron* **1985**, *41*, 1427.

²⁰³These conclusions are generally accepted though the reasoning given here may be oversimplified. For discussions, see Closs, Ref. 200, pp. 203-210; Bethell *Adv. Phys. Org. Chem.*, Ref. 200, pp. 194-200; Hoffmann *J. Am. Chem. Soc.* **1968**, *90*, 1475.

²⁰⁴See, for example, Hay; Hunt; Goddard *Chem. Phys. Lett.* **1972**, *13*, 30; Dewar; Haddon; Weiner *J. Am. Chem. Soc.* **1974**, *96*, 253; Frey; Kennedy *J. Chem. Soc., Chem. Commun.* **1975**, 233; Lucchese; Schaefer *J. Am. Chem. Soc.* **1977**, *99*, 6765; Roos; Siegbahn *J. Am. Chem. Soc.* **1977**, *99*, 7716; Lengel; Zare *J. Am. Chem. Soc.* **1978**, *100*, 7495; Borden; Davidson, Ref. 187, pp. 128, 134; Leopold; Murray; Lineberger *J. Chem. Phys.* **1984**, *81*, 1048.

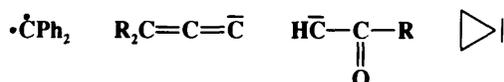
²⁰⁵Kopecky; Hammond; Leermakers *J. Am. Chem. Soc.* **1961**, *83*, 2397, **1962**, *84*, 1015; Duncan; Cveticanić *J. Am. Chem. Soc.* **1962**, *84*, 3593.

²⁰⁶For a review of the kinetics of CH_2 reactions, see Laufer *Rev. Chem. Intermed.* **1981**, *4*, 225-257.

a chance to decay to the triplet state.²⁰⁷ As to other carbenes, some react as triplets, some as singlets, and others as singlets or triplets, depending on how they are generated.

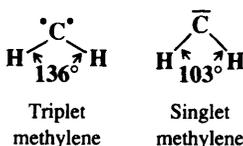
There is a limitation to the use of stereospecificity of addition as a diagnostic test for singlet or triplet carbenes.²⁰⁸ When carbenes are generated by photolytic methods, they are often in a highly excited singlet state. When they add to the double bond, the addition is stereospecific; but the cyclopropane formed carries excess energy; i.e., it is in an excited state. It has been shown that under certain conditions (low pressures in the gas phase) the excited cyclopropane may undergo cis-trans isomerization *after* it is formed, so that triplet carbene may seem to be involved although in reality the singlet was present.²⁰⁹

The most common carbenes are CH₂ and CCl₂,²¹⁰ but many others have been reported, e.g.,²¹¹



Studies of the ir spectrum of CCl₂ trapped at low temperatures in solid argon indicate that the ground state for this species is the singlet.²¹²

The geometrical structure of triplet methylene can be investigated by esr measurements,²¹³ since triplet species are diradicals. Such measurements made on triplet CH₂ trapped in matrices at very low temperatures (4 K) show that triplet CH₂ is a bent molecule, with an angle of about 136°.²¹⁴ Epr measurements cannot be made on singlet species, but from electronic spectra of CH₂ formed in flash photolysis of diazomethane it was concluded that singlet CH₂ is also bent, with an angle of about 103°.²¹⁵ Singlet CCl₂²¹² and CBr₂²¹⁶ are also



bent, with angles of 100 and 114°, respectively. It has long been known that triplet aryl carbenes are bent.²¹⁷

²⁰⁷Decay of singlet and triplet CH₂ has been detected in solution, as well as in the gas phase: Turro; Cha; Gould *J. Am. Chem. Soc.* **1987**, *109*, 2101.

²⁰⁸For other methods of distinguishing singlet from triplet carbenes, see Hendrick; Jones *Tetrahedron Lett.* **1978**, 4249; Creary *J. Am. Chem. Soc.* **1980**, *102*, 1611.

²⁰⁹Rabinovitch; Tschuikow-Roux; Schlag *J. Am. Chem. Soc.* **1959**, *81*, 1081; Frey *Proc. R. Soc. London, Ser. A* **1959**, *251*, 575. It has been reported that a singlet carbene (CBr₂) can add nonstereospecifically: Lambert; Larson; Bosch *Tetrahedron Lett.* **1983**, *24*, 3799.

²¹⁰For reviews of halocarbenes, see Burton; Hahnfeld *Fluorine Chem. Rev.* **1977**, *8*, 119-188; Margrave; Sharp; Wilson *Fort. Chem. Forsch.* **1972**, *26*, 1-35, pp. 3-13.

²¹¹For reviews of unsaturated carbenes, see Stang *Acc. Chem. Res.* **1982**, *15*, 348-354; *Chem. Rev.* **1978**, *78*, 383-403. For a review of carbalkoxy-carbenes, see Marchand; Brockway *Chem. Rev.* **1974**, *74*, 431-469. For a review of arylcarbenes, see Schuster *Adv. Phys. Org. Chem.* **1986**, *22*, 311-361. For a review of carbenes with neighboring hetero atoms, see Taylor *Tetrahedron* **1982**, *38*, 2751-2772.

²¹²Andrews *J. Chem. Phys.* **1968**, *48*, 979.

²¹³The technique of spin trapping (p. 187) has been applied to the detection of transient triplet carbenes: Forrester; Sadd *J. Chem. Soc., Perkin Trans. 2* **1982**, 1273.

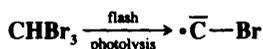
²¹⁴Wasserman; Kuck; Hutton; Yager *J. Am. Chem. Soc.* **1970**, *92*, 7491; Wasserman; Yager; Kuck *Chem. Phys. Lett.* **1970**, *7*, 409; Wasserman; Kuck; Hutton; Anderson; Yager *J. Chem. Phys.* **1971**, *54*, 4120; Bernheim; Bernard; Wang; Wood; Skell *J. Chem. Phys.* **1970**, *53*, 1280, **1971**, *54*, 3223.

²¹⁵Herzberg; Shoosmith *Nature* **1959**, *183*, 1801; Herzberg *Proc. R. Soc. London, Ser. A* **1961**, *262*, 291; Herzberg; Johns *Proc. R. Soc. London, Ser. A* **1967**, *295*, 107, *J. Chem. Phys.* **1971**, *54*, 2276.

²¹⁶Ivey; Schulze; Leggett; Kohl *J. Chem. Phys.* **1974**, *60*, 3174.

²¹⁷Trozzolo; Wasserman; Yager *J. Am. Chem. Soc.* **1965**, *87*, 129; Senthilnathan; Platz *J. Am. Chem. Soc.* **1981**, *103*, 5503; Gilbert; Griller; Nazran *J. Org. Chem.* **1985**, *50*, 4738.

Flash photolysis of CHBr_3 produced the intermediate CBr^{218}

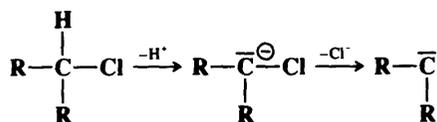


This is a *carbyne*. The intermediates CF and CCl were generated similarly from CHFBr_2 and CHClBr_2 , respectively.

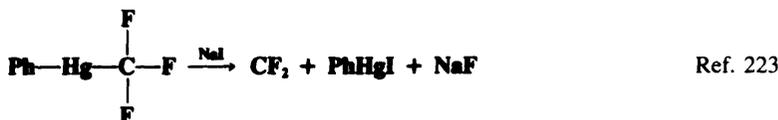
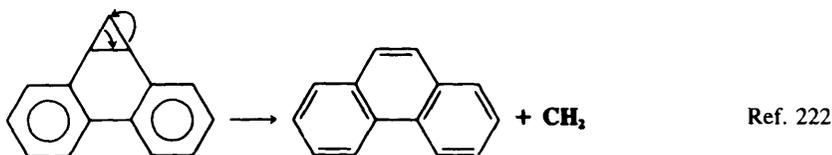
The Generation and Fate of Carbenes²¹⁹

Carbenes are chiefly formed in two ways, though other pathways are also known.

1. In α elimination, a carbon loses a group without its electron pair, usually a proton, and then a group with its pair, usually a halide ion:²²⁰



The most common example is formation of dichlorocarbene by treatment of chloroform with a base (see reaction 0-3), but many other examples are known, a few of which are



2. Disintegration of compounds containing certain types of double bonds:



²¹⁸Ruzsicska; Jodhan; Choi; Strausz *J. Am. Chem. Soc.* **1983**, *105*, 2489.

²¹⁹For reviews, see Jones *Acc. Chem. Res.* **1974**, *7*, 415-421; Kirmse, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 9; Elsevier: New York, 1973, pp. 373-415; Ref. 200. For a review of electrochemical methods of carbene generation, see Petrosyan; Niyazymbetov *Russ. Chem. Rev.* **1969**, *58*, 644-653.

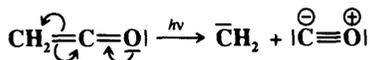
²²⁰For a review of formation of carbenes in this manner, see Kirmse *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1-10 [*Angew. Chem.* *77*, 1-10].

²²¹Wagner *Proc. Chem. Soc.* **1959**, 229.

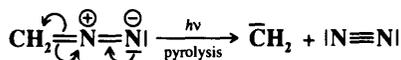
²²²Richardson; Durrett; Martin; Putnam; Slaymaker; Dvoretzky *J. Am. Chem. Soc.* **1965**, *87*, 2763. For reviews of this type of reaction, see Hoffmann *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 529, 537 [*Angew. Chem.* *83*, 595-603]; Griffin *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 537-547 [*Angew. Chem.* *83*, 604-613]. See also Hoffmann *Acc. Chem. Res.* **1985**, *18*, 248-253.

²²³Seyferth; Hopper; Darragh *J. Am. Chem. Soc.* **1969**, *91*, 6536; Seyferth *Acc. Chem. Res.* **1972**, *5*, 65-74.

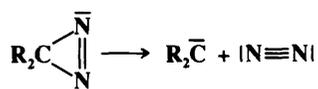
The two most important ways of forming CH_2 are examples: the photolysis of ketene



and the isoelectronic decomposition of diazomethane.²²⁴



Diazirines (isomeric with diazoalkanes) also give carbenes:²²⁵

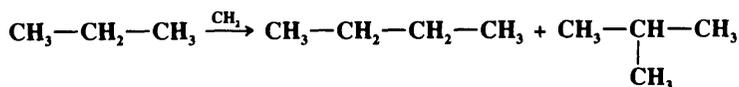


Because most carbenes are so reactive, it is often difficult to prove that they are actually present in a given reaction. In many instances where a carbene is *apparently* produced by an α elimination or by disintegration of a double-bond compound there is evidence that no free carbene is actually involved. The neutral term *carbenoid* is used where it is known that a free carbene is not present or in cases where there is doubt. α -Halo organometallic compounds R_2CXM are often called carbenoids because they readily give α elimination reactions²²⁶ (for example, see 2-39).

The reactions of carbenes are more varied than those of the species previously discussed in this chapter.

1. Additions to carbon-carbon double bonds have already been mentioned. Carbenes also add to aromatic systems, but the immediate products rearrange, usually with ring enlargement (see 5-50). Additions of carbenes to other double bonds, such as $\text{C}=\text{N}$ (6-61 and 6-62), and to triple bonds have also been reported.

2. An unusual reaction of carbenes is that of insertion into C-H bonds (2-20). Thus CH_2 reacts with methane to give ethane and with propane to give *n*-butane and isobutane.



This reaction is virtually useless for synthetic purposes but illustrates the extreme reactivity of carbene. Treatment in the liquid phase of an alkane such as pentane with carbene formed from the photolysis of diazomethane gives the three possible products in statistical ratios²²⁷ demonstrating that carbene is displaying no selectivity. For many years, it was a generally accepted principle that the lower the selectivity the greater the reactivity; however, this

²²⁴For a review, see Regitz; Maas *Diazo Compounds*; Academic Press: New York, 1986, pp. 170-184.

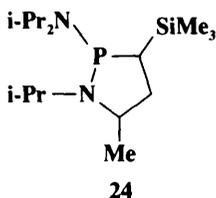
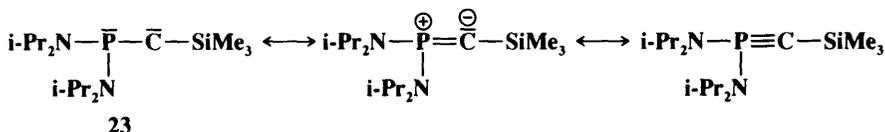
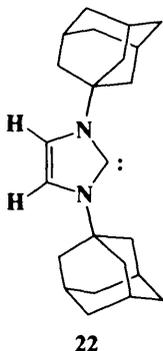
²²⁵For a treatise, see Liu *Chemistry of Diazirines*, 2 vols.; CRC Press: Boca Raton, FL, 1987. For reviews, see Liu *Chem. Soc. Rev.* **1982**, *11*, 127-140; Frey *Adv. Photochem.* **1966**, *4*, 225-256.

²²⁶For a review, see Nefedov; D'yachenko; Prokof'ev *Russ. Chem. Rev.* **1977**, *46*, 941-966.

²²⁷Doering; Buttery; Laughlin; Chaudhuri *J. Am. Chem. Soc.* **1956**, *78*, 3224; Richardson; Simmons; Dvoretzky *J. Am. Chem. Soc.* **1961**, *83*, 1934; Halberstadt; McNesby *J. Am. Chem. Soc.* **1967**, *89*, 3417.

principle is no longer regarded as general because many exceptions have been found.²²⁸ Singlet CH₂ generated by photolysis of diazomethane is probably the most reactive organic species known, but triplet CH₂ is somewhat less reactive, and other carbenes are still less reactive. The following series of carbenes of decreasing reactivity has been proposed on the basis of discrimination between insertion and addition reactions: CH₂ > HCCOOR > PhCH > BrCH ≈ ClCH.²²⁹ Dihalocarbenes generally do not give insertion reactions at all. Insertion of carbenes into other bonds has also been demonstrated, though not insertion into C—C bonds.^{229a}

Two carbenes that are stable at room temperature have been reported.²³⁰ These are **22** and **23**. In the absence of oxygen and moisture **22** exists as stable crystals with a melting point of 240-241°C.^{230a} Its structure was proved by x-ray crystallography. **23**, which is in resonance with an ylide form and with a form containing a P≡C bond, is a red oil that



²²⁸For reviews of this question, see Buncel; Wilson *J. Chem. Educ.* **1987**, *64*, 475-480; Johnson *Tetrahedron* **1980**, *36*, 3461-3480; *Chem. Rev.* **1975**, *75*, 755-765; Giese *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 125-136 [*Angew. Chem.* *89*, 162-173]; Pross *Adv. Phys. Org. Chem.* **1977**, *14*, 69-132. See also Ritchie; Sawada *J. Am. Chem. Soc.* **1977**, *99*, 3754; Argile; Ruasse *Tetrahedron Lett.* **1980**, *21*, 1327; Godfrey *J. Chem. Soc., Perkin Trans. 2* **1981**, 645; Kurz; El-Nasr *J. Am. Chem. Soc.* **1982**, *104*, 5823; Srinivasan; Shunmugasundaram; Arumugam *J. Chem. Soc., Perkin Trans. 2* **1985**, 17; Bordwell; Branca; Cripe *Isr. J. Chem.* **1985**, *26*, 357; Formosinho *J. Chem. Soc., Perkin Trans. 2* **1988**, 839; Johnson; Stratton *J. Chem. Soc., Perkin Trans. 2* **1988**, 1903. For a group of papers on this subject, see *Isr. J. Chem.* **1985**, *26*, 303-428.

²²⁹Closs; Coyle *J. Am. Chem. Soc.* **1965**, *87*, 4270.

^{229a}See, for example, Doering; Knox; Jones *J. Org. Chem.* **1959**, *24*, 136; Franzen *Liebigs Ann. Chem.* **1959**, 627, 22; Bradley; Ledwith *J. Chem. Soc.* **1961**, 1495; Frey; Voisey *Chem. Commun.* **1966**, 454; Seyferth; Damrauer; Mui; Jula *J. Am. Chem. Soc.* **1968**, *90*, 2944; Tomioka; Ozaki; Izawa *Tetrahedron* **1985**, *41*, 4987; Frey; Walsh; Watts *J. Chem. Soc., Chem. Commun.* **1989**, 284.

²³⁰For a discussion, see Regitz *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 674 [*Angew. Chem.* *103*, 691].

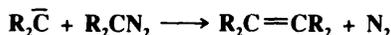
^{230a}Arduengo; Harlow; Kline *J. Am. Chem. Soc.* **1991**, *113*, 361.

undergoes internal insertion (the carbene carbon inserts into one of the C—H bonds of an isopropyl group to give **24**) when heated to 300°C.²³¹

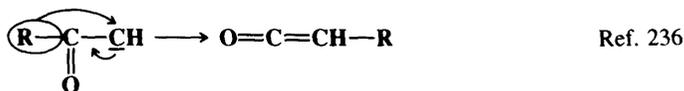
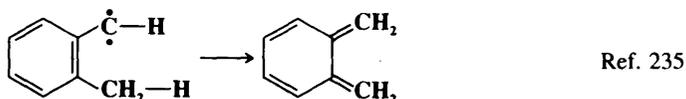
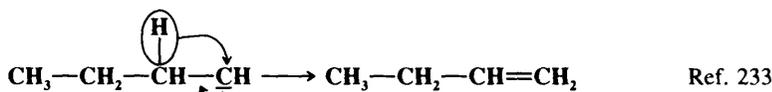
3. It would seem that dimerization should be an important reaction of carbenes



but it is not, because the reactivity is so great that the carbene species do not have time to find each other and because the dimer generally has so much energy that it dissociates again. Apparent dimerizations have been observed, but it is likely that the products in many reported instances of "dimerization" do not arise from an actual dimerization of two carbenes but from attack by a carbene on a molecule of carbene precursor, e.g.,



4. Alkylcarbenes can undergo rearrangement, with migration of alkyl or hydrogen.^{231a} Indeed these rearrangements are generally so rapid²³² that additions to multiple bonds and insertion reactions, which are so common for CH₂, are seldom encountered with alkyl or dialkyl carbenes. Unlike rearrangement of the species previously encountered in this chapter, most rearrangements of carbenes directly give stable molecules. Some examples are



The rearrangement of acylcarbenes to ketenes is called the Wolff rearrangement (**8-8**). A few rearrangements in which carbenes rearrange to other carbenes are also known.²³⁷ Of course, the new carbene must stabilize itself in one of the ways we have mentioned.

²³¹Igau; Grutzmacher; Baccaredo; Bertrand *J. Am. Chem. Soc.* **1991**, *113*, 6463; Igau; Baccaredo; Trinquier; Bertrand *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 621 [*Angew. Chem.* *101*, 617]. See also Gillette; Baccaredo; Bertrand *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1429 [*Angew. Chem.* *102*, 1486].

^{231a}For reviews of carbene and nitrene rearrangements, see Brown, Ref. 189, pp. 115-163; Wentrup *Adv. Heterocycl. Chem.* **1981**, *28*, 231-361, *React. Intermed. (Plenum)* **1980**, *1*, 263-319, *Top. Curr. Chem.* **1976**, *62*, 173-251; Jones, in de Mayo, Ref. 91, vol. 1, pp. 95-160; Schaefer *Acc. Chem. Res.* **1979**, *12*, 288-296; Kirmse, Ref. 200, pp. 457-496.

²³²The activation energy for the 1,2-hydrogen shift has been estimated at 1.1 kcal/mole (4.5 kJ/mol), an exceedingly low value; Stevens; Liu; Soundararajan; Paik *Tetrahedron Lett.* **1989**, *30*, 481.

²³³Kirmse; Doering *Tetrahedron* **1960**, *11*, 266. For kinetic studies of the rearrangement: Cl- \bar{C} -CHR₂ → ClCH=CR₂, see Liu; Bonneau *J. Am. Chem. Soc.* **1989**, *111*, 6873; Jackson; Soundararajan; White; Liu; Bonneau; Platz *J. Am. Chem. Soc.* **1989**, *111*, 6874; Ho; Krogh-Jespersen; Moss; Shen; Sheridan; Subramanian *J. Am. Chem. Soc.* **1989**, *111*, 6875; LaVilla; Goodman *J. Am. Chem. Soc.* **1989**, *111*, 6877.

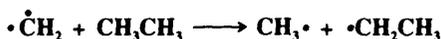
²³⁴Friedman; Shechter *J. Am. Chem. Soc.* **1960**, *82*, 1002.

²³⁵McMahon; Chapman *J. Am. Chem. Soc.* **1987**, *109*, 683.

²³⁶Friedman; Berger *J. Am. Chem. Soc.* **1961**, *83*, 492, 500.

²³⁷For a review, see Jones *Acc. Chem. Res.* **1977**, *10*, 353-359.

5. Triplet carbenes can abstract hydrogen or other atoms to give free radicals, e.g.,



This is not surprising, since triplet carbenes are free radicals. But singlet carbenes can also give this reaction, though in this case only halogen atoms are abstracted, not hydrogen.²³⁸

NITRENES

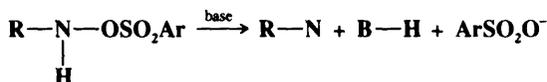
Nitrenes,²³⁹ R—N, are the nitrogen analogs of carbenes, and most of what we have said about carbenes also applies to them. Nitrenes are too reactive for isolation under ordinary conditions. Alkyl nitrenes have been isolated by trapping in matrices at 4 K,²⁴⁰ while aryl nitrenes, which are less reactive, can be trapped at 77 K.²⁴¹ The ground state of NH, and probably of most nitrenes,²⁴² is a triplet, though nitrenes can be generated in both triplet and singlet states. In additions of EtOOC—N to C=C double bonds two species are involved,



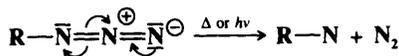
one of which adds stereospecifically and the other not. By analogy with Skell's proposal involving carbenes (p. 196) these are taken to be the singlet and triplet species, respectively.²⁴³

The two principal means of generating nitrenes are analogous to those used to form carbenes.

1. *Elimination.* An example is



2. *Breakdown of certain double-bond compounds.* The most common method of forming nitrenes is photolytic or thermal decomposition of azides,²⁴⁴



²³⁸Roth *J. Am. Chem. Soc.* **1971**, *93*, 1527, 4935, *Acc. Chem. Res.* **1977**, *10*, 85-91.

²³⁹For monographs, see Scriven *Azides and Nitrenes*; Academic Press: New York, 1984; Lwowski *Nitrenes*; Wiley: New York, 1970. For reviews, see Scriven *React. Intermed. (Plenum)* **1982**, *2*, 1-54; Lwowski *React. Intermed. (Wiley)* **1985**, *3*, 305-332, **1981**, *2*, 315-334, **1978**, *1*, 197-227, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 897-906 [*Angew. Chem.* **79**, 922-931]; Abramovitch, in McManus, Ref. 1, pp. 127-192; Hünig *Helv. Chim. Acta* **1971**, *54*, 1721-1747; Belloli *J. Chem. Educ.* **1971**, *48*, 422-426; Kuznetsov; Ioffe *Russ. Chem. Rev.* **1989**, *58*, 732-746 (N- and O-nitrenes); Meth-Cohn *Acc. Chem. Res.* **1987**, *20*, 18-27 (oxycarbonylnitrenes); Abramovitch; Sutherland *Fortsch. Chem. Forsch.* **1970**, *16*, 1-33 (sulfonyl nitrenes); Ioffe; Kuznetsov *Russ. Chem. Rev.* **1972**, *41*, 131-146 (N-nitrenes).

²⁴⁰Wasserman; Smolinsky; Yager *J. Am. Chem. Soc.* **1964**, *86*, 3166. For the structure of CH₃-N, as determined in the gas phase, see Carrick; Brazier; Bernath; Engelking *J. Am. Chem. Soc.* **1987**, *109*, 5100.

²⁴¹Smolinsky; Wasserman; Yager *J. Am. Chem. Soc.* **1962**, *84*, 3220. For a review, see Sheridan, Ref. 201, pp. 159-248.

²⁴²A few nitrenes have been shown to have singlet ground states. See Sigman; Autrey; Schuster *J. Am. Chem. Soc.* **1988**, *110*, 4297.

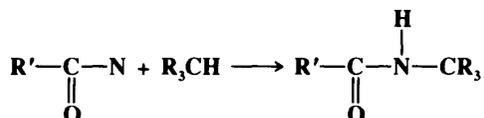
²⁴³McConaghy; Lwowski *J. Am. Chem. Soc.* **1967**, *89*, 2357, 4450; Mishra; Rice; Lwowski *J. Org. Chem.* **1968**, *33*, 481.

²⁴⁴For reviews, see Dyal, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement D*, pt. 1; Wiley: New York, 1983, pp. 287-320; Dürr; Kober *Top. Curr. Chem.* **1976**, *66*, 89-114; L'Abbé *Chem. Rev.* **1969**, *69*, 345-363.

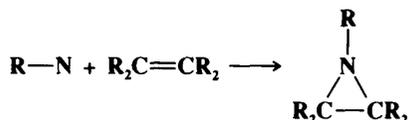
The unsubstituted nitrene NH has been generated by photolysis of or electric discharge through NH_3 , N_2H_4 , or HN_3 .

The reactions of nitrenes are also similar to those of carbenes.²⁴⁵ As in that case, many reactions in which nitrene intermediates are suspected probably do not involve free nitrenes. It is often very difficult to obtain proof in any given case that a free nitrene is or is not an intermediate.

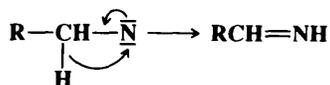
1. *Insertion* (see 2-12). Nitrenes, especially acyl nitrenes and sulfonyl nitrenes, can insert into C—H and certain other bonds, e.g.,



2. *Addition to C=C bonds* (see 5-42):

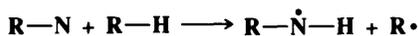


3. *Rearrangements*.^{231a} Alkyl nitrenes do not generally give either of the two preceding reactions because rearrangement is more rapid, e.g.,



Such rearrangements are so rapid that it is usually difficult to exclude the possibility that a free nitrene was never present at all, i.e., that migration takes place at the same time that the nitrene is formed²⁴⁶ (see p. 1091).

4. *Abstraction*, e.g.,



5. *Dimerization*. One of the principal reactions of NH is dimerization to diimide N_2H_2 . Azobenzenes are often obtained in reactions where aryl nitrenes are implicated:²⁴⁷



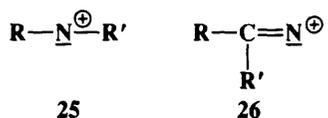
It would thus seem that dimerization is more important for nitrenes than it is for carbenes, but again it has not been proved that free nitrenes are actually involved.

²⁴⁵For a discussion of nitrene reactivity, see Subbaraj; Subba Rao; Lwowski *J. Org. Chem.* **1989**, *54*, 3945.

²⁴⁶For example, see Moriarty; Reardon *Tetrahedron* **1970**, *26*, 1379; Abramovitch; Kyba *J. Am. Chem. Soc.* **1971**, *93*, 1537.

²⁴⁷See, for example, Leyva Platz; Pery; Wirtz *J. Am. Chem. Soc.* **1986**, *108*, 3783.

At least two types of *nitrenium ions*, the nitrogen analogs of carbocations, can exist as intermediates, though much less work has been done in this area than on carbocations. In one type (**25**) the nitrogen is bonded to two atoms and in the other (**26**) to only one atom.²⁴⁸



When R = H in **25** the species is a protonated nitrene. Like carbenes and nitrenes, nitrenium ions can exist in singlet or triplet states.²⁴⁹

²⁴⁸For reviews of **25**, see Abramovitch; Jeyaraman, in *Scriven Azides and Nitrenes*, Ref. 239, pp. 297-357; Gassman *Acc. Chem. Res.* **1970**, 3, 26-33. For a review of **26**, see Lansbury, in *Lwowski Nitrenes*, Ref. 239, pp. 405-419.

²⁴⁹Gassman; Cryberg *J. Am. Chem. Soc.* **1969**, 91, 5176.

6

MECHANISMS AND METHODS OF DETERMINING THEM

A mechanism is the actual process by which a reaction takes place—which bonds are broken, in what order, how many steps are involved, the relative rate of each step, etc. In order to state a mechanism completely, we should have to specify the positions of all atoms, including those in solvent molecules, and the energy of the system, at every point in the process. A proposed mechanism must fit all the facts available. It is always subject to change as new facts are discovered. The usual course is that the gross features of a mechanism are the first to be known and then increasing attention is paid to finer details. The tendency is always to probe more deeply, to get more detailed descriptions.

Although for most reactions gross mechanisms can be written today with a good degree of assurance, no mechanism is known completely. There is much about the fine details which is still puzzling, and for some reactions even the gross mechanism is not yet clear. The problems involved are difficult because there are so many variables. Many examples are known where reactions proceed by different mechanisms under different conditions. In some cases there are several proposed mechanisms, each of which completely explains all the data.

Types of Mechanism

In most reactions of organic compounds one or more covalent bonds are broken. We can divide organic mechanisms into three basic types, depending on how the bonds break.

1. If a bond breaks in such a way that both electrons remain with one fragment, the mechanism is called *heterolytic*. Such reactions do not necessarily involve ionic intermediates, though they usually do. The important thing is that the electrons are never unpaired. For most reactions it is convenient to call one reactant the *attacking reagent* and the other the *substrate*. In this book we shall always designate as the substrate that molecule that supplies carbon to the new bond. When carbon-carbon bonds are formed, it is necessary to be arbitrary about which is the substrate and which the attacking reagent. In heterolytic reactions the reagent generally brings a pair of electrons to the substrate or takes a pair of electrons from it. A reagent that brings an electron pair is called a *nucleophile* and the reaction is *nucleophilic*. A reagent that takes an electron pair is called an *electrophile* and the reaction is *electrophilic*. In a reaction in which the substrate molecule becomes cleaved, part of it (the part not containing the carbon) is usually called the *leaving group*. A leaving group that carries away an electron pair is called a *nucleofuge*. If it comes away without the electron pair, it is called an *electrofuge*.

2. If a bond breaks in such a way that each fragment gets one electron, free radicals are formed and such reactions are said to take place by *homolytic* or *free-radical mechanisms*.

3. It would seem that all bonds must break in one of the two ways previously noted. But there is a third type of mechanism in which electrons (usually six, but sometimes some other number) move in a closed ring. There are no intermediates, ions or free radicals, and it is impossible to say whether the electrons are paired or unpaired. Reactions with this type of mechanism are called *pericyclic*.¹

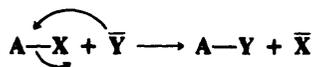
Examples of all three types of mechanisms are given in the next section.

Types of Reaction

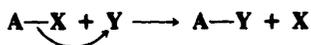
The number and range of organic reactions is so great as to seem bewildering, but actually almost all of them can be fitted into just six categories. In the description of the six types that follows, the immediate products are shown, though in many cases they then react with something else. All the species are shown without charges, since differently charged reactants can undergo analogous changes. The descriptions given here are purely formal and are for the purpose of classification and comparison. All are discussed in detail in Part 2 of this book.

1. *Substitutions*. If heterolytic, these can be classified as nucleophilic or electrophilic depending on which reactant is designated as the substrate and which as the attacking reagent (very often Y must first be formed by a previous bond cleavage).

a. Nucleophilic substitution (Chapters 10, 13).



b. Electrophilic substitution (Chapters 11, 12).



c. Free-radical substitution (Chapter 14).



In free-radical substitution, Y[•] is usually produced by a previous free-radical cleavage, and X[•] goes on to react further.

2. *Additions to double or triple bonds* (Chapters 15, 16). These reactions can take place by all three of the mechanistic possibilities.

a. Electrophilic addition (heterolytic).

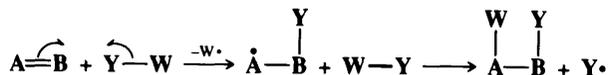


b. Nucleophilic addition (heterolytic).

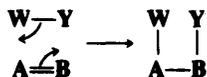


¹For a classification of pericyclic reactions, see Hendrickson *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 47-76 [*Angew. Chem.* **86**, 71-100].

c. Free-radical addition (homolytic).

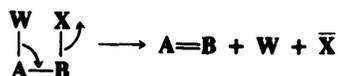


d. Simultaneous addition (pericyclic).



The examples show Y and W coming from the same molecule, but very often (except in simultaneous addition) they come from different molecules. Also, the examples show the Y—W bond cleaving at the same time that Y is bonding to B, but often (again except for simultaneous addition) this cleavage takes place earlier.

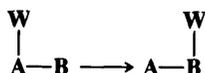
3. β Elimination (Chapter 17).



These reactions can take place by either heterolytic or pericyclic mechanisms. Examples of the latter are shown on p. 1006. Free-radical β eliminations are extremely rare. In heterolytic eliminations W and X may or may not leave simultaneously and may or may not combine.

4. *Rearrangement* (Chapter 18). Many rearrangements involve migration of an atom or group from one atom to another. There are three types, depending on how many electrons the migrating atom or group carries with it.

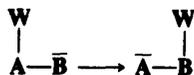
a. Migration with electron pair (nucleophilic).



b. Migration with one electron (free-radical).



c. Migration without electrons (electrophilic; rare).



The illustrations show 1,2 rearrangements, in which the migrating group moves to the adjacent atom. These are the most common, although longer rearrangements are also possible. There are also some rearrangements that do not involve simple migration at all (see Chapter 18). Some of the latter involve pericyclic mechanisms.

5. *Oxidation and reduction* (Chapter 19). Many oxidation and reduction reactions fall naturally into one of the four types mentioned above, but many others do not. For a description of oxidation–reduction mechanistic types, see p. 1159.

6. Combinations of the above.

Note that arrows are used to show movement of *electrons*. An arrow always follows the motion of electrons and never of a nucleus or anything else (it is understood that the rest of the molecule follows the electrons). Ordinary arrows (double-headed) follow electron pairs, while single-headed arrows follow unpaired electrons. Double-headed arrows are also used in pericyclic reactions for convenience, though in these reactions we do not really know how or in which direction the electrons are moving.

Thermodynamic Requirements for Reaction

In order for a reaction to take place spontaneously, the free energy of the products must be lower than the free energy of the reactants; i.e., ΔG must be negative. Reactions can go the other way, of course, but only if free energy is added. Like water on the surface of the earth, which only flows downhill and never uphill (though it can be carried or pumped uphill), molecules seek the lowest possible potential energy. Free energy is made up of two components, enthalpy H and entropy S . These quantities are related by the equation

$$\Delta G = \Delta H - T\Delta S$$

The enthalpy change in a reaction is essentially the difference in bond energies (including resonance, strain, and solvation energies) between the reactants and the products. The enthalpy change can be calculated by totaling the bond energies of all the bonds broken, subtracting from this the total of the bond energies of all the bonds formed, and adding any changes in resonance, strain, or solvation energies. Entropy changes are quite different, and refer to the disorder or randomness of the system. The less order in a system, the greater the entropy. The preferred conditions in nature are *low* enthalpy and *high* entropy, and in reacting systems, enthalpy spontaneously decreases while entropy spontaneously increases.

For many reactions entropy effects are small and it is the enthalpy that mainly determines whether the reaction can take place spontaneously. However, in certain types of reaction entropy is important and can dominate enthalpy. We shall discuss several examples.

1. In general, liquids have lower entropies than gases, since the molecules of gas have much more freedom and randomness. Solids, of course, have still lower entropies. Any reaction in which the reactants are all liquids and one or more of the products is a gas is therefore thermodynamically favored by the increased entropy; the equilibrium constant for that reaction will be higher than it would otherwise be. Similarly, the entropy of a gaseous substance is higher than that of the same substance dissolved in a solvent.

2. In a reaction in which the number of product molecules is equal to the number of reactant molecules, e.g., $A + B \rightarrow C + D$, entropy effects are usually small, but if the number of molecules is increased, e.g., $A \rightarrow B + C$, there is a large gain in entropy because more arrangements in space are possible when more molecules are present. Reactions in which a molecule is cleaved into two or more parts are therefore thermodynamically favored by the entropy factor. Conversely, reactions in which the number of product molecules is less than the number of reactant molecules show entropy decreases, and in such cases there must be a sizable decrease in enthalpy to overcome the unfavorable entropy change.

3. Although reactions in which molecules are cleaved into two or more pieces have favorable entropy effects, many potential cleavages do not take place because of large

increases in enthalpy. An example is cleavage of ethane into two methyl radicals. In this case a bond of about 79 kcal/mol (330 kJ/mol) is broken, and no new bond is formed to compensate for this enthalpy increase. However, ethane can be cleaved at very high temperatures, which illustrates the principle that *entropy becomes more important as the temperature increases*, as is obvious from the equation $\Delta G = \Delta H - T\Delta S$. The enthalpy term is independent of temperature, while the entropy term is directly proportional to the absolute temperature.

4. An acyclic molecule has more entropy than a similar cyclic molecule because there are more conformations (compare hexane and cyclohexane). Ring opening therefore means a gain in entropy and ring closing a loss.

Kinetic Requirements for Reaction

Just because a reaction has a negative ΔG does not necessarily mean that it will take place in a reasonable period of time. A negative ΔG is a *necessary* but not a *sufficient* condition for a reaction to occur spontaneously. For example, the reaction between H_2 and O_2 to give H_2O has a large negative ΔG , but mixtures of H_2 and O_2 can be kept at room temperature for many centuries without reacting to any significant extent. In order for a reaction to take place, *free energy of activation* ΔG^\ddagger must be added.² This situation is illustrated in Figure 6.1,³ which is an energy profile for a one-step reaction without an intermediate. In this type of diagram the horizontal axis (called the *reaction coordinate*)⁴ signifies the progression of the reaction. ΔG_f^\ddagger is the free energy of activation for the forward reaction. If the reaction shown in Figure 6.1 is reversible, ΔG_r^\ddagger must be greater than ΔG_f^\ddagger , since it is the sum of ΔG and ΔG_f^\ddagger .

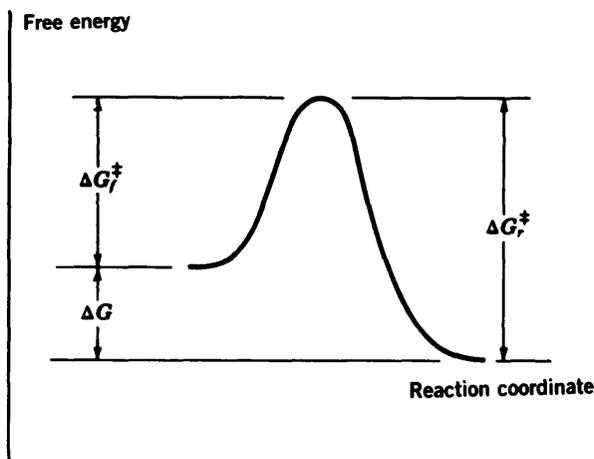


FIGURE 6.1 Free-energy profile of a reaction without an intermediate where the products have a lower free energy than the reactants.

²For mixtures of H_2 and O_2 this can be done by striking a match.

³Strictly speaking, this is an energy profile for a reaction of the type $XY + Z \rightarrow X + YZ$. However, it may be applied, in an approximate way, to other reactions.

⁴For a review of reaction coordinates and structure–energy relationships, see Grunwald *Prog. Phys. Org. Chem.* **1990**, *17*, 55-105.

When a reaction between two or more molecules has progressed to the point corresponding to the top of the curve, the term *transition state* is applied to the positions of the nuclei and electrons. The transition state possesses a definite geometry and charge distribution but has no finite existence; the system passes through it. The system at this point is called an *activated complex*.⁵

In the *transition-state theory*⁶ the starting materials and the activated complex are taken to be in equilibrium, the equilibrium constant being designated K^* . According to the theory, all activated complexes go on to product at the same rate (which, though at first sight surprising, is not unreasonable, when we consider that they are all "falling downhill") so that the rate constant (see p. 220) of the reaction depends only on the position of the equilibrium between the starting materials and the activated complex, i.e., on the value of K^* . ΔG^* is related to K^* by

$$\Delta G^* = -2.3RT \log K^*$$

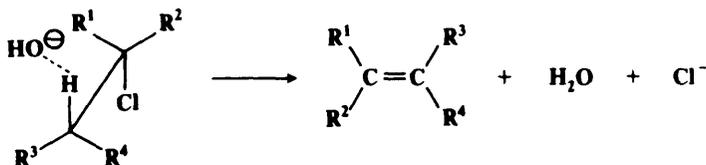
so that a higher value of ΔG^* is associated with a smaller rate constant. The rates of nearly all reactions increase with increasing temperature because the additional energy thus supplied helps the molecules to overcome the activation energy barrier. Some reactions have no free energy of activation at all, meaning that K^* is essentially infinite and that virtually all collisions lead to reaction. Such processes are said to be *diffusion-controlled*.⁷

Like ΔG , ΔG^* is made up of enthalpy and entropy components

$$\Delta G^* = \Delta H^* - T\Delta S^*$$

ΔH^* , the *enthalpy of activation*, is the difference in bond energies, including strain, resonance, and solvation energies, between the starting compounds and the *transition state*. In many reactions bonds have been broken or partially broken by the time the transition state is reached; the energy necessary for this is ΔH^* . It is true that additional energy will be supplied by the formation of new bonds, but if this occurs after the transition state, it can affect only ΔH and not ΔH^* .

Entropy of activation ΔS^* , which is the difference in entropy between the starting compounds and the transition state, becomes important when two reacting molecules must approach each other in a specific orientation in order for the reaction to take place. For example, the reaction between a simple noncyclic alkyl chloride and hydroxide ion to give an alkene (7-13) takes place only if, in the transition state, the reactants are oriented as shown.



Not only must the OH^- be near the hydrogen, but the hydrogen must be oriented anti to the chlorine atom.⁸ When the two reacting molecules collide, if the OH^- should be near

⁵For a discussion of transition states, see Laidler *J. Chem. Educ.* **1988**, 65, 540.

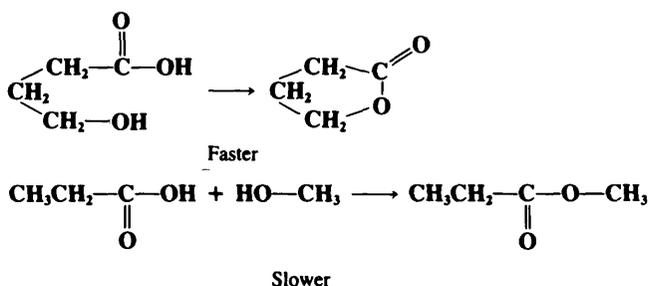
⁶For fuller discussions, see Kreevoy; Truhlar, in Bernasconi, Ref. 25, pt. 1, pp. 13-95; Moore; Pearson *Kinetics and Mechanism*, 3rd ed.; Wiley: New York, 1981, pp. 137-181; Klump *Reactivity in Organic Chemistry*; Wiley: New York, 1982; pp. 227-378.

⁷For a monograph on diffusion-controlled reactions, see Rice, *Comprehensive Chemical Kinetics*, Vol. 25 (edited by Bamford; Tipper; Compton); Elsevier: New York, 1985.

⁸As we shall see in Chapter 17, with some molecules elimination is also possible if the hydrogen is oriented syn, instead of anti, to the chlorine atom. Of course, this orientation also requires a considerable loss of entropy.

the chlorine atom or near R^1 or R^2 , no reaction can take place. In order for a reaction to occur, the molecules must surrender the freedom they normally have to assume many possible arrangements in space and adopt only that one that leads to reaction. Thus, a considerable loss in entropy is involved, i.e., ΔS^* is negative.

Entropy of activation is also responsible for the difficulty in closing rings⁹ larger than six-membered. Consider a ring-closing reaction in which the two groups that must interact are situated on the ends of a ten-carbon chain. In order for reaction to take place, the groups must encounter each other. But a ten-carbon chain has many conformations, and in only a few of these are the ends of the chain near each other. Thus, forming the transition state requires a great loss of entropy.¹⁰ This factor is also present, though less so, in closing rings of six members or less (except three-membered rings), but with rings of this size the entropy loss is less than that of bringing two individual molecules together. For example, a reaction between an OH group and a COOH group in the same molecule to form a lactone with a five- or six-membered ring takes place much faster than the same reaction between a molecule containing an OH group and another containing a COOH group. Though ΔH^* is about the



same, ΔS^* is much less for the cyclic case. However, if the ring to be closed has three or four members, small-angle strain is introduced and the favorable ΔS^* may not be sufficient to overcome the unfavorable ΔH^* change. Table 6.1 shows the relative rate constants for the closing of rings of 3 to 23 members all by the same reaction.¹¹ Reactions in which the transition state has more disorder than the starting compounds, e.g., the pyrolytic conversion of cyclopropane to propene, have positive ΔS^* values and are thus favored by the entropy effect.

Reactions with intermediates are two-step (or more) processes. In these reactions there is an energy "well." There are two transition states, each with an energy higher than the intermediate (Figure 6.2). The deeper the well, the more stable the intermediate. In Figure 6.2a, the second peak is higher than the first. The opposite situation is shown in Figure 6.2b. Note that in reactions in which the second peak is higher than the first, the overall ΔG^* is less than the sum of the ΔG^* values for the two steps. Minima in free-energy-profile diagrams (*intermediates*) correspond to real species which have a finite though very short

⁹For discussions of the entropy and enthalpy of ring-closing reactions, see De Tar; Luthra *J. Am. Chem. Soc.* **1980**, *102*, 4505; Mandolini *Bull. Soc. Chim. Fr.* **1988**, 173. For a related discussion, see Menger *Acc. Chem. Res.* **1985**, *18*, 128-134.

¹⁰For reviews of the cyclization of acyclic molecules, see Nakagaki; Sakuragi; Mutai *J. Phys. Org. Chem.* **1989**, *2*, 187-204; Mandolini *Adv. Phys. Org. Chem.* **1986**, *22*, 1-111. For a review of the cyclization and conformation of hydrocarbon chains, see Winnik *Chem. Rev.* **1981**, *81*, 491-524. For a review of steric and electronic effects in heterolytic ring closures, see Valters *Russ. Chem. Rev.* **1982**, *51*, 788-801.

¹¹The values for 4, 5, and 6 are from Mandolini *J. Am. Chem. Soc.* **1978**, *100*, 550; the others are from Galli; Illuminati; Mandolini; Tamborra *J. Am. Chem. Soc.* **1977**, *99*, 2591. See also Illuminati; Mandolini *Acc. Chem. Res.* **1981**, *14*, 95-102. See, however, van der Kerk; Verhoeven; Stirling *J. Chem. Soc., Perkin Trans. 2* **1985**, 1355; Benedetti; Stirling *J. Chem. Soc., Perkin Trans. 2* **1986**, 605.

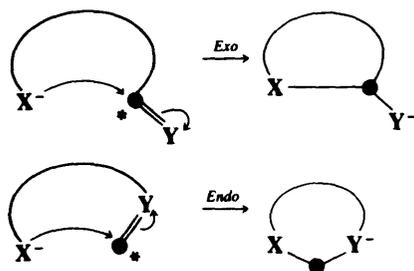
TABLE 6.1 Relative rate constants at 50°C
(Eight-membered ring = 1) for the reaction
 $\text{Br}(\text{CH}_2)_{n-2}\text{CO}_2^- \rightarrow (\text{CH}_2)_{n-2}\text{C}=\text{O}$, where
 $n = \text{the ring size}^{11}$

Ring size	Relative rate
3	21.7
4	5.4×10^3
5	1.5×10^6
6	1.7×10^4
7	97.3
8	1.00
9	1.12
10	3.35
11	8.51
12	10.6
13	32.2
14	41.9
15	45.1
16	52.0
18	51.2
23	60.4

existence. These may be the carbocations, carbanions, free radicals, etc., discussed in Chapter 5 or molecules in which all the atoms have their normal valences. In either case, under the reaction conditions they do not live long (because ΔG_2^\ddagger is small) but rapidly go on to products. Maxima in these curves, however, do not correspond to actual species but only to transition states in which bond breaking and/or bond making have partially taken place. Transition states have only a transient existence with an essentially zero lifetime.¹²

The Baldwin Rules for Ring Closure

In previous sections, we discussed, in a general way, the kinetic and thermodynamic aspects of ring-closure reactions. J. E. Baldwin has supplied a more specific set of rules for certain closings of 3- to 7-membered rings.¹³ These rules distinguish two types of ring closure, called



¹²Despite their transient existences, it is possible to study transition states of certain reactions in the gas phase with a technique called laser femtochemistry: Zewall; Bernstein *Chem. Eng. News* **1988**, 66, No. 45 (Nov. 7), 24-43. For another method, see Collings; Polanyi; Smith; Stolow; Tarr *Phys. Rev. Lett.* **1987**, 59, 2551.

¹³Baldwin *J. Chem. Soc., Chem. Commun.* **1976**, 734; Baldwin in *Further Perspectives in Organic Chemistry* (Ciba Foundation Symposium 53); Elsevier North Holland: Amsterdam, 1979, pp. 85-99. See also Baldwin; Thomas; Kruse; Silberman *J. Org. Chem.* **1977**, 42, 3846; Baldwin; Lusch *Tetrahedron* **1982**, 38, 2939; Anselme *Tetrahedron Lett.* **1977**, 3615; Fountain; Gerhardt *Tetrahedron Lett.* **1978**, 3985.

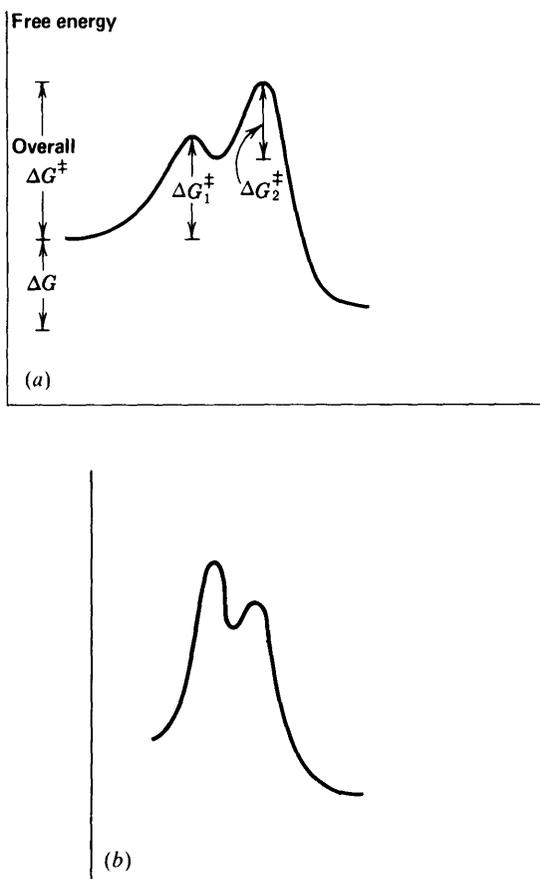


FIGURE 6.2 (a) Free-energy profile for a reaction with an intermediate. ΔG_1^\ddagger and ΔG_2^\ddagger are the free energy of activation for the first and second stages, respectively. (b) Free-energy profile for a reaction with an intermediate in which the first peak is higher than the second.

Exo and *Endo*, and three kinds of atoms at the starred positions: *Tet* for sp^3 , *Trig* for sp^2 , and *Dig* for sp . The following are Baldwin's rules for closing rings of 3 to 7 members.

Rule 1. Tetrahedral systems

- (a) 3 to 7-*Exo-Tet* are all favored processes
- (b) 5 to 6-*Endo-Tet* are disfavored

Rule 2. Trigonal systems

- (a) 3 to 7-*Exo-Trig* are favored
- (b) 3 to 5-*Endo-Trig* are disfavored¹⁴
- (c) 6 to 7-*Endo-Trig* are favored

¹⁴For some exceptions to the rule in this case, see Trost; Bonk *J. Am. Chem. Soc.* **1985**, *107*, 1778; Auvray; Knochel; Normant *Tetrahedron Lett.* **1985**, *26*, 4455; Torres; Larson *Tetrahedron Lett.* **1986**, *27*, 2223.

Rule 3. Digonal systems

- (a) 3 to 4-*Exo-Dig* are disfavored
- (b) 5 to 7-*Exo-Dig* are favored
- (c) 3 to 7-*Endo-Dig* are favored

“Disfavored” does not mean it cannot be done—only that it is more difficult than the favored cases. These rules are empirical and have a stereochemical basis. The favored pathways are those in which the length and nature of the linking chain enables the terminal atoms to achieve the proper geometries for reaction. The disfavored cases require severe distortion of bond angles and distances. Many cases in the literature are in substantial accord with these rules.

Kinetic and Thermodynamic Control

There are many cases in which a compound under a given set of reaction conditions can undergo competing reactions to give different products:



Figure 6.3 shows a free-energy profile for a reaction in which B is thermodynamically more stable than C (lower ΔG), but C is formed faster (lower ΔG^\ddagger). If neither reaction is reversible, C will be formed in larger amount because it is formed faster. The product is said to be *kinetically controlled*. However, if the reactions are reversible, this will not necessarily be the case. If such a process is stopped well before the equilibrium has been established, the reaction will be kinetically controlled since more of the faster-formed product will be present. However, if the reaction is permitted to approach equilibrium, the predominant or even exclusive product will be B. Under these conditions the C that is first formed reverts to A.

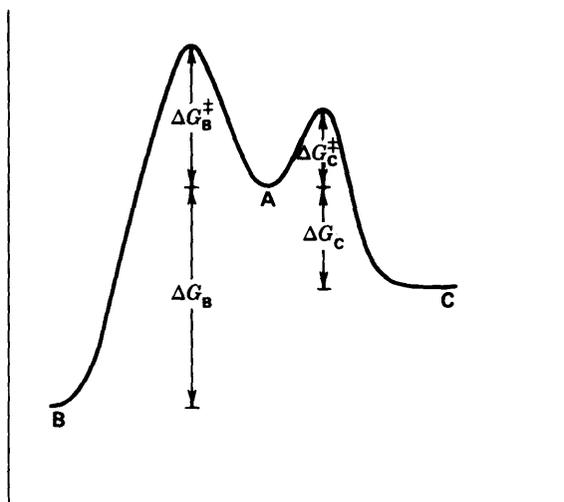


FIGURE 6.3 Free-energy profile illustrating kinetic versus thermodynamic control of product. The starting compound (A) can react to give either B or C.

while the more stable B does so much less. We say the product is *thermodynamically controlled*.¹⁵ Of course, Figure 6.3 does not describe all reactions in which a compound A can give two different products. In many cases the more stable product is also the one that is formed faster. In such cases the product of kinetic control is also the product of thermodynamic control.

The Hammond Postulate

Since transition states have zero lifetimes, it is impossible to observe them directly and information about their geometries must be obtained from inference. In some cases our inferences can be very strong. For example, in the S_N2 reaction (p. 294) between CH₃I and I⁻ (a reaction in which the product is identical to the starting compound), the transition state should be perfectly symmetrical. In most cases, however, we cannot reach such easy conclusions, and we are greatly aided by the *Hammond postulate*,¹⁶ which states that for any single reaction step, *the geometry of the transition state for that step resembles the side to which it is closer in free energy*. Thus, for an exothermic reaction like that shown in Figure 6.1, the transition state resembles the reactants more than the products, though not much more because there is a substantial ΔG^* on both sides. The postulate is most useful in dealing with reactions with intermediates. In the reaction illustrated in Figure 6.2a, the first transition state lies much closer in energy to the intermediate than to the reactants, and we can predict that the geometry of the transition state resembles that of the intermediate more than it does that of the reactants. Likewise, the second transition state also has a free energy much closer to that of the intermediate than to the products, so that both transition states resemble the intermediate more than they do the products or reactants. This is generally the case in reactions that involve very reactive intermediates. Since we usually know more about the structure of intermediates than of transition states, we often use our knowledge of intermediates to draw conclusions about the transition states (for examples, see pp. 340, 750).

Microscopic Reversibility

In the course of a reaction the nuclei and electrons assume positions that at each point correspond to the lowest free energies possible. If the reaction is reversible, these positions must be the same in the reverse process, too. This means that the forward and reverse reactions (run under the same conditions) must proceed by the same mechanism. This is called the *principle of microscopic reversibility*. For example, if in a reaction A → B there is an intermediate C, then C must also be an intermediate in the reaction B → A. This is a useful principle since it enables us to know the mechanism of reactions in which the equilibrium lies far over to one side. Reversible photochemical reactions are an exception, since a molecule that has been excited photochemically does not have to lose its energy in the same way (Chapter 7).

Marcus Theory

It is often useful to compare the reactivity of one compound with that of similar compounds. What we would like to do is to find out how a reaction coordinate (and in particular the

¹⁵For a discussion of thermodynamic vs. kinetic control, see Klumpp, Ref. 6, pp. 36-89.

¹⁶Hammond *J. Am. Chem. Soc.* **1955**, *77*, 334. For a discussion, see Fărcasiu *J. Chem. Educ.* **1975**, *52*, 76-79.

transition state) changes when one reactant molecule is replaced by a similar molecule. Marcus theory is a method for doing this.¹⁷

In this theory the activation energy ΔG^* is thought of as consisting of two parts.

1. An *intrinsic* free energy of activation, which would exist if the reactants and products had the same ΔG° .¹⁸ This is a kinetic part, called the *intrinsic barrier* ΔG_{int}^* .

2. A thermodynamic part, which arises from the ΔG° for the reaction.

The Marcus equation says that the overall ΔG^* for a one-step reaction is¹⁹

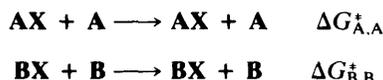
$$\Delta G^* = \Delta G_{\text{int}}^* + \frac{1}{2}\Delta G^\Delta + \frac{(\Delta G^\Delta)^2}{16(\Delta G_{\text{int}}^* - w^R)}$$

where the term ΔG^Δ stands for

$$\Delta G^\Delta = \Delta G^\circ - w^R + w^P$$

w^R , a work term, is the free energy required to bring the reactants together and w^P is the work required to form the successor configuration from the products.

For a reaction of the type $\text{AX} + \text{B} \rightarrow \text{BX}$, the intrinsic barrier²⁰ ΔG_{int}^* is taken to be the average ΔG^* for the two symmetrical reactions



so that

$$\Delta G^* = \frac{1}{2}(\Delta G_{\text{A,A}}^* + \Delta G_{\text{B,B}}^*)$$

One type of process that can successfully be treated by the Marcus equation is the $\text{S}_{\text{N}}2$ mechanism (p. 294)



When R is CH_3 the process is called *methyl transfer*.²¹ For such reactions the work terms w^R and w^P are assumed to be very small compared to ΔG° , and can be neglected, so that the Marcus equation simplifies to

$$\Delta G^* = \Delta G_{\text{int}}^* + \frac{1}{2}\Delta G^\circ + \frac{(\Delta G^\circ)^2}{16\Delta G_{\text{int}}^*}$$

The Marcus equation allows ΔG^* for $\text{RX} + \text{Y} \rightarrow \text{RY} + \text{X}$ to be calculated from the barriers of the two symmetrical reactions $\text{RX} + \text{X} \rightarrow \text{RX} + \text{X}$ and $\text{RY} + \text{Y} \rightarrow \text{RY} + \text{Y}$. The results of such calculations are generally in agreement with the Hammond postulate.

Marcus theory can be applied to any single-step process where something is transferred

¹⁷For reviews, see Albery *Annu. Rev. Phys. Chem.* **1980**, *31*, 227-263; Kreevoy; Truhlar, in Bernasconi, Ref. 25, pt. 1, pp. 13-95.

¹⁸ ΔG° is the standard free energy; that is, ΔG at atmospheric pressure.

¹⁹Albery; Kreevoy, Ref. 21, pp. 98-99.

²⁰For discussions of intrinsic barriers, see Lee *J. Chem. Soc., Perkin Trans. 2* **1989**, 943; *Chem. Soc. Rev.* **1990**, *19*, 133-145.

²¹For a review of Marcus theory applied to methyl transfer, see Albery; Kreevoy *Adv. Phys. Org. Chem.* **1978**, *16*, 87-157. See also Ref. 20; Lewis; Kukes; Slater *J. Am. Chem. Soc.* **1980**, *102*, 1619; Lewis, Hu *J. Am. Chem. Soc.* **1984**, *106*, 3292; Lewis; McLaughlin; Douglas *J. Am. Chem. Soc.* **1985**, *107*, 6668; Lewis *Bull. Soc. Chim. Fr.* **1988**, 259.

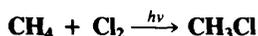
from one particle to another. It was originally derived for electron transfers,²² and then extended to transfers of H⁺ (see p. 258), H⁻,²³ and H•²⁴ as well as methyl transfers.

METHODS OF DETERMINING MECHANISMS

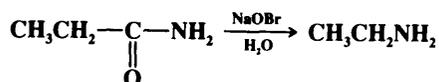
There are a number of commonly used methods for determining mechanisms.²⁵ In most cases one method is not sufficient, and the problem is generally approached from several directions.

Identification of Products

Obviously any mechanism proposed for a reaction must account for all the products obtained and for their relative proportions, including products formed by side reactions. Incorrect mechanisms for the von Richter reaction (3-25) were accepted for many years because it was not realized that nitrogen was a major product. A proposed mechanism cannot be correct if it fails to predict the products in approximately the observed proportions. For example, any mechanism for the reaction



that fails to account for the formation of a small amount of ethane cannot be correct (see 4-1), and any mechanism proposed for the Hofmann rearrangement (8-14):

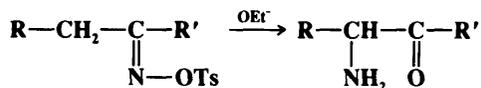


must account for the fact that the missing carbon appears as CO₂.

Determination of the Presence of an Intermediate

Intermediates are postulated in many mechanisms. There are several ways, none of them foolproof,²⁶ for attempting to learn whether or not an intermediate is present and, if so, its structure.

1. *Isolation of an intermediate.* It is sometimes possible to isolate an intermediate from a reaction mixture by stopping the reaction after a short time or by the use of very mild conditions. For example, in the Neber rearrangement (8-13)



²²Marcus *J. Phys. Chem.* **1963**, 67, 853. *Annu. Rev. Phys. Chem.* **1964**, 15, 155-196; Ebersson *Electron Transfer Reactions in Organic Chemistry*; Springer: New York, 1987.

²³Kreevoy; Lee *J. Am. Chem. Soc.* **1984**, 106, 2550; Lee; Ostović; Kreevoy *J. Am. Chem. Soc.* **1988**, 110, 3989; Kim; Lee; Kreevoy *J. Am. Chem. Soc.* **1990**, 112, 1889.

²⁴See for example Dneprovskii; Eliseenkov *J. Org. Chem. USSR* **1988**, 24, 243.

²⁵For a treatise on this subject, see Bernasconi *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (vol. 6 of *Weissberger Techniques of Chemistry*), 2 pts.; Wiley: New York, 1986. For a monograph, see Carpenter *Determination of Organic Reaction Mechanisms*; Wiley: New York, 1984.

²⁶For a discussion, see Martin *J. Chem. Educ.* **1985**, 62, 789.

2-nitronaphthalene gave 13% 1-naphthoic acid under the same conditions.³⁰ This proved that 2-nitronaphthalene must have been converted to 1-naphthoic acid by a route that does not involve 1-cyanonaphthalene. It also showed that even the conclusion that *p*-chlorobenzonitrile was an intermediate in the conversion of *m*-nitrochlorobenzene to *p*-chlorobenzoic acid must now be suspect, since it is not likely that the mechanism would substantially change in going from the naphthalene to the benzene system.

The Study of Catalysis³¹

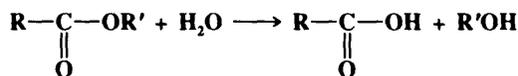
Much information about the mechanism of a reaction can be obtained from a knowledge of which substances catalyze the reaction, which inhibit it, and which do neither. Of course, just as a mechanism must be compatible with the products, so must it be compatible with its catalysts. In general, catalysts perform their actions by providing an alternate pathway for the reaction in which ΔG^* is less than it would be without the catalyst. Catalysts do not change ΔG .

Isotopic Labeling³²

Much useful information has been obtained by using molecules that have been isotopically labeled and tracing the path of the reaction in that way. For example, in the reaction



does the CN group in the product come from the CN in the BrCN? The use of ¹⁴C supplied the answer, since R¹⁴CO₂⁻ gave *radioactive* RCN.³³ This surprising result saved a lot of labor, since it ruled out a mechanism involving the replacement of CO₂ by CN (see 6-59). Other radioactive isotopes are also frequently used as tracers, but even stable isotopes can be used. An example is the hydrolysis of esters



Which bond of the ester is broken, the acyl—O or the alkyl—O bond? The answer is found by the use of H₂¹⁸O. If the acyl—O bond breaks, the labeled oxygen will appear in the acid; otherwise it will be in the alcohol (see 0-10). Although neither compound is radioactive, the one that contains ¹⁸O can be determined by submitting both to mass spectrometry. In a similar way, deuterium can be used as a label for hydrogen. In this case it is not necessary to use mass spectrometry, since ir and nmr spectra can be used to determine when deuterium has been substituted for hydrogen. ¹³C is also nonradioactive; it can be detected by ¹³C nmr.³⁴

In the labeling technique, it is not generally necessary to use completely labeled compounds. Partially labeled material is usually sufficient.

³⁰Bunnett; Rauhut *J. Org. Chem.* **1956**, *21*, 944.

³¹For treatises, see Jencks *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; Bender *Mechanisms of Homogeneous Catalysis from Protons to Proteins*; Wiley: New York, 1971. For reviews, see Coenen *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 57-64; and in Bernasconi, Ref. 25, pt. 1, the articles by Keeffe; Kresge, pp. 747-790; Haller; Delgass, pp. 951-979.

³²For reviews see Wentrup, in Bernasconi, Ref. 25, pt. 1, pp. 613-661; Collins *Adv. Phys. Org. Chem.* **1964**, *2*, 3-91. See also the series *Isotopes in Organic Chemistry*.

³³Douglas; Eccles; Almond *Can. J. Chem.* **1953**, *31*, 1127; Douglas; Burditt *Can. J. Chem.* **1958**, *36*, 1256.

³⁴For a review, see Hinton; Oka; Fry *Isot. Org. Chem.* **1977**, *3*, 41-104.

Stereochemical Evidence³⁵

If the products of a reaction are capable of existing in more than one stereoisomeric form, the form that is obtained may give information about the mechanism. For example, (+)-malic acid was discovered by Walden³⁶ to give (–)-chlorosuccinic acid when treated with PCl_5 and the (+) enantiomer when treated with SOCl_2 , showing that the mechanisms of these apparently similar conversions could not be the same (see pp. 295, 327). Much useful information has been obtained about nucleophilic substitution, elimination, rearrangement, and addition reactions from this type of experiment. The isomers involved need not be enantiomers. Thus, the fact that *cis*-2-butene treated with KMnO_4 gives *meso*-2,3-butanediol and not the racemic mixture is evidence that the two OH groups attack the double bond from the same side (see reaction 5-35).

Kinetic Evidence³⁷

The rate of a homogeneous reaction³⁸ is the rate of disappearance of a reactant or appearance of a product. The rate nearly always changes with time, since it is usually proportional to concentration and the concentration of reactants decreases with time. However, the rate is not always proportional to the concentration of all reactants. In some cases a change in the concentration of a reactant produces no change at all in the rate, while in other cases the rate may be proportional to the concentration of a substance (a catalyst) that does not even appear in the stoichiometric equation. A study of which reactants affect the rate often tells a good deal about the mechanism.

If the rate is proportional to the change in concentration of only one reactant (A), the *rate law* (the rate of change of concentration of A with time t) is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}]$$

where k is the *rate constant* for the reaction. There is a minus sign because the concentration of A decreases with time. A reaction that follows such a rate law is called a *first-order reaction*. The units of k for a first-order reaction are sec^{-1} . The rate of a *second-order reaction* is proportional to the concentration of two reactants, or to the square of the concentration of one:

$$\frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}][\mathbf{B}] \quad \text{or} \quad \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}]^2$$

For a second-order reaction the units are $\text{liters mol}^{-1} \text{sec}^{-1}$ or some other units expressing the reciprocal of concentration or pressure per unit time interval.

Similar expressions can be written for third-order reactions. A reaction whose rate is proportional to $[\mathbf{A}]$ and to $[\mathbf{B}]$ is said to be first order in A and in B, second order overall.

³⁵For lengthy treatments of the relationship between stereochemistry and mechanism, see Billups; Houk; Stevens, in Bernasconi, Ref. 25, pt. 1, pp. 663-746; Eliel *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; Newman *Steric Effects in Organic Chemistry*; Wiley, New York, 1956.

³⁶Walden *Ber.* **1896**, 29, 136, **1897**, 30, 3149, **1899**, 32, 1833.

³⁷For the use of kinetics in determining mechanisms, see Connors *Chemical Kinetics*; VCH: New York, 1990; Zuman; Patel *Techniques in Organic Reaction Kinetics*; Wiley: New York, 1984; Drenth; Kwart *Kinetics Applied to Organic Reactions*; Marcel Dekker: New York, 1980; Hammett *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970, pp. 53-100; Gardiner *Rates and Mechanisms of Chemical Reactions*; W.A. Benjamin: New York, 1969; Leffler; Grunwald *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963; Jencks, Ref. 31, pp. 555-614; Refs. 6 and 25.

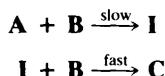
³⁸A homogeneous reaction occurs in one phase. Heterogeneous kinetics have been studied much less.

A reaction rate can be measured in terms of any reactant or product, but the rates so determined are not necessarily the same. For example, if the stoichiometry of a reaction is $2A + B \rightarrow C + D$ then, on a molar basis, A must disappear twice as fast as B, so that $-d[A]/dt$ and $-d[B]/dt$ are not equal but the former is twice as large as the latter.

The rate law of a reaction is an experimentally determined fact. From this fact we attempt to learn the *molecularity*, which may be defined as the number of molecules that come together to form the activated complex. It is obvious that if we know how many (and which) molecules take part in the activated complex, we know a good deal about the mechanism. The experimentally determined rate order is not necessarily the same as the molecularity. Any reaction, no matter how many steps are involved, has only one rate law, but each step of the mechanism has its own molecularity. For reactions that take place in one step (reactions without an intermediate) the order is the same as the molecularity. A first-order, one-step reaction is always unimolecular; a one-step reaction that is second order in A always involves two molecules of A; if it is first order in A and in B, then a molecule of A reacts with one of B, etc. For reactions that take place in more than one step, the order *for each step* is the same as the molecularity *for that step*. This fact enables us to predict the rate law for any proposed mechanism, though the calculations may get lengthy at times.³⁹ If any one step of a mechanism is considerably slower than all the others (this is usually the case), the rate of the overall reaction is essentially the same as that of the slow step, which is consequently called the *rate-determining step*.⁴⁰

For reactions that take place in two or more steps, two broad cases can be distinguished:

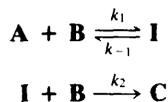
1. The first step is slower than any subsequent step and is consequently rate-determining. In such cases, the rate law simply includes the reactants that participate in the slow step. For example, if the reaction $A + 2B \rightarrow C$ has the mechanism



where I is an intermediate, the reaction is second order, with the rate law

$$\text{Rate} = \frac{-d[A]}{dt} = k[A][B]$$

2. When the first step is not rate-determining, determination of the rate law is usually much more complicated. For example, consider the mechanism



where the first step is a rapid attainment of equilibrium, followed by a slow reaction to give C. The rate of disappearance of A is

$$\frac{-d[A]}{dt} = k_1[A][B] - k_{-1}[I]$$

³⁹For a discussion of how order is related to molecularity in many complex situations, see Szabó, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 2; Elsevier: New York, 1969, pp. 1-80.

⁴⁰Many chemists prefer to use the term *rate-limiting step* or *rate-controlling step* for the slow step, rather than *rate-determining step*. See the definitions in Gold; Loening; McNaught; Sehmi *IUPAC Compendium of Chemical Terminology*; Blackwell Scientific Publications: Oxford, 1987, p. 337. For a discussion of rate-determining steps, see Laidler *J. Chem. Educ.* **1988**, 65, 250.

Both terms must be included because A is being formed by the reverse reaction as well as being used up by the forward reaction. This equation is of very little help as it stands since we cannot measure the concentration of the intermediate. However, the combined rate law for the formation and disappearance of I is

$$\frac{d[\mathbf{I}]}{dt} = k_1[\mathbf{A}][\mathbf{B}] - k_{-1}[\mathbf{I}] - k_2[\mathbf{I}][\mathbf{B}]$$

At first glance we seem no better off with this equation, but we can make the assumption that *the concentration of I does not change with time*, since it is an intermediate that is used up (going either to A + B or to C) as fast as it is formed. This assumption, called the assumption of the *steady state*,⁴¹ enables us to set $d[\mathbf{I}]/dt$ equal to zero and hence to solve for [I] in terms of the measurable quantities [A] and [B]:

$$[\mathbf{I}] = \frac{k_1[\mathbf{A}][\mathbf{B}]}{k_2[\mathbf{B}] + k_{-1}}$$

We now insert this value for [I] into the original rate expression to obtain

$$-\frac{d[\mathbf{A}]}{dt} = \frac{k_1k_2[\mathbf{A}][\mathbf{B}]^2}{k_2[\mathbf{B}] + k_{-1}}$$

Note that this rate law is valid whatever the values of k_1 , k_{-1} , and k_2 . However, our original hypothesis was that the first step was faster than the second, or that

$$k_1[\mathbf{A}][\mathbf{B}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

Since the first step is an equilibrium

$$k_1[\mathbf{A}][\mathbf{B}] = k_{-1}[\mathbf{I}]$$

we have

$$k_{-1}[\mathbf{I}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

Canceling [I], we get

$$k_{-1} \gg k_2[\mathbf{B}]$$

We may thus neglect $k_2[\mathbf{B}]$ in comparison with k_{-1} and obtain

$$-\frac{d[\mathbf{A}]}{dt} = \frac{k_1k_2}{k_{-1}} [\mathbf{A}][\mathbf{B}]^2$$

The overall rate is thus third order: first order in A and second order in B. Incidentally, if the first step is rate-determining (as was the case in the preceding paragraph), then

$$k_2[\mathbf{B}] \gg k_{-1} \quad \text{and} \quad \frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}][\mathbf{B}]$$

which is the same rate law we deduced from the rule that where the first step is rate-determining, the rate law includes the reactants that participate in that step.

It is possible for a reaction to involve A and B in the rate-determining step, though only [A] appears in the rate law. This occurs when a large excess of B is present, say 100 times

⁴¹For a discussion, see Raines; Hansen *J. Chem. Educ.* **1988**, 65, 757.

the molar quantity of A. In this case the complete reaction of A uses up only 1 mole of B, leaving 99 moles. It is not easy to measure the change in concentration of B with time in such a case, and it is seldom attempted, especially when B is also the solvent. Since [B], for practical purposes, does not change with time, the reaction appears to be first order in A though actually both A and B are involved in the rate-determining step. This is often referred to as a *pseudo-first-order* reaction. Pseudo-order reactions can also come about when one reactant is a catalyst whose concentration does not change with time because it is replenished as fast as it is used up and when a reaction is conducted in a medium that keeps the concentration of a reactant constant, e.g., in a buffer solution where H^+ or OH^- is a reactant. Pseudo-first-order conditions are frequently used in kinetic investigations for convenience in experimentation and calculations.

What is actually being measured is the change in concentration of a product or a reactant with time. Many methods have been used to make such measurements.⁴² The choice of a method depends on its convenience and its applicability to the reaction being studied. Among the most common methods are:

1. *Periodic or continuous spectral readings.* In many cases the reaction can be carried out in the cell while it is in the instrument. Then all that is necessary is that the instrument be read, periodically or continuously. Among the methods used are ir and uv spectroscopy, polarimetry, nmr, and esr.⁴³

2. *Quenching and analyzing.* A series of reactions can be set up and each stopped in some way (perhaps by suddenly lowering the temperature or adding an inhibitor) after a different amount of time has elapsed. The materials are then analyzed by spectral readings, titrations, chromatography, polarimetry, or any other method.

3. *Removal of aliquots at intervals.* Each aliquot is then analyzed as in method 2.

4. *Measurement of changes in total pressure, for gas-phase reactions.*⁴⁴

5. *Calorimetric methods.* The output or absorption of heat can be measured at time intervals.

Special methods exist for kinetic measurements of very fast reactions.⁴⁵

In any case what is usually obtained is a graph showing how a concentration varies with time. This must be interpreted⁴⁶ to obtain a rate law and a value of k . If a reaction obeys simple first- or second-order kinetics, the interpretation is generally not difficult. For example, if the concentration at the start is A_0 , the first-order rate law

$$\frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}] \quad \text{or} \quad \frac{-d[\mathbf{A}]}{[\mathbf{A}]} = k dt$$

can be integrated between the limits $t = 0$ and $t = t$ to give

$$-\ln \frac{[\mathbf{A}]}{A_0} = kt \quad \text{or} \quad \ln [\mathbf{A}] = -kt + \ln A_0$$

⁴²For a monograph on methods of interpreting kinetic data, see Zuman; Patel, Ref. 37. For a review of methods of obtaining kinetic data, see Batt, in Bamford; Tipper, Ref. 39, vol. 1, 1969, pp. 1-111.

⁴³For a review of esr to measure kinetics, see Norman *Chem. Soc. Rev.* **1979**, 8, 1-27.

⁴⁴For a review of the kinetics of reactions in solution at high pressures, see le Noble *Prog. Phys. Org. Chem.* **1967**, 5, 207-330. For reviews of synthetic reactions under high pressure, see Matsumoto; Sera; Uchida *Synthesis* **1985**, 1-26; Matsumoto; Sera *Synthesis* **1985**, 999-1027.

⁴⁵For reviews, see Connors, Ref. 37, pp. 133-186; Zuman; Patel, Ref. 37, pp. 247-327; Krüger *Chem. Soc. Rev.* **1982**, 11, 227-255; Hague, in Bamford; Tipper, Ref. 39, vol. 1, pp. 112-179, Elsevier, New York, 1969; Bernasconi, Ref. 25, pt. 2. See also Bamford; Tipper, Ref. 39, vol. 24, 1983.

⁴⁶For discussions, much fuller than that given here, of methods for interpreting kinetic data, see Connors, Ref. 37, pp. 17-131; Ritchie *Physical Organic Chemistry*, 2nd ed.; Marcel Dekker: New York, 1990, pp. 1-35; Zuman; Patel, Ref. 37; Margerison, in Bamford; Tipper, Ref. 39, vol. 1, pp. 343-421, 1969; Moore; Pearson, Ref. 6, pp. 12-82; in Bernasconi, Ref. 25, pt. 1, the articles by Bunnett, pp. 251-372, Noyes, pp. 373-423, Bernasconi, pp. 425-485, Wiberg, pp. 981-1019.

Therefore, if a plot of $\ln [A]$ against t is linear, the reaction is first order and k can be obtained from the slope. For first-order reactions it is customary to express the rate not only by the rate constant k but also by the *half-life*, which is the time required for half of any given quantity of a reactant to be used up. Since the half-life $t_{1/2}$ is the time required for $[A]$ to reach $A_0/2$, we may say that

$$\ln \frac{A_0}{2} = kt_{1/2} + \ln A_0$$

so that

$$t_{1/2} = \frac{\ln\left(\frac{A_0}{A_0/2}\right)}{k} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

For the general case of a reaction first order in A and first order in B, second order overall, integration is complicated, but it can be simplified if equimolar amounts of A and B are used, so that $A_0 = B_0$. In this case

$$\frac{-d[A]}{dt} = k[A][B]$$

is equivalent to

$$\frac{-d[A]}{dt} = k[A]^2 \quad \text{or} \quad \frac{-d[A]}{[A]^2} = k dt$$

Integrating as before gives

$$\frac{1}{[A]} - \frac{1}{A_0} = kt$$

Thus, under equimolar conditions, if a plot of $1/[A]$ against t is linear, the reaction is second order with a slope of k . It is obvious that the same will hold true for a reaction second order in A.⁴⁷

Although many reaction-rate studies do give linear plots, which can therefore be easily interpreted, the results in many other studies are not so simple. In some cases a reaction may be first order at low concentrations but second order at higher concentrations. In other cases fractional orders are obtained, and even negative orders. The interpretation of complex kinetics often requires much skill and effort. Even where the kinetics are relatively simple, there is often a problem in interpreting the data because of the difficulty of obtaining precise enough measurements.⁴⁸

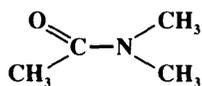
Nmr spectra can be used to obtain kinetic information in a completely different manner from that mentioned on p. 223. This method, which involves the study of nmr line shapes,⁴⁹ depends on the fact that nmr spectra have an inherent time factor: if a proton changes its environment less rapidly than about 10^3 times per second, an nmr spectrum shows a separate peak for each position the proton assumes. For example, if the rate of rotation around the

⁴⁷We have given the integrated equations for simple first- and second-order kinetics. For integrated equations for a large number of kinetic types, see Margerison, Ref. 46, p. 361.

⁴⁸See Hammett, Ref. 37, pp. 62-70.

⁴⁹For a monograph, see Oki *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: New York, 1985. For reviews, see Fraenkel, in Bernasconi, Ref. 25, pt. 2, pp. 547-604; Aganov; Klochkov; Samitov *Russ. Chem. Rev.* **1985**, 54, 931-947; Roberts *Pure Appl. Chem.* **1979**, 51, 1037-1047; Binsch *Top. Stereochem.* **1968**, 3, 97-192; Johnson *Adv. Magn. Reson.* **1965**, 1, 33-102.

C—N bond of N,N-dimethylacetamide is slower than 10^3 rotations per second, the two N-methyl groups each have separate chemical shifts since they are not equivalent, one being



cis to the oxygen and the other trans. However, if the environmental change takes place more rapidly than about 10^3 times per second, only one line is found, at a chemical shift that is the weighted average of the two individual positions. In many cases, two or more lines are found at low temperatures, but as the temperature is increased, the lines coalesce because the interconversion rate increases with temperature and passes the 10^3 per second mark. From studies of the way line shapes change with temperature it is often possible to calculate rates of reactions and of conformational changes. This method is not limited to changes in proton line shapes but can also be used for other atoms that give nmr spectra and for esr spectra.

Several types of mechanistic information can be obtained from kinetic studies.

1. From the order of a reaction, information can be obtained about which molecules and how many take part in the rate-determining step. Such knowledge is very useful and often essential in elucidating a mechanism. For any mechanism that can be proposed for a given reaction, a corresponding rate law can be calculated by the methods discussed on pp. 221-223. If the experimentally obtained rate law fails to agree with this, the proposed mechanism is wrong. However, it is often difficult to relate the order of a reaction to the mechanism, especially when the order is fractional or negative. In addition, it is frequently the case that two or more proposed mechanisms for a reaction are kinetically indistinguishable, i.e., they predict the same rate law.

2. Probably the most useful data obtained kinetically are the rate constants themselves. They are important since they can tell us the effect on the rate of a reaction of changes in the structure of the reactants (see Chapter 9), the solvent, the ionic strength, the addition of catalysts, etc.

3. If the rate is measured at several temperatures, in most cases a plot of $\ln k$ against $1/T$ (T stands for absolute temperature) is nearly linear⁵⁰ with a negative slope, and fits the equation

$$\ln k = \frac{-E_a}{RT} + \ln A$$

where R is the gas constant and A a constant called the *frequency factor*. This permits the calculation of E_a , which is the Arrhenius activation energy of the reaction. ΔH^* can then be obtained by

$$E_a = \Delta H^* + RT$$

It is also possible to use these data to calculate ΔS^* by the formula⁵¹

$$\frac{\Delta S^*}{4.576} = \log k - 10.753 - \log T + \frac{E_a}{4.576T}$$

⁵⁰For a review of cases where such a plot is nonlinear, see Blandamer; Burgess; Robertson; Scott *Chem. Rev.* **1982**, *82*, 259-286.

⁵¹For a derivation of this equation, see Bunnett, in Bernasconi, *Ref.* 25, pt. 1, p. 287.

for energies in calorie units. For joule units the formula is

$$\frac{\Delta S^*}{19.15} = \log k - 10.753 - \log T + \frac{E_a}{19.15T}$$

One then obtains ΔG^* from $\Delta G^* = \Delta H^* - T\Delta S^*$.

Isotope Effects

When a hydrogen in a reactant molecule is replaced by deuterium, there is often a change in the rate. Such changes are known as *deuterium isotope effects*⁵² and are expressed by the ratio k_H/k_D . The ground-state vibrational energy (called the zero-point vibrational energy) of a bond depends on the mass of the atoms and is lower when the reduced mass is higher.⁵³ Therefore, D—C, D—O, D—N bonds, etc., have lower energies in the ground state than the corresponding H—C, H—O, H—N bonds, etc. Complete dissociation of a deuterium bond consequently requires more energy than that for a corresponding hydrogen bond in the same environment (Figure 6.4). If an H—C, H—O, or H—N bond is not broken at all in a reaction or is broken in a non-rate-determining step, substitution of deuterium for hydrogen causes no change in the rate (see below for an exception to this statement), but

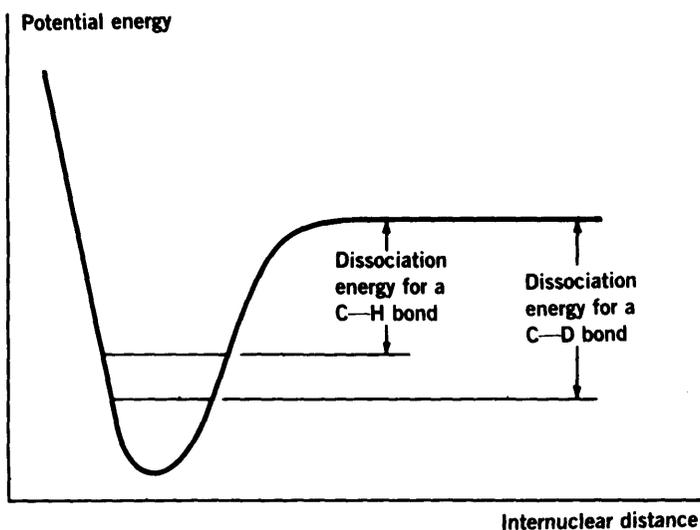


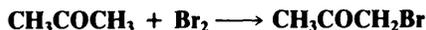
FIGURE 6.4 A C—D bond has a lower zero-point energy than does a corresponding C—H bond; thus the dissociation energy is higher.

⁵²For a monograph, see Melander; Saunders *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980. For reviews, see Isaacs *Physical Organic Chemistry*; Longman Scientific and Technical: Essex, 1987, pp. 255-281; Lewis *Top. Curr. Chem.* **1978**, *74*, 31-44; Saunders, in Bernasconi, Ref. 25, pp. 565-611; Bell *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973, pp. 226-296, *Chem. Soc. Rev.* **1974**, *3*, 513-544; Bigeleisen; Lee; Mandel *Annu. Rev. Phys. Chem.* **1973**, *24*, 407-440; Wolfsberg *Annu. Rev. Phys. Chem.* **1969**, *20*, 449-478; Saunders *Surv. Prog. Chem.* **1966**, *3*, 109-146; Simon; Palm *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 920-933 [*Angew. Chem.* **78**, 993-1007]; Jencks, Ref. 31, pp. 243-281. For a review of temperature dependence of primary isotope effects as a mechanistic criterion, see Kwart *Acc. Chem. Res.* **1982**, *15*, 401-408. For a review of the effect of pressure on isotope effects, see Isaacs, *Isot. Org. Chem.* **1984**, *6*, 67-105. For a review of isotope effects in the study of reactions in which there is branching from a common intermediate, see Thibblin; Ahlberg *Chem. Soc. Rev.* **1989**, *18*, 209-224. See also the series *Isotopes in Organic Chemistry*.

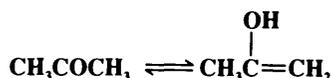
⁵³The reduced mass μ of two atoms connected by a covalent bond is $\mu = m_1 m_2 / (m_1 + m_2)$.

if the bond is broken in the rate-determining step, the rate must be lowered by the substitution.

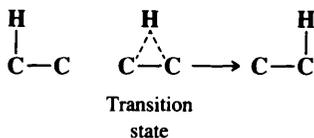
This provides a valuable diagnostic tool for determination of mechanism. For example, in the bromination of acetone (2-4)



the fact that the rate is independent of the bromine concentration led to the postulate that the rate-determining step was prior tautomerization of the acetone:



In turn, the rate-determining step of the tautomerization involves cleavage of a C—H bond (see 2-3). Thus there should be a substantial isotope effect if deuterated acetone is brominated. In fact, $k_{\text{H}}/k_{\text{D}}$ was found to be about 7.⁵⁴ Deuterium isotope effects usually range from 1 (no isotope effect at all) to about 7 or 8, though in a few cases, larger⁵⁵ or smaller values have been reported.⁵⁶ Values of $k_{\text{H}}/k_{\text{D}}$ smaller than 1 are called *inverse isotope effects*. Isotope effects are greatest when, in the transition state, the hydrogen is symmetrically bonded to the atoms between which it is being transferred.⁵⁷ Also, calculations show that isotope effects are at a maximum when the hydrogen in the transition state is on the straight line connecting the two atoms between which the hydrogen is being transferred and that for sufficiently nonlinear configurations they decrease to $k_{\text{H}}/k_{\text{D}} = 1$ to 2.⁵⁸ Of course, in open systems there is no reason for the transition state to be nonlinear, but this is not the case in many intramolecular mechanisms, e.g., in a 1,2 migration of a hydrogen



To measure isotope effects it is not always necessary to prepare deuterium-enriched starting compounds. It can also be done by measuring the change in deuterium concentration at specific sites between a compound containing deuterium in natural abundance and the reaction product, using a high field nmr instrument.⁵⁹

⁵⁴Rcitz: *Kopp Z. Phys. Chem., Abt. A* **1939**, 184, 429.

⁵⁵For an example of a reaction with a deuterium isotope effect of 24.2, see Lewis; Funderburk *J. Am. Chem. Soc.* **1967**, 89, 2322. The high isotope effect in this case has been ascribed to *tunneling* of the proton: because it is so small a hydrogen atom can sometimes get through a thin potential barrier without going over the top, i.e., without obtaining the usually necessary activation energy. A deuterium, with a larger mass, is less able to do this. The phenomenon of tunneling is a consequence of the uncertainty principle. $k_{\text{H}}/k_{\text{T}}$ for the same reaction is 79: Lewis; Robinson *J. Am. Chem. Soc.* **1968**, 90, 4337. An even larger deuterium isotope effect (~50) has been reported for the oxidation of benzyl alcohol. This has also been ascribed to tunneling: Roecker; Meyer *J. Am. Chem. Soc.* **1987**, 109, 746. For discussions of high isotope effects, see Kresge; Powell *J. Am. Chem. Soc.* **1981**, 103, 201; Caldin; Mateo; Warrick *J. Am. Chem. Soc.* **1981**, 103, 202. For arguments that high isotope effects can be caused by factors other than tunneling, see McLennan *Aust. J. Chem.* **1979**, 32, 1883; Thibblin *J. Phys. Org. Chem.* **1988**, 1, 161; Kresge; Powell *J. Phys. Org. Chem.* **1990**, 3, 55.

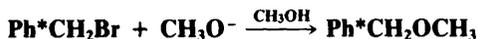
⁵⁶For a review of a method for calculating the magnitude of isotope effects, see Sims; Lewis *Isot. Org. Chem.* **1984**, 6, 161-259.

⁵⁷Kwart; Latimore *J. Am. Chem. Soc.* **1971**, 93, 3770; Pryor; Kneipp *J. Am. Chem. Soc.* **1971**, 93, 5584; Bell; Cox *J. Chem. Soc. B* **1971**, 783; Bethell; Hare; Kearney *J. Chem. Soc., Perkin Trans. 2* **1981**, 684, and references cited in these papers. See, however, Motell; Boone; Fink *Tetrahedron* **1978**, 34, 1619.

⁵⁸More O'Ferrall *J. Chem. Soc. B* **1970**, 785, and references cited therein.

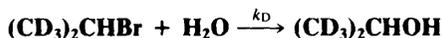
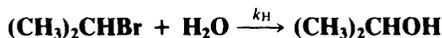
⁵⁹Pascal; Baum; Wagner; Rodgers; Huang *J. Am. Chem. Soc.* **1986**, 108, 6477.

The substitution of tritium for hydrogen gives isotope effects that are numerically larger. Isotope effects have also been observed with other elements, but they are much smaller, about 1.02 to 1.10. For example, $k_{12}\text{C}/k_{13}\text{C}$ for



is 1.053.⁶⁰ Although they are small, heavy-atom isotope effects can be measured quite accurately and are often very useful.⁶¹

Deuterium isotope effects have been found even where it is certain that the C—H bond does not break at all in the reaction. Such effects are called *secondary isotope effects*,⁶² the term *primary isotope effect* being reserved for the type discussed previously. Secondary isotope effects can be divided into α and β effects. In a β secondary isotope effect, substitution of deuterium for hydrogen β to the position of bond breaking slows the reaction. An example is solvolysis of isopropyl bromide:



where $k_{\text{H}}/k_{\text{D}}$ was found to be 1.34.⁶³ The cause of β isotope effects has been a matter of much controversy, but they are most likely due to hyperconjugation effects in the transition state. The effects are greatest when the transition state has considerable carbocation character.⁶⁴ Although the C—H bond in question is not broken in the transition state, the carbocation is stabilized by hyperconjugation involving this bond. Because of hyperconjugation, the difference in vibrational energy between the C—H bond and the C—D bond in the transition state is less than it is in the ground state, so the reaction is slowed by substitution of deuterium for hydrogen.

Support for hyperconjugation as the major cause of β isotope effects is the fact that the effect is greatest when D is anti to the leaving group⁶⁵ (because of the requirement that all atoms in a resonance system be coplanar, planarity of the D—C—C—X system would most greatly increase the hyperconjugation), and the fact that secondary isotope effects can be transmitted through unsaturated systems.⁶⁶ There is evidence that at least some β isotope effects are steric in origin⁶⁷ (e.g., a CD_3 group has a smaller steric requirement than a CH_3 group) and a field-effect explanation has also been suggested (CD_3 is apparently a better electron donor than CH_3 ⁶⁸), but hyperconjugation is the most probable cause in most instances.⁶⁹ Part of the difficulty in attempting to explain these effects is their small size,

⁶⁰Stothers; Bourns *Can. J. Chem.* **1962**, *40*, 2007. See also Ando; Yamataka; Tamura; Hanafusa *J. Am. Chem. Soc.* **1982**, *104*, 5493.

⁶¹For a review of carbon isotope effects, see Willi *Isot. Org. Chem.* **1977**, *3*, 237-283.

⁶²For reviews, see Westaway *Isot. Org. Chem.* **1987**, *7*, 275-392; Sunko; Hehre *Prog. Phys. Org. Chem.* **1983**, *14*, 205-246; Shiner, in Collins; Bowman *Isotope Effects in Chemical Reactions*; Van Nostrand-Reinhold: Princeton, 1970, pp. 90-159; Laszlo; Welvert *Bull. Soc. Chim. Fr.* **1966**, 2412-2438; Halevi *Prog. Phys. Org. Chem.* **1963**, *1*, 109-221. For a review of model calculations of secondary isotope effects, see McLennan *Isot. Org. Chem.* **1987**, *7*, 393-480. See also Ref. 56.

⁶³Leffek; Llewellyn; Robertson *Can. J. Chem.* **1960**, *38*, 2171.

⁶⁴Bender; Feng *J. Am. Chem. Soc.* **1960**, *82*, 6318; Jones; Bender *J. Am. Chem. Soc.* **1960**, *82*, 6322.

⁶⁵Shiner; Murr; Heinemann *J. Am. Chem. Soc.* **1963**, *85*, 2413; Shiner; Humphrey *J. Am. Chem. Soc.* **1963**, *85*, 2416; Shiner; Jewett *J. Am. Chem. Soc.* **1964**, *86*, 945; DeFrees; Hehre; Sunko *J. Am. Chem. Soc.* **1979**, *101*, 2323. See also Siehl; Walter *J. Chem. Soc., Chem. Commun.* **1985**, 76.

⁶⁶Shiner; Kriz *J. Am. Chem. Soc.* **1964**, *86*, 2643.

⁶⁷Bartell *J. Am. Chem. Soc.* **1961**, *83*, 3567; Brown; Azzaro; Koelling; McDonald *J. Am. Chem. Soc.* **1966**, *88*, 2520; Kaplan; Thornton *J. Am. Chem. Soc.* **1967**, *89*, 6644; Carter; Dahlgren *Acta Chem. Scand.* **1970**, *24*, 633; Leffek; Matheson *Can. J. Chem.* **1971**, *49*, 439; Sherrod; Boekelheide *J. Am. Chem. Soc.* **1972**, *94*, 5513.

⁶⁸Halevi; Nussim; Ron *J. Chem. Soc.* **1963**, 866; Halevi; Nussim *J. Chem. Soc.* **1963**, 876.

⁶⁹Karabatsos; Sonnichsen; Papaioannou; Scheppele; Shone *J. Am. Chem. Soc.* **1967**, *89*, 463; Kresge; Preto *J. Am. Chem. Soc.* **1967**, *89*, 5510; Jewett; Dunlap *J. Am. Chem. Soc.* **1968**, *90*, 809; Sunko; Szele; Hehre *J. Am. Chem. Soc.* **1977**, *99*, 5000; Kluger; Brandl *J. Org. Chem.* **1986**, *51*, 3964.

ranging only as high as about 1.5.⁷⁰ Another complicating factor is that they can change with temperature. In one case⁷¹ k_H/k_D was 1.00 ± 0.01 at 0°C, 0.90 ± 0.01 at 25°C, and 1.15 ± 0.09 at 65°C. Whatever the cause, there seems to be a good correlation between β secondary isotope effects and carbocation character in the transition state, and they are thus a useful tool for probing mechanisms.

The other type of secondary isotope effect results from a replacement of hydrogen by deuterium at the carbon containing the leaving group. These (called α secondary isotope effects) are varied, with values so far reported⁷² ranging from 0.87 to 1.26.⁷³ These effects are also correlated with carbocation character. Nucleophilic substitutions that do not proceed through carbocation intermediates (S_N2 reactions) have α isotope effects near unity.⁷⁴ Those that do involve carbocations (S_N1 reactions) have higher α isotope effects, which depend on the nature of the leaving group.⁷⁵ The accepted explanation for α isotope effects is that one of the bending C—H vibrations is affected by the substitution of D for H more or less strongly in the transition state than in the ground state.⁷⁶ Depending on the nature of the transition state, this may increase or decrease the rate of the reaction. α isotope effects on S_N2 reactions can vary with concentration,⁷⁷ an effect attributed to a change from a free nucleophile to one that is part of an ion pair⁷⁸ (see p. 350). This illustrates the use of secondary isotope effects as a means of studying transition state structure. γ secondary isotope effects have also been reported.⁷⁹

Another kind of isotope effect is the *solvent isotope effect*.⁸⁰ Reaction rates often change when the solvent is changed from H₂O to D₂O or from ROH to ROD. These changes may be due to any of three factors or a combination of all of them.

1. The solvent may be a reactant. If an O—H bond of the solvent is broken in the rate-determining step, there will be a primary isotope effect. If the molecules involved are D₂O or D₃O⁺ there may also be a secondary effect caused by the O—D bonds that are not breaking.

2. The substrate molecules may become labeled with deuterium by rapid hydrogen exchange, and then the newly labeled molecule may become cleaved in the rate-determining step.

3. The extent or nature of solvent-solute interactions may be different in the deuterated and nondeuterated solvents; this may change the energies of the transition state and hence the activation energy of the reaction. These are secondary isotope effects. Two physical models for this third factor have been constructed.⁸¹

⁷⁰A value for k_{CH_3}/k_{CD_3} of 2.13 was reported for one case: Liu; Wu *Tetrahedron Lett.* **1986**, 27, 3623.

⁷¹Halevi; Margolin *Proc. Chem. Soc.* **1964**, 174.

⁷²A value of 2.0 has been reported in one case, for a cis-trans isomerization, rather than a nucleophilic substitution: Caldwell; Misawa; Healy; Dewar *J. Am. Chem. Soc.* **1987**, 109, 6869.

⁷³Shiner; Buddenbaum; Murr; Lamaty *J. Am. Chem. Soc.* **1968**, 90, 418; Harris; Hall; Schleyer *J. Am. Chem. Soc.* **1971**, 93, 2551.

⁷⁴For reported exceptions, see Tanaka; Kaji; Hayami *Chem. Lett.* **1972**, 1223; Westaway *Tetrahedron Lett.* **1975**, 4229.

⁷⁵Shiner; Dowd *J. Am. Chem. Soc.* **1971**, 93, 1029; Shiner; Fisher *J. Am. Chem. Soc.* **1971**, 93, 2553; Willi; Ho; Ghanbarpour *J. Org. Chem.* **1972**, 37, 1185; Shiner; Neumann; Fisher *J. Am. Chem. Soc.* **1982**, 104, 354; and references cited in these papers.

⁷⁶Streitwieser; Jagow; Fahey; Suzuki *J. Am. Chem. Soc.* **1958**, 80, 2326.

⁷⁷Westaway; Waszczylo; Smith; Rangappa *Tetrahedron Lett.* **1985**, 26, 25.

⁷⁸Westaway; Lai *Can. J. Chem.* **1988**, 66, 1263.

⁷⁹Leffek; Llewellyn; Robertson *J. Am. Chem. Soc.* **1960**, 82, 6315, *Chem. Ind. (London)* **1960**, 588; Werstiuk; Timmins; Cappelli *Can. J. Chem.* **1980**, 58, 1738.

⁸⁰For reviews, see Alvarez; Schowen *Isot. Org. Chem.* **1987**, 7, 1-60; Kresge; More O'Ferrall, Powell *Isot. Org. Chem.* **1987**, 7, 177-273; Schowen *Prog. Phys. Org. Chem.* **1972**, 9, 275-332; Gold *Adv. Phys. Org. Chem.* **1969**, 7, 259-331; Laughton; Robertson, in Coetzee; Ritchie *Solute-Solvent Interactions*; Marcel Dekker: New York, 1969, pp. 399-538. For a review of the effect of isotopic changes in the solvent on the properties of nonreacting solutes, see Arnett; McKelvey, in Coetzee; Ritchie, cited above, pp. 343-398.

⁸¹Swain; Bader *Tetrahedron* **1960**, 10, 182; Bunton; Shiner *J. Am. Chem. Soc.* **1961**, 83, 42, 3207, 3214; Swain; Thornton *J. Am. Chem. Soc.* **1961**, 83, 3884, 3890. See also Mitton; Gresser; Schowen *J. Am. Chem. Soc.* **1969**, 91, 2045.

It is obvious that in many cases the first and third factors at least, and often the second, are working simultaneously. Attempts have been made to separate them.⁸²

The methods described in this chapter are not the only means of determining mechanisms. In an attempt to elucidate a mechanism, the investigator is limited only by his or her ingenuity.

⁸²More O'Ferrall; Koepl; Kresge *J. Am. Chem. Soc.* **1971**, 93, 9.

7

PHOTOCHEMISTRY

Most reactions carried out in organic chemistry laboratories take place between molecules all of which are in their ground electronic states. In a *photochemical reaction*,¹ however, a reacting molecule has been previously promoted by absorption of light to an electronically excited state. A molecule in an excited state must lose its extra energy in some manner; it cannot remain in the excited condition for long. However, a chemical reaction is not the only possible means of relinquishing the extra energy. In this chapter we first discuss electronically excited states and the processes of promotion to these states. Then we examine the possible pathways open to the excited molecule, first the physical and then the chemical pathways. The subject of electronic spectra is closely related to photochemistry.

Excited States and the Ground State

Electrons can move from the ground-state energy level of a molecule to a higher level (i.e., an unoccupied orbital of higher energy) if outside energy is supplied. In a photochemical process this energy is in the form of light. Light of any wavelength has associated with it an energy value given by $E = h\nu$, where ν is the frequency of the light ($\nu =$ velocity of light c divided by the wavelength λ) and h is Planck's constant. Since the energy levels of a molecule are quantized, the amount of energy required to raise an electron in a given molecule from one level to a higher one is a fixed quantity. Only light with exactly the frequency corresponding to this amount of energy will cause the electron to move to the higher level. If light of another frequency (too high or too low) is sent through a sample, it will pass out without a loss in intensity, since the molecules will not absorb it. However, if light of the correct frequency is passed in, the energy will be used by the molecules for electron promotion and hence the light that leaves the sample will be diminished in intensity or altogether gone. A *spectrophotometer* is an instrument that allows light of a given frequency to pass through a sample and that detects (by means of a phototube) the amount of light that has been transmitted, i.e., not absorbed. A spectrophotometer compares the intensity of the transmitted light with that of the incident light. Automatic instruments gradually and continuously change the frequency, and an automatic recorder plots a graph of absorption vs. frequency or wavelength.

¹There are many books on photochemistry. Some recent ones are Michl; Bonačić-Koutecký *Electronic Aspects of Organic Photochemistry*; Wiley: New York, 1990; Scaiano *Handbook of Organic Photochemistry*, 2 vols.; CRC Press: Boca Raton, FL, 1989; Coxon; Halton *Organic Photochemistry*, 2nd ed.; Cambridge University Press: Cambridge, 1987; Coyle *Photochemistry in Organic Synthesis*; Royal Society of Chemistry: London, 1986; *Introduction to Organic Photochemistry*; Wiley: New York, 1986; Horspool *Synthetic Organic Photochemistry*; Plenum: New York, 1984; Margaretha *Preparative Organic Photochemistry*, *Top. Curr. Chem.* **1982**, *103*; Turro *Modern Molecular Photochemistry*; W.A. Benjamin: New York, 1978; Rohatgi-Mukherjee *Fundamentals of Photochemistry*; Wiley: New York, 1978; Barltrop; Coyle *Principles of Photochemistry*; Wiley: New York, 1978. For a comprehensive older treatise, see Calvert; Pitts *Photochemistry*; Wiley: New York, 1966. For a review of the photochemistry of radicals and carbenes, see Scaiano; Johnston *Org. Photochem.* **1989**, *10*, 309-355. For a history of photochemistry, see Roth *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1193-1207 [*Angew. Chem.* *101*, 1220-1234]. For a glossary of terms used in photochemistry, see Braslavsky; Houk *Pure Appl. Chem.* **1988**, *60*, 1055-1106. See also the series, *Advances in Photochemistry, Organic Photochemistry*, and *Excited States*.

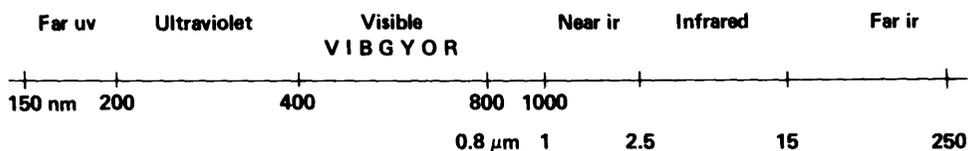


FIGURE 7.1 The uv, visible, and ir portions of the spectrum.

The energy of electronic transitions corresponds to light in the visible, uv, and far-uv regions of the spectrum (Figure 7.1). Absorption positions are normally expressed in wave-length units, usually nanometers (nm).² If a compound absorbs in the visible, it is colored, possessing a color complementary to that which is absorbed.³ Thus a compound absorbing in the violet is yellow. The far-uv region is studied by organic chemists less often than the visible or ordinary uv regions because special vacuum instruments are required owing to the fact that oxygen and nitrogen absorb in these regions.

From these considerations it would seem that an electronic spectrum should consist of one or more sharp peaks, each corresponding to the transfer of an electron from one electronic level to another. Under ordinary conditions the peaks are seldom sharp. In order to understand why, it is necessary to realize that molecules are constantly vibrating and rotating and that these motions are also quantized. A molecule at any time is not only in a given electronic state but also in a given vibrational and rotational state. The difference between two adjacent vibrational levels is much smaller than the difference between adjacent electronic levels, and the difference between adjacent rotational levels is smaller still. A typical situation is shown in Figure 7.2. When an electron moves from one electronic level to another, it moves from a given vibrational and rotational level within that electronic level to some vibrational and rotational level at the next electronic level. A given sample contains a large number of molecules, and even if all of them are in the ground electronic state, they are still distributed among the vibrational and rotational states (though the ground vibrational state V_0 is most heavily populated). This means that not just one wavelength of light will be absorbed but a number of them close together, with the most probable transition causing the most intense peak. But in molecules containing more than a few atoms there are so many possible transitions and these are so close together that what is observed is a relatively broad band. The height of the peak depends on the number of molecules making the transition and is proportional to $\log \epsilon$, where ϵ is the *extinction coefficient*. The extinction coefficient can be expressed by $\epsilon = E/cl$, where c is the concentration in moles per liter, l is the cell length in centimeters, and $E = \log I_0/I$, where I_0 is the intensity of the incident light and I of the transmitted light. The wavelength is usually reported as λ_{\max} , meaning that this is the top of the peak. Purely vibrational transitions, such as between V_0 and V_1 of E_1 , which require much less energy, are found in the ir region and are the basis of ir spectra. Purely rotational transitions are found in the far-ir and microwave (beyond the far-ir) regions.

A uv or visible absorption peak is caused by the promotion of an electron in one orbital (usually a ground-state orbital) to a higher orbital. Normally the amount of energy necessary to make this transition depends mostly on the nature of the two orbitals involved and much less on the rest of the molecule. Therefore, a simple functional group such as the $C=C$ double bond always causes absorption in the same general area. A group that causes absorption is called a *chromophore*.

²Formerly, millimicrons ($m\mu$) were frequently used; numerically they are the same as nanometers.

³For monographs, see Zollinger *Color Chemistry*; VCH: New York, 1987; Gordon; Gregory *Organic Chemistry in Colour*; Springer: New York, 1983; Griffiths *Colour and Constitution of Organic Molecules*; Academic Press: New York, 1976. See also Fabian; Zahradnik *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 677-694 [*Angew. Chem.* *101*, 693-710].

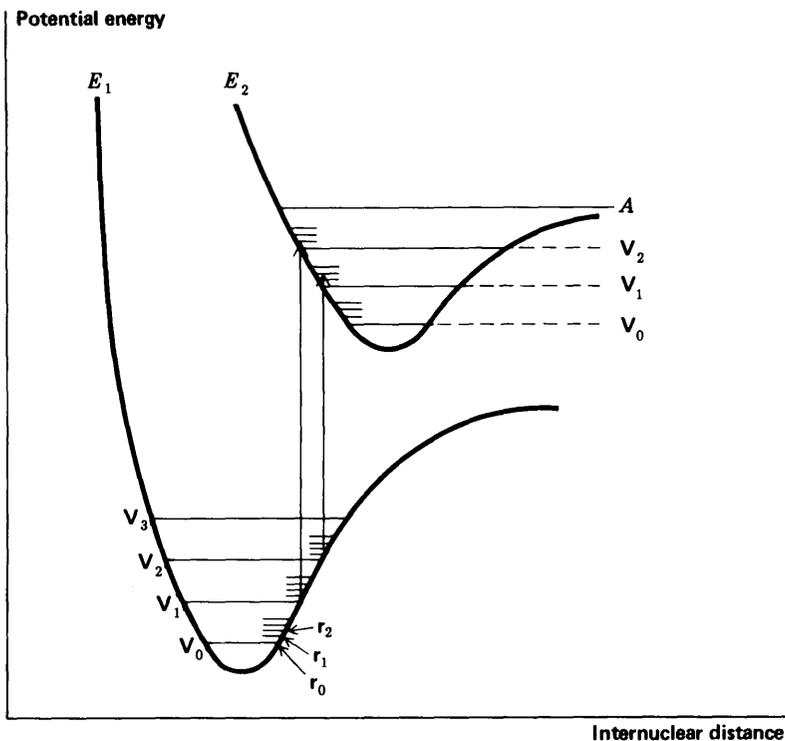


FIGURE 7.2 Energy curves for a diatomic molecule. Two possible transitions are shown. When an electron has been excited to the point marked A, the molecule may cleave (p. 236).

Singlet and Triplet States. “Forbidden” Transitions

In most organic molecules, all electrons in the ground state are paired, with each member of a pair possessing opposite spin as demanded by the Pauli principle. When one of a pair of electrons is promoted to an orbital of higher energy, the two electrons no longer share an orbital, and the promoted electron may, in principle, have the same spin as its former partner or the opposite spin. As we saw in Chapter 5, a molecule in which two unpaired electrons have the same spin is called a *triplet*, while one in which all spins are paired is a *singlet*. Thus, at least in principle, for every excited singlet state there is a corresponding triplet state. In most cases, the triplet state has a lower energy than the corresponding singlet because of Hund's rule. Therefore, a different amount of energy and hence a different wavelength is required to promote an electron from the ground state (which is almost always a singlet) to an excited singlet than to the corresponding triplet state.

It would thus seem that promotion of a given electron in a molecule could result either in a singlet or a triplet excited state depending on the amount of energy added. However, this is often not the case because transitions between energy levels are governed by selection rules, which state that certain transitions are “forbidden.” There are several types of “forbidden” transitions, two of which are more important than the others.

1. Spin-forbidden transitions. Transitions in which the spin of an electron changes are not allowed, because a change from one spin to the opposite involves a change in angular momentum and such a change would violate the law of conservation of angular momentum.

Therefore, singlet–triplet and triplet–singlet transitions are forbidden, whereas singlet–singlet and triplet–triplet transitions are allowed.

2. Symmetry-forbidden transitions. Among the transitions in this class are those in which a molecule has a center of symmetry. In such cases, a $g \rightarrow g$ or $u \rightarrow u$ transition (see p. 5) is “forbidden,” while a $g \rightarrow u$ or $u \rightarrow g$ transition is allowed.

We have put the word “forbidden” into quotation marks because these transitions are not actually forbidden but only highly improbable. In most cases promotions from a singlet ground state to a triplet excited state are so improbable that they cannot be observed, and it is safe to state that in most molecules only singlet–singlet promotions take place. However, this rule does break down in certain cases, most often when a heavy atom (such as iodine) is present in the molecule, in which cases it can be shown from spectra that singlet–triplet promotions are occurring.⁴ Symmetry-forbidden transitions can frequently be observed, though usually with low intensity.

Types of Excitation

When an electron in a molecule is promoted (normally only one electron in any molecule), it usually goes into the lowest available vacant orbital, though promotion to higher orbitals is also possible. For most organic molecules there are consequently four types of electronic excitation:

1. $\sigma \rightarrow \sigma^*$. Alkanes, which have no n or π electrons, can be excited only in this way.⁵
2. $n \rightarrow \sigma^*$. Alcohols, amines,⁶ ethers, etc. can also be excited in this manner.
3. $\pi \rightarrow \pi^*$. This pathway is open to alkenes as well as to aldehydes, carboxylic esters, etc.
4. $n \rightarrow \pi^*$. Aldehydes, ketones, carboxylic esters, etc. can undergo this promotion as well as the other three.

The four excitation types above are listed in what is normally the order of decreasing energy. Thus light of the highest energy (in the far uv) is necessary for $\sigma \rightarrow \sigma^*$ excitation, while $n \rightarrow \pi^*$ promotions are caused by ordinary uv light. However, the order may sometimes be altered in some solvents.

In 1,3-butadiene (and other compounds with two conjugated double bonds) there are two π and two π^* orbitals (p. 31). The energy difference between the higher π (χ_2) and the lower π^* (χ_3) orbital is less than the difference between the π and π^* orbitals of ethylene. Therefore 1,3-butadiene requires less energy than ethylene, and thus light of a higher wavelength, to promote an electron. This is a general phenomenon, and it may be stated that, in general, *the more conjugation in a molecule, the more the absorption is displaced toward higher wavelengths* (see Table 7.1).⁷ When a chromophore absorbs at a certain wavelength and the substitution of one group for another causes absorption at a longer wavelength, a *bathochromic shift* is said to have occurred. The opposite kind of shift is called *hypsochromic*.

Of the four excitation types listed above, the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ are far more important in organic photochemistry than the other two. Compounds containing C=O groups can be excited in both ways, giving rise to at least two peaks in the uv.

⁴For a review of photochemical heavy-atom effects, see Koziar; Cowan *Acc. Chem. Res.* **1978**, *11*, 334-341.

⁵An n electron is one in an unshared pair.

⁶For a review of the photochemistry of amines, see Malkin; Kuz'min *Russ. Chem. Rev.* **1985**, *54*, 1041-1057.

⁷Bohlmann; Mannhardt *Chem. Ber.* **1956**, *89*, 1307.

TABLE 7.1 Ultraviolet absorption⁷ of $\text{CH}_3-(\text{CH}=\text{CH})_n-\text{CH}_3$ for some values of n

n	nm
2	227
3	263
6	352
9	413

As we have seen, a chromophore is a group that causes a molecule to absorb light. Examples of chromophores in the visible or uv are $\text{C}=\text{O}$, $\text{N}=\text{N}$,⁸ Ph, and NO_2 . Some chromophores in the far uv (beyond 200 nm) are $\text{C}=\text{C}$, $\text{C}\equiv\text{C}$, Cl, and OH. An *auxochrome* is a group that displaces (through resonance) and usually intensifies the absorption of a chromophore present in the same molecule. Groups such as Cl, OH, and NH_2 are generally regarded as auxochromes since they shift (usually bathochromically) the uv and visible bands of chromophores such as Ph or $\text{C}=\text{O}$ (see Table 7.2).⁹ Since auxochromes are themselves chromophores (to be sure, generally in the far-uv), it is sometimes difficult to decide which group in a molecule is an auxochrome and which a chromophore. For example, in acetophenone (PhCOMe) is the chromophore Ph or $\text{C}=\text{O}$? In such cases the distinction becomes practically meaningless.

TABLE 7.2 Some uv peaks of substituted benzenes in water, or water with a trace of methanol (for solubility)

Note how auxochromes shift and usually intensify the peaks⁹

	Primary band		Secondary band	
	λ_{max} , nm	ϵ_{max}	λ_{max} , nm	ϵ_{max}
PhH	203.5	7,400	254	204
PhCl	209.5	7,400	263.5	190
PhOH	210.5	6,200	270	1,450
PhOMe	217	6,400	269	1,480
PhCN	224	13,000	271	1,000
PhCOOH	230	11,600	273	970
PhNH₂	230	8,600	280	1,430
PhO⁻	235	9,400	287	2,600
PhAc	245.5	9,800		
PhCHO	249.5	11,400		
PhNO₂	268.5	7,800		

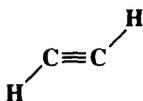
⁸For a review of the azo group as a chromophore, see Rau *Angew. Chem. Int. Ed. Engl.* **1973**, 224-235 [*Angew. Chem.* **85**, 248-258].

⁹These values are from Jaffé; *Orchin Theory and Applications of Ultraviolet Spectroscopy*; Wiley: New York, 1962, p. 257.

Nomenclature and Properties of Excited States

An excited state of a molecule can be regarded as a distinct chemical species, different from the ground state of the same molecule and from other excited states. It is obvious that we need some method of naming excited states. Unfortunately, there are several methods in use, depending on whether one is primarily interested in photochemistry, spectroscopy, or molecular-orbital theory.¹⁰ One of the most common methods simply designates the original and newly occupied orbitals, with or without a superscript to indicate singlet or triplet. Thus the singlet state arising from promotion of a π to a π^* orbital in ethylene would be the $^1(\pi, \pi^*)$ state or the π, π^* singlet state. Another very common method can be used even in cases where one is not certain which orbitals are involved. The lowest-energy excited state is called S_1 , the next S_2 , etc., and triplet states are similarly labeled T_1 , T_2 , T_3 , etc. In this notation the ground state is S_0 . Other notational systems exist, but in this book we shall confine ourselves to the two types just mentioned.

The properties of excited states are not easy to measure because of their generally short lifetimes and low concentrations, but enough work has been done for us to know that they often differ from the ground state in geometry, dipole moment and acid or base strength.¹¹ For example, acetylene, which is linear in the ground state, has a trans geometry



with approximately sp^2 carbons in the $^1(\pi, \pi^*)$ state.¹² Similarly, the $^1(\pi, \pi^*)$ and the $^3(\pi, \pi^*)$ states of ethylene have a perpendicular and not a planar geometry,¹³ and the $^1(n, \pi^*)$ and $^3(n, \pi^*)$ states of formaldehyde are both pyramidal.¹⁴ Triplet species tend to stabilize themselves by distortion, which relieves interaction between the unpaired electrons. Obviously, if the geometry is different, the dipole moment will probably differ also and the change in geometry and electron distribution often results in a change in acid or base strength.¹⁵ For example, the S_1 state of 2-naphthol is a much stronger acid ($pK = 3.1$) than the ground state (S_0) of the same molecule ($pK = 9.5$).¹⁶

Photolytic Cleavage

We have said that when a molecule absorbs a quantum of light, it is promoted to an excited state. Actually, that is not the only possible outcome. Because the energy of visible and uv light is of the same order of magnitude as that of covalent bonds (Table 7.3), another

¹⁰For discussions of excited-state notation and other terms in photochemistry, see Pitts; Wilkinson; Hammond *Adv. Photochem.* **1963**, *1*, 1-21; Porter; Balzani; Moggi *Adv. Photochem.* **1974**, *9*, 147-196. See also Braslavsky; Houk, Ref. 1.

¹¹For reviews of the structures of excited states, see Zink; Shin *Adv. Photochem.* **1991**, *16*, 119-214; Innes *Excited States* **1975**, *2*, 1-32; Hirakawa; Masamichi *Vib. Spectra Struct.* **1983**, *12*, 145-204.

¹²Ingold; King *J. Chem. Soc.* **1953**, 2702, 2704, 2708, 2725, 2745. For a review of acetylene photochemistry, see Coyle *Org. Photochem.* **1985**, *7*, 1-73.

¹³Merer; Mulliken *Chem. Rev.* **1969**, *69*, 639-656.

¹⁴Robinson; Di Giorgio *Can. J. Chem.* **1958**, *36*, 31; Bucnker; Peyerimhoff *J. Chem. Phys.* **1970**, *53*, 1368; Garrison; Schaefer; Lester *J. Chem. Phys.* **1974**, *61*, 3039; Streitwieser; Kohler *J. Am. Chem. Soc.* **1988**, *110*, 3769. For reviews of excited states of formaldehyde, see Buck *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 193-198, 225-233; Moule; Walsh *Chem. Rev.* **1975**, *75*, 67-84.

¹⁵For a review of acid-base properties of excited states, see Ireland; Wyatt *Adv. Phys. Org. Chem.* **1976**, *12*, 131-221.

¹⁶Weller *Z. Phys. Chem. (Frankfurt am Main)* **1955**, *3*, 238, *Discuss. Faraday Soc.* **1959**, *27*, 28.

TABLE 7.3 Typical energies for some covalent single bonds (see Table 1.7) and the corresponding approximate wavelengths

Bond	<i>E</i>		nm
	kcal/mol	kJ/mol	
C—H	95	397	300
C—O	88	368	325
C—C	83	347	345
Cl—Cl	58	243	495
O—O	35	146	820

possibility is that the molecule may cleave into two parts, a process known as *photolysis*. There are three situations that can lead to cleavage:

1. The promotion may bring the molecule to a vibrational level so high that it lies above the right-hand portion of the E_2 curve (line *A* in Figure 7.2). In such a case the excited molecule cleaves at its first vibration.

2. Even where the promotion is to a lower vibrational level, one which lies wholly within the E_2 curve (such as V_1 or V_2), the molecule may still cleave. As Figure 7.2 shows, equilibrium distances are greater in excited states than in the ground state. The *Franck-Condon principle* states that promotion of an electron takes place much faster than a single vibration (the promotion takes about 10^{-15} sec; a vibration about 10^{-12} sec). Therefore, when an electron is suddenly promoted, even to a low vibrational level, the distance between the atoms is essentially unchanged and the bond finds itself in a compressed condition like a pressed-in spring; this condition may be relieved by an outward surge that is sufficient to break the bond.

3. In some cases the excited state is entirely dissociative (Figure 7.3), i.e., there is no

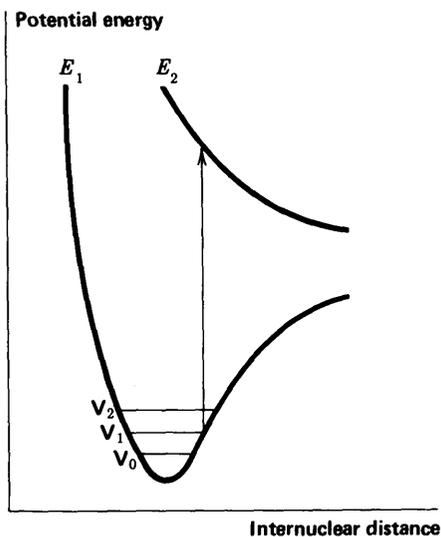


FIGURE 7.3 Promotion to a dissociative state results in bond cleavage.

distance where attraction outweighs repulsion, and the bond must cleave. An example is the hydrogen molecule, where a $\sigma \rightarrow \sigma^*$ promotion always results in cleavage.

A photolytic cleavage can break the molecule into two smaller molecules or into two free radicals (see p. 243). Cleavage into two ions, though known, is much rarer. Once free radicals are produced by a photolysis, they behave like free radicals produced in any other way (Chapter 5) except that they may be in excited states, and this can cause differences in behavior.

The Fate of the Excited Molecule: Physical Processes

When a molecule has been photochemically promoted to an excited state, it does not remain there for long. Most promotions are from the S_0 to the S_1 state. As we have seen, promotions from S_0 to triplet states are "forbidden." Promotions to S_2 and higher singlet states take place, but in liquids and solids these higher states usually drop very rapidly to the S_1 state (about 10^{-13} to 10^{-11} sec). The energy lost when an S_2 or S_3 molecule drops to S_1 is given up in small increments to the environment by collisions with neighboring molecules. Such a process is called an *energy cascade*. In a similar manner, the initial excitation and the decay from higher singlet states initially populate many of the vibrational levels of S_1 , but these also cascade, down to the lowest vibrational level of S_1 . Therefore, in most cases, the lowest vibrational level of the S_1 state is the only important excited singlet state.¹⁷ This state can undergo various physical and chemical processes. In the following list, we describe the physical pathways open to molecules in the S_1 and excited triplet states. These pathways are also shown in a modified Jablonski diagram (Figure 7.4) and in Table 7.4.

1. A molecule in the S_1 state can cascade down through the vibrational levels of the S_0 state and thus return to the ground state by giving up its energy in small increments to the environment, but this is generally quite slow because the amount of energy is large. The process is called *internal conversion* (IC). Because it is slow, most molecules in the S_1 state adopt other pathways.¹⁸

2. A molecule in the S_1 state can drop to some low vibrational level of the S_0 state all at once by giving off the energy in the form of light. This process, which generally happens within 10^{-9} sec, is called *fluorescence*. This pathway is not very common either (because it is relatively slow), except for small molecules, e.g., diatomic, and rigid molecules, e.g., aromatic. For most other compounds fluorescence is very weak or undetectable. For compounds that do fluoresce, the fluorescence emission spectra are usually the approximate mirror images of the absorption spectra. This comes about because the fluorescing molecules all drop from the lowest vibrational level of the S_1 state to various vibrational levels of S_0 , while excitation is from the lowest vibrational level of S_0 to various levels of S_1 (Figure 7.5). The only peak in common is the one (called the 0-0 peak) that results from transitions between the lowest vibrational levels of the two states. In solution, even the 0-0 peak may be noncoincident because the two states are solvated differently. Fluorescence nearly always arises from a $S_1 \rightarrow S_0$ transition, though azulene (p. 49) and its simple derivatives are exceptions,¹⁹ emitting fluorescence from $S_2 \rightarrow S_0$ transitions.

¹⁷For a review of physical and chemical processes undergone by higher states, see Turro; Ramamurthy; Cherry; Farneth *Chem. Rev.* **1978**, *78*, 125-145.

¹⁸For a monograph on radiationless transitions, see Lin *Radiationless Transitions*; Academic Press: New York, 1980. For reviews, see Kommandeur *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 421-428; Freed *Acc. Chem. Res.* **1978**, *11*, 74-80.

¹⁹For other exceptions, see Gregory; Hirayama; Lipsky *J. Chem. Phys.* **1973**, *58*, 4697; Sugihara; Wakabayashi; Murata; Jinguji; Nakazawa; Persy; Wirz *J. Am. Chem. Soc.* **1985**, *107*, 5894, and references cited in these papers. See also Ref. 17, pp. 126-129.

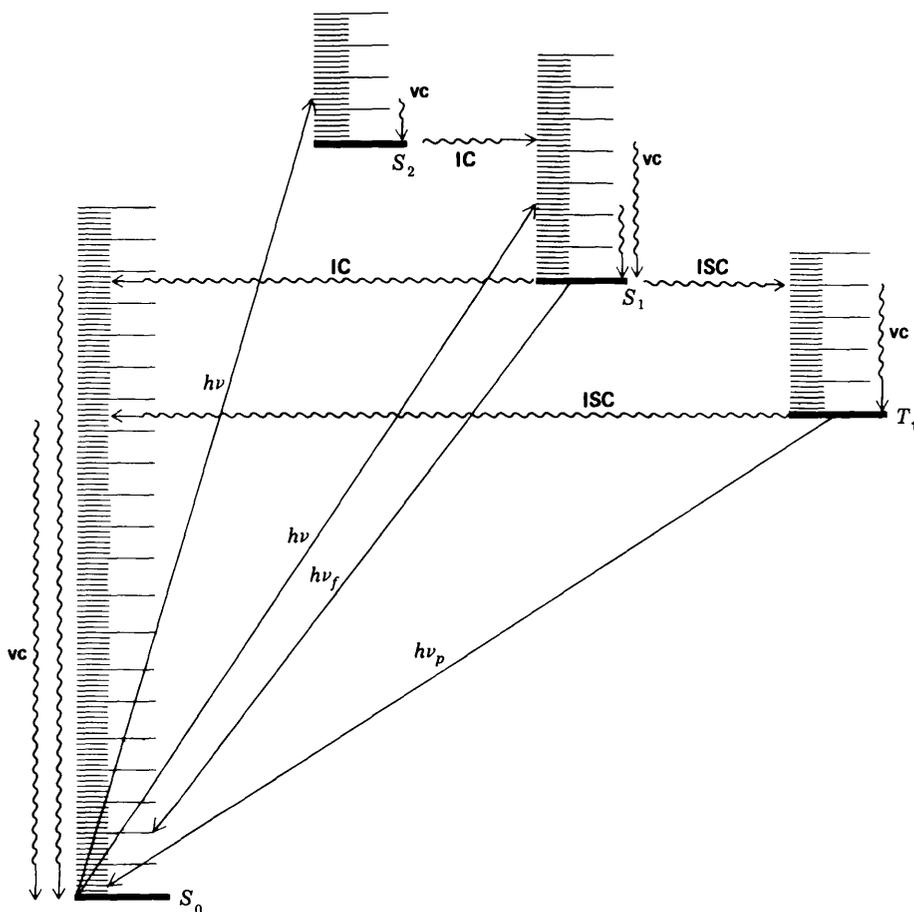


FIGURE 7.4 Modified Jablonski diagram showing transitions between excited states and the ground state. Radiative processes are shown by straight lines, radiationless processes by wavy lines. IC = internal conversion; ISC = intersystem crossing, vc = vibrational cascade; $h\nu_f$ = fluorescence; $h\nu_p$ = phosphorescence.

Because of the possibility of fluorescence, any chemical reactions of the S_1 state must take place very fast, or fluorescence will occur before they can happen.

3. Most molecules (though by no means all) in the S_1 state must undergo an *intersystem crossing* (ISC) to the lowest triplet state T_1 .²⁰ An important example is benzophenone, of which approximately 100% of the molecules that are excited to the S_1 state cross over to the T_1 .²¹ Intersystem crossing from singlet to triplet is of course a “forbidden” pathway, since the angular-momentum problem (p. 233) must be taken care of, but this often takes place by compensations elsewhere in the system. Intersystem crossings take place without loss of energy. Since a singlet state usually has a higher energy than the corresponding

²⁰Intersystem crossing from S_1 to T_2 and higher triplet states has also been reported in some aromatic molecules: Li; *Lim Chem. Phys.* **1972**, 57, 605; Sharf; *Silbey Chem. Phys. Lett.* **1970**, 5, 314. See also Schlag; Schneider; Fischer *Annu. Rev. Phys. Chem.* **1971**, 22, 465-526, pp. 490-494. There is evidence that ISC can also occur from the S_2 state of some molecules: Samanta *J. Am. Chem. Soc.* **1991**, 113, 7427.

²¹Moore; Hammond; Foss *J. Am. Chem. Soc.* **1961**, 83, 2789.

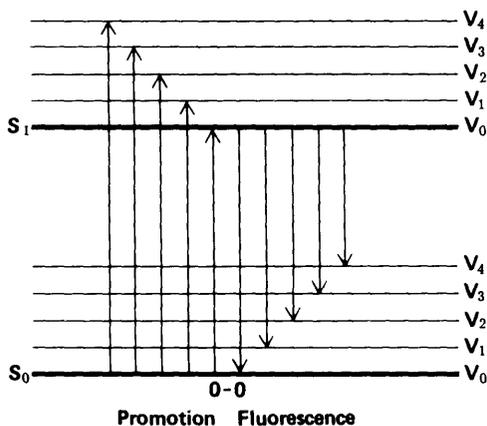
TABLE 7.4 Physical processes undergone by excited molecules

The superscript v indicates vibrationally excited state: excited states higher than S_0 or T_1 are omitted

$S_0 + h\nu \rightarrow S_1^v$	Excitation
$S_1^v \rightsquigarrow S_1 + \text{heat}$	Vibrational relaxation
$S_1 \rightarrow S_0 + h\nu$	Fluorescence
$S_1 \rightsquigarrow S_0 + \text{heat}$	Internal conversion
$S_1 \rightsquigarrow T_1^v$	Intersystem crossing
$T_1^v \rightsquigarrow T_1 + \text{heat}$	Vibrational relaxation
$T_1 \rightarrow S_0 + h\nu$	Phosphorescence
$T_1 \rightsquigarrow S_0 + \text{heat}$	Intersystem crossing
$S_1 + A_{(S_0)} \rightarrow S_0 + A_{(S_1)}$	Singlet-singlet transfer (photosensitization)
$T_1 + A_{(S_0)} \rightarrow S_0 + A_{(T_1)}$	Triplet-triplet transfer (photosensitization)

triplet, this means that energy must be given up. One way for this to happen is for the S_1 molecule to cross to a T_1 state at a high vibrational level and then for the T_1 to cascade down to its lowest vibrational level (see Figure 7.4). This cascade is very rapid (10^{-12} sec). When T_2 or higher states are populated, they too rapidly cascade to the lowest vibrational level of the T_1 state.

4. A molecule in the T_1 state may return to the S_0 state by giving up heat (intersystem crossing) or light (this is called *phosphorescence*).²² Of course, the angular-momentum difficulty exists here, so that both intersystem crossing and phosphorescence are very slow ($\sim 10^{-3}$ to 10^1 sec). This means that T_1 states generally have much longer lifetimes than S_1 states. When they occur in the same molecule, phosphorescence is found at lower frequencies than fluorescence (because of the higher difference in energy between S_1 and S_0 than between T_1 and S_0) and is longer-lived (because of the longer lifetime of the T_1 state).

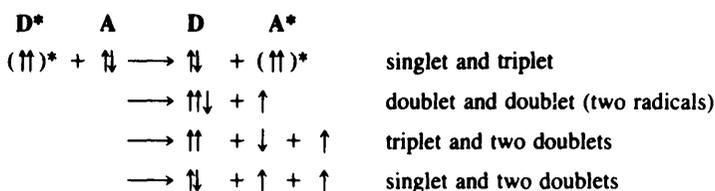
**FIGURE 7.5** Promotion and fluorescence between S_1 and S_0 states.

²²For a review of physical processes of triplet states, see Lower; El-Sayed *Chem. Rev.* **1966**, *66*, 199-241. For a review of physical and chemical processes of triplet states see Wagner; Hammond *Adv. Photochem.* **1968**, *5*, 21-156.

5. If nothing else happens to it first, a molecule in an excited state (S_1 or T_1) may transfer its excess energy all at once to another molecule in the environment, in a process called *photosensitization*.²³ The excited molecule (which we shall call D for donor) thus drops to S_0 while the other molecule (A for acceptor) becomes excited:



Thus there are *two* ways for a molecule to reach an excited state—by absorption of a quantum of light or by transfer from a previously excited molecule.²⁴ The donor D is also called a *photosensitizer*. This energy transfer is subject to the *Wigner spin-conservation rule*, which is actually a special case of the law of conservation of momentum we encountered previously. According to the Wigner rule, the total electron spin does not change after the energy transfer. For example, when a triplet species interacts with a singlet these are some allowed possibilities:²⁵



In all these cases the products have three electrons spinning “up” and the fourth “down” (as do the starting molecules). However, formation of, say, two triplets ($\uparrow\uparrow + \downarrow\downarrow$) or two singlets ($\uparrow\downarrow + \uparrow\downarrow$), whether ground states or excited, would violate the rule.

In the two most important types of photosensitization, both of which are in accord with the Wigner rule, a triplet excited state generates another triplet and a singlet generates a singlet:



Singlet-singlet transfer can take place over relatively long distances, e.g., 40 Å, but triplet transfer normally requires a collision between the molecules.²⁶ Both types of photosensitization can be useful for creating excited states when they are difficult to achieve by direct irradiation. Photosensitization is therefore an important method for carrying out photochemical reactions when a molecule cannot be brought to the desired excited state by direct absorption of light. Triplet-triplet transfer is especially important because triplet states are usually much more difficult to prepare by direct irradiation than singlet states (often impossible) and because triplet states, having longer lifetimes, are much more likely than singlets to transfer energy by photosensitization. Photosensitization can also be accomplished by electron transfer.²⁷

²³For reviews, see Albini *Synthesis* **1981**, 249-264; Turro; Dalton; Weiss *Org. Photochem.* **1969**, 2, 1-62.

²⁴There is also a third way: in certain cases excited states can be produced directly in ordinary reactions. For a review, see White; Miano; Watkins; Breaux *Angew. Chem. Int. Ed. Engl.* **1974**, 13, 229-243 [*Angew. Chem.* **86**, 292-307].

²⁵For another table of this kind, see Calvert; Pitts, Ref. 1, p. 89.

²⁶Long-range triplet-triplet transfer has been observed in a few cases: Bennett; Schwenker; Kellogg *J. Chem. Phys.* **1964**, 41, 3040; Ermolaev; Sveshnikova *Izv. Akad. Nauk SSSR, Ser. Fiz.* **1962**, 26, 29 [*C. A.* **1962**, 57, 1688]. *Opt. Spectrosc. (USSR)* **1964**, 16, 320.

²⁷For a review, see Kavarnos; Turro *Chem. Rev.* **1986**, 86, 401-449. See also Mariano, Ref. 35.

In choosing a photosensitizer one should avoid a compound that absorbs in the same region as the acceptor because the latter will then compete for the light.²⁸ For examples of the use of photosensitization to accomplish reactions, see 5-37, 5-49.

The Fate of the Excited Molecule: Chemical Processes

Although both excited singlet and triplet species can undergo chemical reactions, they are much more common for triplets, simply because these generally have much longer lifetimes. Excited singlet species, in most cases, have a lifetime of less than 10^{-10} sec and undergo one of the physical processes already discussed before they have a chance to react chemically. Therefore, photochemistry is largely the chemistry of triplet states.²⁹ Table 7.5³⁰ lists many of the possible chemical pathways that can be taken by an excited molecule.³¹ The first four of these are unimolecular reactions; the others are bimolecular. In the case of bimolecular reactions it is rare for two excited molecules to react with each other (because the concentration of excited molecules at any one time is generally low); reactions are between an excited molecule and an unexcited molecule of either the same or another species. The reactions listed in Table 7.5 are primary processes. Secondary reactions often follow, since the primary products are frequently radicals or carbenes; even if they are ordinary molecules, they are often in upper vibrational levels and so have excess energy. In almost all cases the primary products of photochemical reactions are in their ground states, though exceptions are known.³² Of the reactions listed in Table 7.5, the most common are cleavage into radicals (1), decomposition into molecules (2), and (in the presence of a suitable acceptor molecule) photosensitization (7), which we have already discussed. The following are some specific examples of reaction categories (1) to (6). Other examples are discussed in Part 2 of this book.³³

TABLE 7.5 Primary photochemical reactions of an excited molecule **A—B—C**³⁰
Examples are given in the text; the most common are (1), (2), and, in the presence of a suitable acceptor molecule, (7)

$(A-B-C) \longrightarrow A-B\cdot + C\cdot$	Simple cleavage into radicals	(1)
$(A-B-C) \longrightarrow E + F$	Decomposition into molecules	(2)
$(A-B-C) \longrightarrow A-C-B$	Intramolecular rearrangement	(3)
$(A-B-C) \longrightarrow A-B-C'$	Photoisomerization	(4)
$(A-B-C) \xrightarrow{RH} A-B-C-H + R\cdot$	Hydrogen-atom abstraction	(5)
$(A-B-C) \longrightarrow (ABC)_2$	Photodimerization	(6)
$(A-B-C) \xrightarrow{A} ABC + A^*$	Photosensitization	(7)

²⁸For a review of other complications that can take place in photosensitized reactions, see Engel; Monroe *Adv. Photochem.* **1971**, *8*, 245-313.

²⁹For a review of the chemical reactions of triplet states, see Wagner; Hammond, Ref. 22. For other reviews of triplet states, see *Top. Curr. Chem.*, **1975**, vols. 54 and 55.

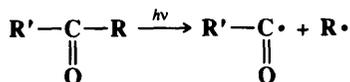
³⁰Adapted from Calvert; Pitts, Ref. 1, p. 367.

³¹For a different kind of classification of photochemical reactions, see Dauben; Salem; Turro *Acc. Chem. Res.* **1975**, *8*, 41. For reviews of photochemical reactions where the molecules are geometrically constrained, see Ramamurthy *Tetrahedron* **1986**, *42*, 5753-5839; Ramamurthy; Eaton *Acc. Chem. Res.* **1988**, *21*, 300-306; Turro; Cox; Paczkowski *Top. Curr. Chem.* **1985**, *129*, 57-97.

³²Turro; Lechtken; Lyons; Hautala; Carnahan; Katz *J. Am. Chem. Soc.* **1973**, *95*, 2035.

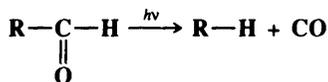
³³For monographs on the use of photochemistry for synthesis, see Ninomiya; Naito *Photochemical Synthesis*; Academic Press: New York, 1989; Coyle *Photochemistry in Organic Synthesis*; Royal Society of Chemistry: London, 1986; Schönberg *Preparative Organic Photochemistry*; Springer: Berlin, 1968.

*Category 1. Simple cleavage into radicals.*³⁴ Aldehydes and ketones absorb in the 230 to 330 nm region. This is assumed to result from an $n \rightarrow \pi^*$ singlet-singlet transition. The excited aldehyde or ketone can then cleave.³⁵

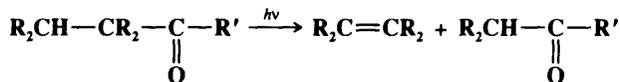


When applied to ketones, this is called *Norrish Type I cleavage* or often just *Type I cleavage*. In a secondary process, the acyl radical $\text{R}'-\text{CO}\cdot$ can then lose CO to give $\text{R}'\cdot$ radicals. Another example of a category 1 process is cleavage of Cl_2 to give two Cl atoms. Other bonds that are easily cleaved by photolysis are the O—O bonds of peroxy compounds and the C—N bonds of aliphatic azo compounds $\text{R}-\text{N}=\text{N}-\text{R}$.³⁶ The latter is an important source of radicals $\text{R}\cdot$, since the other product is the very stable N_2 .

Category 2. Decomposition into molecules. Aldehydes (though not generally ketones) can also cleave in this manner:



This is an extrusion reaction (see Chapter 17). In another example of a process in category 2, aldehydes and ketones with a γ hydrogen can cleave in still another way (a β elimination, see Chapter 17):



This reaction, called *Norrish Type II cleavage*,³⁷ involves intramolecular abstraction of the γ hydrogen followed by cleavage of the resulting diradical³⁸ (a secondary reaction) to give an enol that tautomerizes to the aldehyde or ketone product.³⁹

³⁴For reviews, see Jackson; Okabe *Adv. Photochem.* **1986**, *13*, 1-94; Kresin; Lester *Adv. Photochem.* **1986**, *13*, 95-163.

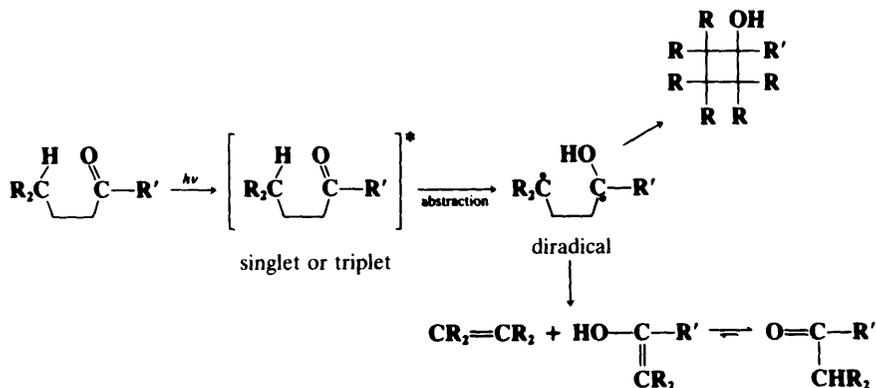
³⁵For full discussions of aldehyde and ketone photochemistry, see Formosinho; Arnaut *Adv. Photochem.* **1991**, *16*, 67-117; Newton, in Coyle, Ref. 33, pp. 39-60; Lee; Lewis *Adv. Photochem.* **1980**, *12*, 1-96; Calvert; Pitts, Ref. 1, pp. 368-427; Coyle; Carless *Chem. Soc. Rev.* **1972**, *1*, 465-480; Pitts; Wan, in Patai *The Chemistry of the Carbonyl Group*; Wiley: New York, 1966, pp. 823-916; Dalton; Turro *Annu. Rev. Phys. Chem.* **1970**, *21*, 499-560; Bérces, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 5; Elsevier: New York, 1972, pp. 277-380; Turro; Dalton; Dawes; Farrington; Hautala; Morton; Niemczyk; Shore *Acc. Chem. Res.* **1972**, *5*, 92-101; Wagner *Top. Curr. Chem.* **1976**, *66*, 1-52; Wagner; Hammond, Ref. 22, pp. 87-129. For reviews of the photochemistry of cyclic ketones, see Weiss *Org. Photochem.* **1981**, *5*, 347-420; Chapman; Weiss *Org. Photochem.* **1973**, *3*, 197-288; Morton; Turro *Adv. Photochem.* **1974**, *9*, 197-309. For reviews of the photochemistry of α -diketones, see Rubin *Top. Curr. Chem.* **1985**, *129*, 1-56. **1969**, *13*, 251-306; Monroe *Adv. Photochem.* **1971**, *8*, 77-108. For a review of the photochemistry of protonated unsaturated carbonyl compounds, see Childs *Rev. Chem. Intermed.* **1980**, *3*, 285-314. For reviews of the photochemistry of C=S compounds, see Coyle *Tetrahedron* **1985**, *41*, 5393-5425; Ramamurthy *Org. Photochem.* **1985**, *7*, 231-338. For a review of the chemistry of C=N compounds, see Mariano *Org. Photochem.* **1987**, *9*, 1-128.

³⁶For reviews of the photochemistry of azo compounds, see Adam; Oppenländer *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 661-672 [*Angew. Chem.* **98**, 659-670]; Dürr; Ruge *Top. Curr. Chem.* **1976**, *66*, 53-87; Drewer, in Patai *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2; Wiley: New York, 1975, pp. 935-1015.

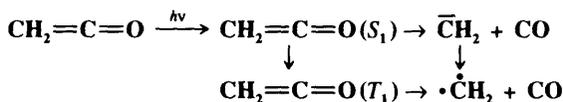
³⁷For thorough discussions of the mechanism, see Wagner, in de Mayo *Rearrangements in Ground and Excited States*, vol. 3; Academic Press: New York, 1980, pp. 381-444. *Acc. Chem. Res.* **1971**, *4*, 168-177; Dalton; Turro, Ref. 35, pp. 526-538.

³⁸For reviews of the diradicals produced in this reaction, see Wilson *Org. Photochem.* **1985**, *7*, 339-466, pp. 349-373; Scaiano; Lissi; Encina *Rev. Chem. Intermed.* **1978**, *2*, 139-196. For a review of a similar process, where δ hydrogens are abstracted, see Wagner *Acc. Chem. Res.* **1989**, *22*, 83-91.

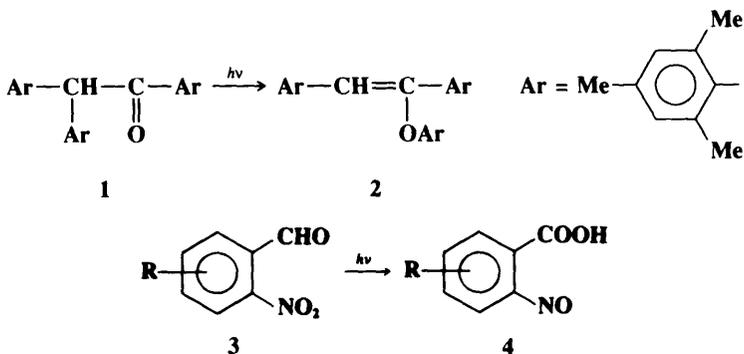
³⁹This mechanism was proposed by Yang; Yang *J. Am. Chem. Soc.* **1958**, *80*, 2913. Among the evidence for this mechanism is the fact that the diradical intermediate has been trapped; Wagner; Zepp *J. Am. Chem. Soc.* **1972**, *94*, 287; Wagner; Kelso; Zepp *J. Am. Chem. Soc.* **1972**, *94*, 7480; Adam; Grabowski; Wilson *Chem. Ber.* **1989**, *122*, 561. See also Caldwell; Dhawan; Moore *J. Am. Chem. Soc.* **1985**, *107*, 5163.



Both singlet and triplet n, π^* states undergo the reaction.⁴⁰ The intermediate diradical can also cyclize to a cyclobutanone, which is often a side product. Carboxylic esters, anhydrides, and other carbonyl compounds can also give this reaction.⁴¹ The photolysis of ketene to CH_2 (p. 199) is still another example of a reaction in category 2. Both singlet and triplet CH_2 are generated, the latter in two ways:



Category 3. Intramolecular rearrangement. Two examples are the rearrangement of the trimesityl compound **1** to the enol ether **2**,⁴² and irradiation of *o*-nitrobenzaldehydes **3** to give *o*-nitrosobenzoic acids **4**.⁴³



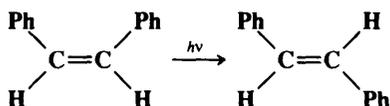
⁴⁰Wagner; Hammond *J. Am. Chem. Soc.* **1965**, *87*, 4009; Dougherty *J. Am. Chem. Soc.* **1965**, *87*, 4011; Ausloos; Rebbert *J. Am. Chem. Soc.* **1964**, *86*, 4512; Casey; Boggs *J. Am. Chem. Soc.* **1972**, *94*, 6457.

⁴¹For a review of the photochemistry of carboxylic acids and acid derivatives, see Givens; Levi, in Patai *The Chemistry of Acid Derivatives*, pt. 1; Wiley: New York, 1979, pp. 641-753.

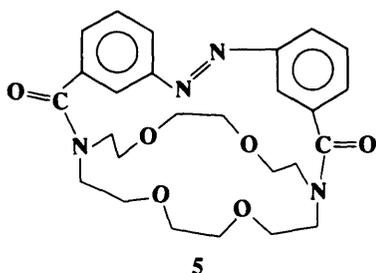
⁴²Hart; Lin *Tetrahedron Lett.* **1985**, *26*, 575; Wagner; Zhou *J. Am. Chem. Soc.* **1988**, *110*, 611.

⁴³For a review of this and closely related reactions, see Morrison, in Feuer *The Chemistry of the Nitro and Nitroso Groups*, pt. 1; Wiley: New York, 1969, pp. 165-213, 185-191. For a review of photochemical rearrangements of benzene derivatives, see Kaupp *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 243-275 [*Angew. Chem.* *92*, 245-276]. See also Yip; Sharma *Res. Chem. Intermed.* **1989**, *11*, 109.

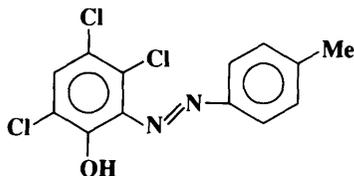
Category 4. Photoisomerization. The most common reaction in this category is photochemical *cis*–*trans* isomerization.⁴⁴ For example, *cis*-stilbene can be converted to the *trans* isomer:



The isomerization takes place because the excited states, both S_1 and T_1 , of many olefins have a perpendicular instead of a planar geometry (p. 236), so *cis*–*trans* isomerism disappears upon excitation. When the excited molecule drops back to the S_0 state, either isomer can be formed. A useful example is the photochemical conversion of *cis*-cyclooctene to the much less stable *trans* isomer.⁴⁵ Another interesting example of this isomerization involves azo crown ethers. The crown ether **5**, in which the $N=N$ bond is *anti*, preferentially binds NH_4^+ , Li^+ , and Na^+ , but the *syn* isomer preferentially binds K^+ and Rb^+ (see p. 83). Thus,



5



6

ions can be selectively put in or taken out of solution merely by turning a light source on or off.⁴⁶

In another example, the *trans* azo compound **6** is converted to its *cis* isomer when exposed to light. In this case⁴⁷ the *cis* isomer is a stronger acid than the *trans*. The *trans* isomer is dissolved in a system containing a base, wherein a liquid membrane separates two sides, one of which is illuminated, the other kept dark. On the illuminated side, the light converts the *trans* isomer to the *cis*. The *cis* isomer, being a stronger acid, donates its proton to the base, converting *cis* $ArOH$ to *cis* ArO^- . This ion migrates to the dark side, where it rapidly reverts to the *trans* ion, which reacquires a proton. Because each cycle forms one H_3O^+ ion in the illuminated compartment and one OH^- ion in the dark compartment, the process

⁴⁴For reviews of *cis*–*trans* isomerizations, see Sonnet *Tetrahedron* **1980**, 36, 557-604; Schulte-Frohlinde; Görner *Pure Appl. Chem.* **1979**, 51, 279-297; Saltiel; Charlton, in de Mayo, Ref. 37, pp. 25-89; Saltiel; Chang; Megarity; Rousseau; Shannon; Thomas; Uriarte *Pure Appl. Chem.* **1975**, 41, 559-579; Saltiel; D'Agostino; Megarity; Metts; Neuberger; Wrighton; Zafiriou *Org. Photochem.* **1979**, 3, 1-113. For reviews of the photochemistry of alkenes, see Leigh; Srinivasan *Acc. Chem. Res.* **1987**, 20, 107-114; Steinmetz *Org. Photochem.* **1987**, 8, 67-158; Adam; Oppenländer, Ref. 36; Mattes; Farid *Org. Photochem.* **1984**, 6, 233-326; Kropp *Org. Photochem.* **1979**, 4, 1-142; Morrison *Org. Photochem.* **1979**, 4, 143-190; Kaupp *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 150-168 [*Angew. Chem.* **90**, 161-179]. For a review of the photochemistry of allenes and cumulenes, see Johnson *Org. Photochem.* **1985**, 7, 75-147.

⁴⁵For a review of the photoisomerization of stilbenes, see Waldeck *Chem. Rev.* **1991**, 91, 415-436.

⁴⁶Deyrup; Betkouski *J. Org. Chem.* **1972**, 37, 3561.

⁴⁷Shinkai; Nakaji; Nishida; Ogawa; Manabe *J. Am. Chem. Soc.* **1980**, 102, 5860. See also Iric; Kato *J. Am. Chem. Soc.* **1985**, 107, 1024; Shinkai; Miyazaki; Manabe *J. Chem. Soc., Perkin Trans. 1* **1987**, 449; Shinkai; Yoshida; Manabe; Fuchita *J. Chem. Soc., Perkin Trans. 1* **1988**, 1431; Akabori; Kumagai; Habata; Sato *J. Chem. Soc., Perkin Trans. 1* **1989**, 1497; Shinkai; Yoshioka; Nakayama; Manabe *J. Chem. Soc., Perkin Trans. 2* **1990**, 1905. For a review, see Shinkai; Manabe *Top. Curr. Chem.* **1984**, 121, 67-104.

⁴⁸Haberfeld *J. Am. Chem. Soc.* **1987**, 109, 6177.

In choosing a photosensitizer one should avoid a compound that absorbs in the same region as the acceptor because the latter will then compete for the light.²⁸ For examples of the use of photosensitization to accomplish reactions, see 5-37, 5-49.

The Fate of the Excited Molecule: Chemical Processes

Although both excited singlet and triplet species can undergo chemical reactions, they are much more common for triplets, simply because these generally have much longer lifetimes. Excited singlet species, in most cases, have a lifetime of less than 10^{-10} sec and undergo one of the physical processes already discussed before they have a chance to react chemically. Therefore, photochemistry is largely the chemistry of triplet states.²⁹ Table 7.5³⁰ lists many of the possible chemical pathways that can be taken by an excited molecule.³¹ The first four of these are unimolecular reactions; the others are bimolecular. In the case of bimolecular reactions it is rare for two excited molecules to react with each other (because the concentration of excited molecules at any one time is generally low); reactions are between an excited molecule and an unexcited molecule of either the same or another species. The reactions listed in Table 7.5 are primary processes. Secondary reactions often follow, since the primary products are frequently radicals or carbenes; even if they are ordinary molecules, they are often in upper vibrational levels and so have excess energy. In almost all cases the primary products of photochemical reactions are in their ground states, though exceptions are known.³² Of the reactions listed in Table 7.5, the most common are cleavage into radicals (1), decomposition into molecules (2), and (in the presence of a suitable acceptor molecule) photosensitization (7), which we have already discussed. The following are some specific examples of reaction categories (1) to (6). Other examples are discussed in Part 2 of this book.³³

TABLE 7.5 Primary photochemical reactions of an excited molecule **A—B—C**³⁰
Examples are given in the text; the most common are (1), (2), and, in the presence of a suitable acceptor molecule, (7)

$(A-B-C) \longrightarrow A-B\cdot + C\cdot$	Simple cleavage into radicals	(1)
$(A-B-C) \longrightarrow E + F$	Decomposition into molecules	(2)
$(A-B-C) \longrightarrow A-C-B$	Intramolecular rearrangement	(3)
$(A-B-C) \longrightarrow A-B-C'$	Photoisomerization	(4)
$(A-B-C) \xrightarrow{RH} A-B-C-H + R\cdot$	Hydrogen-atom abstraction	(5)
$(A-B-C) \longrightarrow (ABC)_2$	Photodimerization	(6)
$(A-B-C) \xrightarrow{A} ABC + A^*$	Photosensitization	(7)

²⁸For a review of other complications that can take place in photosensitized reactions, see Engel; Monroe *Adv. Photochem.* **1971**, *8*, 245-313.

²⁹For a review of the chemical reactions of triplet states, see Wagner; Hammond, Ref. 22. For other reviews of triplet states, see *Top. Curr. Chem.*, **1975**, vols. 54 and 55.

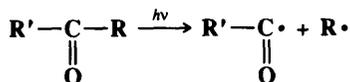
³⁰Adapted from Calvert; Pitts, Ref. 1, p. 367.

³¹For a different kind of classification of photochemical reactions, see Dauben; Salem; Turro *Acc. Chem. Res.* **1975**, *8*, 41. For reviews of photochemical reactions where the molecules are geometrically constrained, see Ramamurthy *Tetrahedron* **1986**, *42*, 5753-5839; Ramamurthy; Eaton *Acc. Chem. Res.* **1988**, *21*, 300-306; Turro; Cox; Paczkowski *Top. Curr. Chem.* **1985**, *129*, 57-97.

³²Turro; Lechtken; Lyons; Hautala; Carnahan; Katz *J. Am. Chem. Soc.* **1973**, *95*, 2035.

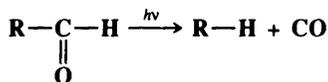
³³For monographs on the use of photochemistry for synthesis, see Ninomiya; Naito *Photochemical Synthesis*; Academic Press: New York, 1989; Coyle *Photochemistry in Organic Synthesis*; Royal Society of Chemistry: London, 1986; Schönberg *Preparative Organic Photochemistry*; Springer: Berlin, 1968.

*Category 1. Simple cleavage into radicals.*³⁴ Aldehydes and ketones absorb in the 230 to 330 nm region. This is assumed to result from an $n \rightarrow \pi^*$ singlet-singlet transition. The excited aldehyde or ketone can then cleave.³⁵

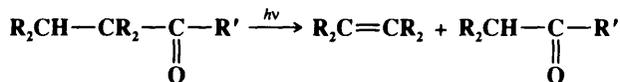


When applied to ketones, this is called *Norrish Type I cleavage* or often just *Type I cleavage*. In a secondary process, the acyl radical $\text{R}'-\text{CO}\cdot$ can then lose CO to give $\text{R}'\cdot$ radicals. Another example of a category 1 process is cleavage of Cl_2 to give two Cl atoms. Other bonds that are easily cleaved by photolysis are the O—O bonds of peroxy compounds and the C—N bonds of aliphatic azo compounds $\text{R}-\text{N}=\text{N}-\text{R}$.³⁶ The latter is an important source of radicals $\text{R}\cdot$, since the other product is the very stable N_2 .

Category 2. Decomposition into molecules. Aldehydes (though not generally ketones) can also cleave in this manner:



This is an extrusion reaction (see Chapter 17). In another example of a process in category 2, aldehydes and ketones with a γ hydrogen can cleave in still another way (a β elimination, see Chapter 17):



This reaction, called *Norrish Type II cleavage*,³⁷ involves intramolecular abstraction of the γ hydrogen followed by cleavage of the resulting diradical³⁸ (a secondary reaction) to give an enol that tautomerizes to the aldehyde or ketone product.³⁹

³⁴For reviews, see Jackson; Okabe *Adv. Photochem.* **1986**, *13*, 1-94; Kresin; Lester *Adv. Photochem.* **1986**, *13*, 95-163.

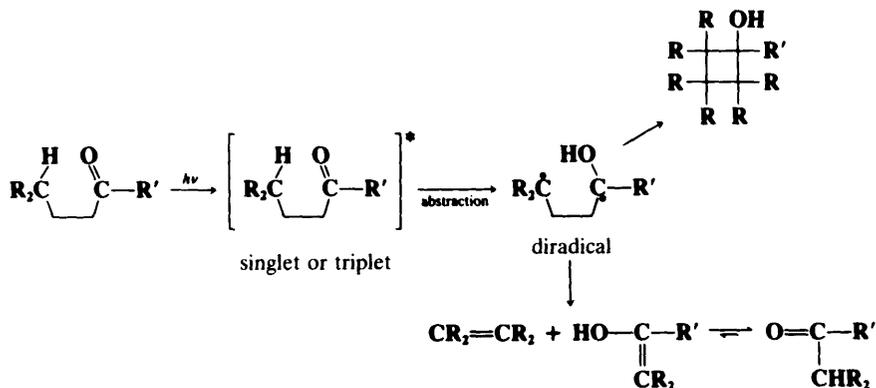
³⁵For full discussions of aldehyde and ketone photochemistry, see Formosinho; Arnaut *Adv. Photochem.* **1991**, *16*, 67-117; Newton, in Coyle, Ref. 33, pp. 39-60; Lee; Lewis *Adv. Photochem.* **1980**, *12*, 1-96; Calvert; Pitts, Ref. 1, pp. 368-427; Coyle; Carless *Chem. Soc. Rev.* **1972**, *1*, 465-480; Pitts; Wan, in Patai *The Chemistry of the Carbonyl Group*; Wiley: New York, 1966, pp. 823-916; Dalton; Turro *Annu. Rev. Phys. Chem.* **1970**, *21*, 499-560; Bérces, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 5; Elsevier: New York, 1972, pp. 277-380; Turro; Dalton; Dawes; Farrington; Hautala; Morton; Niemczyk; Shore *Acc. Chem. Res.* **1972**, *5*, 92-101; Wagner *Top. Curr. Chem.* **1976**, *66*, 1-52; Wagner; Hammond, Ref. 22, pp. 87-129. For reviews of the photochemistry of cyclic ketones, see Weiss *Org. Photochem.* **1981**, *5*, 347-420; Chapman; Weiss *Org. Photochem.* **1973**, *3*, 197-288; Morton; Turro *Adv. Photochem.* **1974**, *9*, 197-309. For reviews of the photochemistry of α -diketones, see Rubin *Top. Curr. Chem.* **1985**, *129*, 1-56. **1969**, *13*, 251-306; Monroe *Adv. Photochem.* **1971**, *8*, 77-108. For a review of the photochemistry of protonated unsaturated carbonyl compounds, see Childs *Rev. Chem. Intermed.* **1980**, *3*, 285-314. For reviews of the photochemistry of C=S compounds, see Coyle *Tetrahedron* **1985**, *41*, 5393-5425; Ramamurthy *Org. Photochem.* **1985**, *7*, 231-338. For a review of the chemistry of C=N compounds, see Mariano *Org. Photochem.* **1987**, *9*, 1-128.

³⁶For reviews of the photochemistry of azo compounds, see Adam; Oppenländer *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 661-672 [*Angew. Chem.* **98**, 659-670]; Dürr; Ruge *Top. Curr. Chem.* **1976**, *66*, 53-87; Drewer, in Patai *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2; Wiley: New York, 1975, pp. 935-1015.

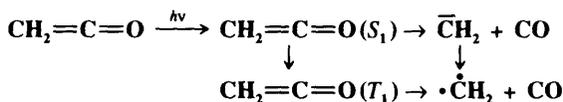
³⁷For thorough discussions of the mechanism, see Wagner, in de Mayo *Rearrangements in Ground and Excited States*, vol. 3; Academic Press: New York, 1980, pp. 381-444. *Acc. Chem. Res.* **1971**, *4*, 168-177; Dalton; Turro, Ref. 35, pp. 526-538.

³⁸For reviews of the diradicals produced in this reaction, see Wilson *Org. Photochem.* **1985**, *7*, 339-466, pp. 349-373; Scaiano; Lissi; Encina *Rev. Chem. Intermed.* **1978**, *2*, 139-196. For a review of a similar process, where δ hydrogens are abstracted, see Wagner *Acc. Chem. Res.* **1989**, *22*, 83-91.

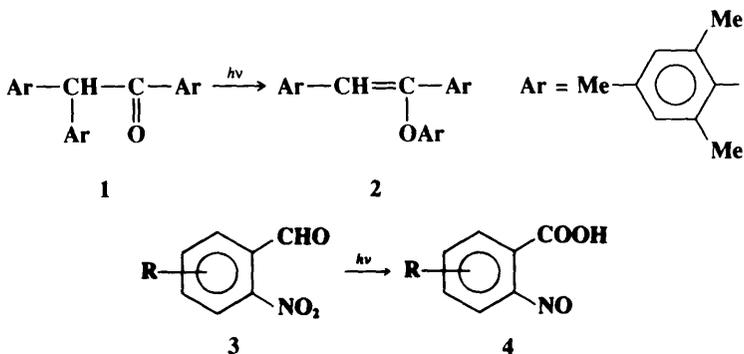
³⁹This mechanism was proposed by Yang; Yang *J. Am. Chem. Soc.* **1958**, *80*, 2913. Among the evidence for this mechanism is the fact that the diradical intermediate has been trapped; Wagner; Zepp *J. Am. Chem. Soc.* **1972**, *94*, 287; Wagner; Kelso; Zepp *J. Am. Chem. Soc.* **1972**, *94*, 7480; Adam; Grabowski; Wilson *Chem. Ber.* **1989**, *122*, 561. See also Caldwell; Dhawan; Moore *J. Am. Chem. Soc.* **1985**, *107*, 5163.



Both singlet and triplet n, π^* states undergo the reaction.⁴⁰ The intermediate diradical can also cyclize to a cyclobutanone, which is often a side product. Carboxylic esters, anhydrides, and other carbonyl compounds can also give this reaction.⁴¹ The photolysis of ketene to CH_2 (p. 199) is still another example of a reaction in category 2. Both singlet and triplet CH_2 are generated, the latter in two ways:



Category 3. Intramolecular rearrangement. Two examples are the rearrangement of the trimesityl compound **1** to the enol ether **2**,⁴² and irradiation of *o*-nitrobenzaldehydes **3** to give *o*-nitrosobenzoic acids **4**.⁴³



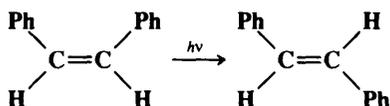
⁴⁰Wagner; Hammond *J. Am. Chem. Soc.* **1965**, *87*, 4009; Dougherty *J. Am. Chem. Soc.* **1965**, *87*, 4011; Ausloos; Rebbert *J. Am. Chem. Soc.* **1964**, *86*, 4512; Casey; Boggs *J. Am. Chem. Soc.* **1972**, *94*, 6457.

⁴¹For a review of the photochemistry of carboxylic acids and acid derivatives, see Givens; Levi, in Patai *The Chemistry of Acid Derivatives*, pt. 1; Wiley: New York, 1979, pp. 641-753.

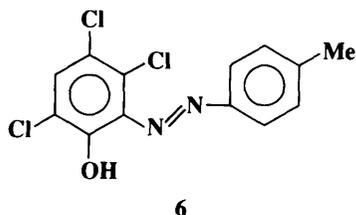
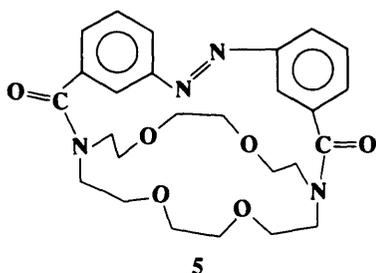
⁴²Hart; Lin *Tetrahedron Lett.* **1985**, *26*, 575; Wagner; Zhou *J. Am. Chem. Soc.* **1988**, *110*, 611.

⁴³For a review of this and closely related reactions, see Morrison, in Feuer *The Chemistry of the Nitro and Nitroso Groups*, pt. 1; Wiley: New York, 1969, pp. 165-213, 185-191. For a review of photochemical rearrangements of benzene derivatives, see Kaupp *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 243-275 [*Angew. Chem.* *92*, 245-276]. See also Yip; Sharma *Res. Chem. Intermed.* **1989**, *11*, 109.

Category 4. Photoisomerization. The most common reaction in this category is photochemical *cis*–*trans* isomerization.⁴⁴ For example, *cis*-stilbene can be converted to the *trans* isomer:



The isomerization takes place because the excited states, both S_1 and T_1 , of many olefins have a perpendicular instead of a planar geometry (p. 236), so *cis*–*trans* isomerism disappears upon excitation. When the excited molecule drops back to the S_0 state, either isomer can be formed. A useful example is the photochemical conversion of *cis*-cyclooctene to the much less stable *trans* isomer.⁴⁵ Another interesting example of this isomerization involves azo crown ethers. The crown ether **5**, in which the $N=N$ bond is *anti*, preferentially binds NH_4^+ , Li^+ , and Na^+ , but the *syn* isomer preferentially binds K^+ and Rb^+ (see p. 83). Thus,



ions can be selectively put in or taken out of solution merely by turning a light source on or off.⁴⁶

In another example, the *trans* azo compound **6** is converted to its *cis* isomer when exposed to light. In this case⁴⁷ the *cis* isomer is a stronger acid than the *trans*. The *trans* isomer is dissolved in a system containing a base, wherein a liquid membrane separates two sides, one of which is illuminated, the other kept dark. On the illuminated side, the light converts the *trans* isomer to the *cis*. The *cis* isomer, being a stronger acid, donates its proton to the base, converting *cis* $ArOH$ to *cis* ArO^- . This ion migrates to the dark side, where it rapidly reverts to the *trans* ion, which reacquires a proton. Because each cycle forms one H_3O^+ ion in the illuminated compartment and one OH^- ion in the dark compartment, the process

⁴⁴For reviews of *cis*–*trans* isomerizations, see Sonnet *Tetrahedron* **1980**, 36, 557-604; Schulte-Frohlinde; Görner *Pure Appl. Chem.* **1979**, 51, 279-297; Saltiel; Charlton, in de Mayo, Ref. 37, pp. 25-89; Saltiel; Chang; Megarity; Rousseau; Shannon; Thomas; Uriarte *Pure Appl. Chem.* **1975**, 41, 559-579; Saltiel; D'Agostino; Megarity; Metts; Neuberger; Wrighton; Zafiriou *Org. Photochem.* **1979**, 3, 1-113. For reviews of the photochemistry of alkenes, see Leigh; Srinivasan *Acc. Chem. Res.* **1987**, 20, 107-114; Steinmetz *Org. Photochem.* **1987**, 8, 67-158; Adam; Oppenländer, Ref. 36; Mattes; Farid *Org. Photochem.* **1984**, 6, 233-326; Kropp *Org. Photochem.* **1979**, 4, 1-142; Morrison *Org. Photochem.* **1979**, 4, 143-190; Kaupp *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 150-168 [*Angew. Chem.* **90**, 161-179]. For a review of the photochemistry of allenes and cumulenes, see Johnson *Org. Photochem.* **1985**, 7, 75-147.

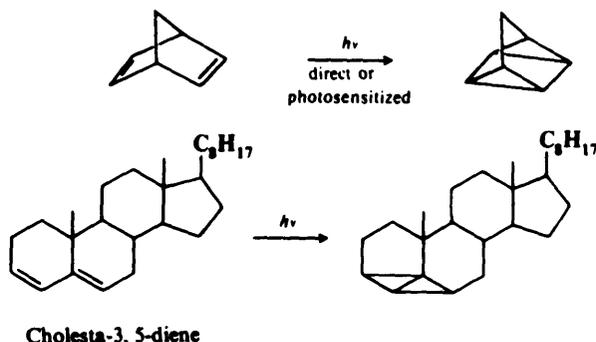
⁴⁵For a review of the photoisomerization of stilbenes, see Waldeck *Chem. Rev.* **1991**, 91, 415-436.

⁴⁶Deyrup; Betkouski *J. Org. Chem.* **1972**, 37, 3561.

⁴⁷Shinkai; Nakaji; Nishida; Ogawa; Manabe *J. Am. Chem. Soc.* **1980**, 102, 5860. See also Iric; Kato *J. Am. Chem. Soc.* **1985**, 107, 1024; Shinkai; Miyazaki; Manabe *J. Chem. Soc., Perkin Trans. 1* **1987**, 449; Shinkai; Yoshida; Manabe; Fuchita *J. Chem. Soc., Perkin Trans. 1* **1988**, 1431; Akabori; Kumagai; Habata; Sato *J. Chem. Soc., Perkin Trans. 1* **1989**, 1497; Shinkai; Yoshioka; Nakayama; Manabe *J. Chem. Soc., Perkin Trans. 2* **1990**, 1905. For a review, see Shinkai; Manabe *Top. Curr. Chem.* **1984**, 121, 67-104.

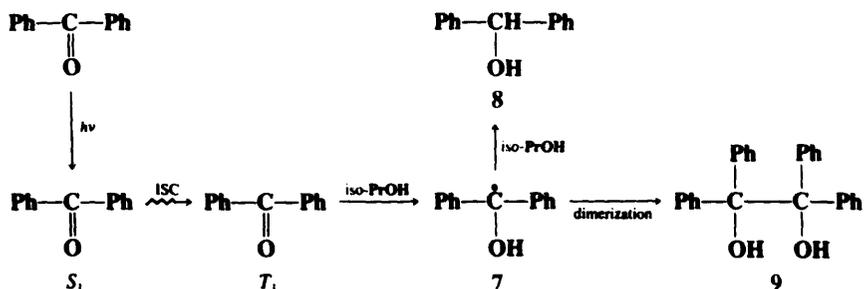
⁴⁸Haberfeld *J. Am. Chem. Soc.* **1987**, 109, 6177.

reverses the normal reaction whereby these ions neutralize each other.⁴⁸ Thus the energy of light is used to do chemical work.⁴⁹ Two other examples of category 4 reactions are⁴⁴



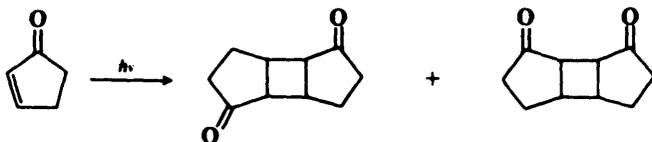
These examples illustrate that the use of photochemical reactions can make it very easy to obtain compounds that would be difficult to get in other ways. Reactions similar to these are discussed at 5-49.

Category 5. Hydrogen atom abstraction. When benzophenone is irradiated in isopropyl alcohol, the initially formed S_1 state crosses to the T_1 state, which abstracts hydrogen from the solvent to give the radical **7**. **7** then abstracts another hydrogen to give benzhydrol (**8**) or dimerizes to benzpinacol (**9**):



An example of intramolecular abstraction has already been given (p. 243).

Category 6. Photodimerization. An example is dimerization of cyclopentenone:⁵¹



See 5-49 for a discussion of this and similar reactions.

⁴⁸Haberfield *J. Am. Chem. Soc.* **1987**, *109*, 6178.

⁴⁹For a review of instances where macrocycles change in response to changes in light, pH, temperature, etc., see Beer *Chem. Soc. Rev.* **1989**, *18*, 409-450. For an example not involving a macrocycle, see Feringa; Jager; de Lange; Meijer *J. Am. Chem. Soc.* **1991**, *113*, 5468.

⁵⁰Hammond; Turro; Fischer *J. Am. Chem. Soc.* **1961**, *83*, 4674; Dauben; Cargill *Tetrahedron* **1961**, *15*, 197; Dauben; Wipke *Pure Appl. Chem.* **1964**, *9*, 539.

⁵¹Eaton *J. Am. Chem. Soc.* **1962**, *84*, 2344, 2454, *Acc. Chem. Res.* **1968**, *1*, 50. For a review of the photochemistry of α,β -unsaturated ketones, see Schuster, in Patai; Rappoport *The Chemistry of Enones*, pt. 2; Wiley: New York, 1989, pp. 623-756.

The Determination of Photochemical Mechanisms⁵²

The methods used for the determination of photochemical mechanisms are largely the same as those used for organic mechanisms in general (Chapter 6): product identification, isotopic tracing, the detection and trapping of intermediates, and kinetics. There are, however, a few new factors: (1) there are generally many products in a photochemical reaction, as many as 10 or 15; (2) in measuring kinetics, there are more variables, since we can study the effect on the rate of the intensity or the wavelength of light; (3) in the detection of intermediates by spectra we can use the technique of *flash photolysis*, which can detect extremely short-lived intermediates.

In addition to these methods, there are two additional techniques.

1. The use of emission (fluorescence and phosphorescence) as well as absorption spectroscopy. From these spectra the presence of as well as the energy and lifetime of singlet and triplet excited states can often be calculated.

2. The study of quantum yields. The *quantum yield* is the fraction of absorbed light that goes to produce a particular result. There are several types. A *primary quantum yield* for a particular process is the fraction of molecules absorbing light that undergo that particular process. Thus, if 10% of all the molecules that are excited to the S_1 state cross over to the T_1 state, the primary quantum yield for that process is 0.10. However, primary quantum yields are often difficult to measure. A *product quantum yield* (usually designated Φ) for a product P that is formed from a photoreaction of an initially excited molecule A can be expressed as

$$\Phi = \frac{\text{number of molecules of P formed}}{\text{number of quanta absorbed by A}}$$

Product quantum yields are much easier to measure. The number of quanta absorbed can be determined by an instrument called an *actinometer*, which is actually a standard photochemical system whose quantum yield is known. An example of the information that can be learned from quantum yields is the following. If the quantum yield of a product is finite and invariant with changes in experimental conditions, it is likely that the product is formed in a primary rate-determining process. Another example: in some reactions, the product quantum yields are found to be well over 1 (perhaps as high as 1000). Such a finding indicates a chain reaction (see p. 678 for a discussion of chain reactions).

⁵²For a review, see Calvert; Pitts, Ref. 1, pp. 580-670.

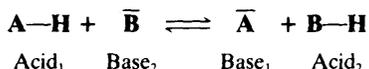
8

ACIDS AND BASES

Two acid-base theories are used in organic chemistry today—the Brønsted theory and the Lewis theory.¹ These theories are quite compatible and are used for different purposes.²

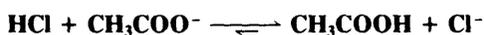
Brønsted Theory

According to this theory, an acid is defined as a *proton donor*³ and a base as a *proton acceptor* (a base must have a pair of electrons available to share with the proton; this is usually present as an unshared pair, but sometimes is in a π orbital). An acid-base reaction is simply the transfer of a proton from an acid to a base. (Protons do not exist free in solution but must be attached to an electron pair). When the acid gives up a proton, the species remaining still retains the electron pair to which the proton was formerly attached. Thus the new species, in theory at least, can reacquire a proton and is therefore a base. It is referred to as the *conjugate base* of the acid. All acids have a conjugate base, and all bases have a *conjugate acid*. All acid-base reactions fit the equation



No charges are shown in this equation, but an acid always has a charge one positive unit higher than that of its conjugate base.

Acid strength may be defined as the tendency to give up a proton and *base strength* as the tendency to accept a proton. Acid–base reactions occur because acids are not equally strong. If an acid, say HCl, is placed in contact with the conjugate base of a weaker acid, say acetate ion, the proton will be transferred because the HCl has a greater tendency to lose its proton than acetic acid. That is, the equilibrium



lies well to the right. On the other hand, treatment of acetic acid with chloride ion gives essentially no reaction, since the weaker acid already has the proton.

This is always the case for any two acids, and by measuring the positions of the equilibrium the relative strengths of acids and bases can be determined.⁴ Of course, if the two acids involved are close to each other in strength, a measurable reaction will occur from both sides, though the position of equilibrium will still be over to the side of the weaker acid

¹For monographs on acids and bases, see Stewart *The Proton: Applications to Organic Chemistry*; Academic Press: New York, 1985; Bell *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973; Finston; Rychman *A New View of Current Acid–Base Theories*; Wiley: New York, 1982.

²For discussion of the historical development of acid–base theory, see Bell *Q. Rev., Chem. Soc.* **1947**, *1*, 113–125; Bell *The Proton in Chemistry*, 1st ed.; Cornell University Press: Ithaca, NY, 1959, pp. 7–17.

³According to IUPAC terminology (Bunnett; Jones *Pure Appl. Chem.* **1988**, *60*, 1115), an acid is a *hydron* donor. IUPAC recommends that the term *proton* be restricted to the nucleus of the hydrogen isotope of mass 1, while the nucleus of the naturally occurring element (which contains about 0.015% deuterium) be called the *hydron* (the nucleus of mass 2 has always been known as the *deuteron*). This accords with the naturally-occurring negative ion, which has long been called the *hydride* ion. In this book, however, we will continue to use *proton* for the naturally occurring form, because most of the literature uses this term.

⁴Although equilibrium is reached in most acid–base reactions extremely rapidly (see p. 254), some are slow (especially those in which the proton is given up by a carbon) and in these cases time must be allowed for the system to come to equilibrium.

(unless the acidities are equal within experimental limits). In this manner it is possible to construct a table in which acids are listed in order of acid strength (Table 8.1).⁵ Next to each acid in Table 8.1 is shown its conjugate base. It is obvious that if the acids in such a table are listed in *decreasing* order of acid strength, the bases must be listed in *increasing* order of base strength, since the stronger the acid, the weaker must be its conjugate base. The pK_a values in Table 8.1 are most accurate in the middle of the table. They are much harder to measure⁶ for very strong and very weak acids, and these values must be regarded as approximate. Qualitatively, it can be determined that HClO_4 is a stronger acid than H_2SO_4 , since a mixture of HClO_4 and H_2SO_4 in 4-methyl-2-pentanone can be titrated to an HClO_4 end point without interference by H_2SO_4 .⁷ Similarly, HClO_4 can be shown to be stronger than HNO_3 or HCl . However, this is not quantitative, and the value of -10 in the table is not much more than an educated guess. The values for RNO_2H^+ , ArNO_2H^+ , HI , RCNH^+ and RSH_2^+ must also be regarded as highly speculative.⁸ A wide variety of pK_a values has been reported for the conjugate acids of even such simple bases as acetone⁹ (-0.24 to -7.2), diethyl ether (-0.30 to -6.2), ethanol (-0.33 to -4.8), methanol (-0.34 to -4.9), and 2-propanol (-0.35 to -5.2), depending on the method used to measure them.¹⁰ Very accurate values can be obtained only for acids weaker than hydronium ion and stronger than water.

The bottom portion of Table 8.1 consists of very weak acids¹¹ (pK_a above ~ 17). In most of these acids, the proton is lost from a carbon atom, and such acids are known as *carbon acids*. pK_a values for such weak acids are often difficult to measure and are known only approximately. The methods used to determine the relative positions of these acids are discussed in Chapter 5.¹² The acidity of carbon acids is proportional to the stability of the carbanions that are their conjugate bases (see p. 175).

The extremely strong acids at the top of the table are known as *super acids* (see p. 166).¹³ The actual species present in the $\text{FSO}_3\text{H-SbF}_5$ mixture are probably $\text{H}[\text{SbF}_5(\text{SO}_3\text{F})]$ and $\text{H}[\text{SbF}_2(\text{SO}_3\text{F})_4]$.¹⁴ The addition of SO_3 causes formation of the still stronger $\text{H}[\text{SbF}_4(\text{SO}_3\text{F})_2]$, $\text{H}[\text{SbF}_3(\text{SO}_3\text{F})_3]$, and $\text{H}[(\text{SbF}_5)_2(\text{SO}_3\text{F})]$.¹⁴

By the use of tables such as Table 8.1, it is possible to determine whether a given acid will react with a given base. For tables in which acids are listed in order of decreasing strength, the rule is that *any acid will react with any base in the table that is below it but not with any above it*.¹⁵ It must be emphasized that the order of acid strength in Table 8.1 applies

⁵Table 8.1 is a thermodynamic acidity scale and applies only to positions of equilibria. For the distinction between thermodynamic and kinetic acidity, see p. 176.

⁶For a review of methods of determining pK_a values, see Cookson *Chem. Rev.* **1974**, *74*, 5-28.

⁷Kolthoff; Bruckenstein, in Kolthoff; Elving *Treatise on Analytical Chemistry*, vol. 1, pt. 1; Wiley: New York, 1959, pp. 475-542, p. 479.

⁸For reviews of organic compounds protonated at O, N, or S, see Olah; White; O'Brien *Chem. Rev.* **1970**, *70*, 561-591; Olah; White; O'Brien, in Olah; Schleyer *Carbonium Ions*, vol. 4; Wiley: New York, 1973, pp. 1697-1781.

⁹For discussions of pK_a determinations for the conjugate acids of ketones, see Bagno; Lucchini; Scorrano *Bull. Soc. Chim. Fr.* **1987**, 563; Touleec *Tetrahedron Lett.* **1988**, *29*, 5541.

¹⁰Rochester *Acidity Functions*; Academic Press: New York, 1970. For discussion of the basicity of such compounds, see Liler *Reaction Mechanisms in Sulfuric Acid*; Academic Press: New York, 1971, pp. 118-139.

¹¹For a monograph on very weak acids, see Reutov; Beletskaya; Butin *CH-Acids*; Pergamon: New York, 1978. For other discussions, see Cram *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965, pp. 1-45; Streitwieser; Hammons *Prog. Phys. Org. Chem.* **1965**, *3*, 41-80.

¹²For reviews of methods used to measure the acidity of carbon acids, see Jones *Q. Rev., Chem. Soc.* **1971**, *25*, 365-378; Fischer; Rewicki *Prog. Org. Chem.* **1968**, *7*, 116-161; Reutov; Beletskaya; Butin, Ref. 11, Chapter 1 [an earlier version of this chapter appeared in *Russ. Chem. Rev.* **1974**, *43*, 17-31]; Ref. 6. For reviews on acidities of carbon acids, see Gau; Assadourian; Veracini *Prog. Phys. Org. Chem.* **1987**, *16*, 237-285; in Buncl; Durst *Comprehensive Carbanion Chemistry*, pt. A; Elsevier: New York, 1980, the reviews by Pellerite; Brauman, pp. 55-96 (gas phase acidities); and Streitwieser; Juaristi; Nebenzahl, pp. 323-381.

¹³For a monograph, see Olah; Prakash; Sommer *Superacids*; Wiley: New York, 1985. For a review, see Gillespie; Pcel *Adv. Phys. Org. Chem.* **1971**, *9*, 1-24. For a review of solid superacids, see Arata *Adv. Catal.* **1990**, *37*, 165-211. For a review of methods of measuring superacidity, see Jost; Sommer *Chem. Intermed.* **1988**, *9*, 171-199.

¹⁴Gillespie *Acc. Chem. Res.* **1968**, *1*, 202-209.

¹⁵These reactions are equilibria. What the rule actually says is that the position of equilibrium will be such that the weaker acid predominates. However, this needs to be taken into account only when the acid and base are close to each other in the table (within about 2 pK units).

TABLE 8.1 pK_a values for many types of acids

The values in boldface are exact values; the others are approximate, especially above 18 and below -2^6

Acid	Base	Approximate pK_a (relative to water)	Ref.
Super acids:			
HF-SbF₅	SbF₆⁻		19
FSO₃H-SbF₅-SO₃			14
FSO₃H-SbF₅			14, 19
FSO₃H	FSO₃⁻		14
RNO₂H⁺	RNO₂	-12	20
ArNO₂H⁺	ArNO₂	-11	20
HClO₄	ClO₄⁻	-10	21
HI	I⁻	-10	21
RCNH⁺	RCN	-10	22
R-C-H OH⁺	R-C-H O	-10	23
H₂SO₄	HSO₄⁻		
HBr	Br⁻	-9	21
Ar-C-OR¹⁷ OH⁺	Ar-C-OR O	-7.4	20
HCl	Cl⁻	-7	21
RSH₂⁺	RSH	-7	20
Ar-C-OH¹⁷ OH⁺	Ar-C-OH O	-7	24
Ar-C-H OH⁺	Ar-C-H O	-7	25
R-C-R OH⁺	R-C-R O	-7	9, 22, 26
ArSO₃H	ArSO₃⁻	-6.5	27
R-C-OR¹⁷ OH⁺	R-C-OR O	-6.5	20
ArOH₂⁺	ArOH	-6.4	28
R-C-OH¹⁷ OH⁺	R-C-OH O	-6	20
Ar-C-R OH⁺	Ar-C-R O	-6	25, 29
Ar-O⁺-R H	Ar-O-R	-6	28, 30
CH(CN)₃	⁻C(CN)₃	-5	31
Ar₃NH⁺	Ar₃N	-5	32
H-C-H OH⁺	H-C-H O	-4	33
R-O⁺-R H	R-O-R	-3.5	22, 30, 34
R₂COH₂⁺	R₂COH	-2	34
R₂CHOH₂⁺	R₂CHOH	-2	34, 35
RCH₂OH₂⁺	RCH₂OH	-2	22, 34, 35
H₃O⁺	H₂O	-1.74	36

TABLE 8.1 (Continued)

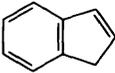
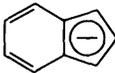
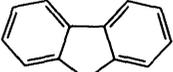
Acid	Base	Approximate pK_a (relative to water)	Ref.
$\text{Ar}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}_2^+$	$\text{Ar}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}_2$	-1.5	37
HNO_3	NO_3^-	-1.4	21
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}_2^+$	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}_2$	-0.5	37
Ar_2NH_2^+	Ar_2NH	1	32
HSO_4^-	SO_4^{2-}	1.99	38
HF	F^-	3.17	38
HONO	NO_2^-	3.29	38
ArNH_3^+	ArNH_2	3-5	39
ArNR_2H^+	ArNR_2	3-5	39
RCOOH	RCOO^-	4-5	39
HCOCH_2CHO	HCO^-CHCHO	5	40
$\text{H}_2\text{CO}_3^{\text{M}}$	HCO_3^-	6.35	38
H_2S	HS^-	7.00	38
ArSH	ArS^-	6-8	41
$\text{CH}_3\text{COCH}_2\text{COCH}_3$	$\text{CH}_3\text{CO}^-\text{CHCOCH}_3$	9	40
HCN	CN^-	9.2	42
NH_4^+	NH_3	9.24	38
ArOH	ArO^-	8-11	43
RCH_2NO_2	RCH^-NO_2	10	44
R_3NH^+	R_3N	10-11	39
RNH_3^+	RNH_2	10-11	39
HCO_3^-	CO_3^{2-}	10.33	38
RSH	RS^-	10-11	41
R_2NH_2^+	R_2NH	11	39
NCCH_2CN	NC^-CHCN	11	40, 45
$\text{CH}_3\text{COCH}_2\text{COOR}$	$\text{CH}_3\text{CO}^-\text{CHCOOR}$	11	40
$\text{CH}_3\text{SO}_2\text{CH}_2\text{SO}_2\text{CH}_3$	$\text{CH}_3\text{SO}_2\text{CH}^-\text{SO}_2\text{CH}_3$	12.5	46
$\text{EtOOCCH}_2\text{COOEt}$	$\text{EtOOC}^-\text{CHCOOEt}$	13	40
CH_3OH	CH_3O^-	15.2	47, 48
H_2O	OH^-	15.74	49
		16	50
RCH_2OH	RCH_2O^-	16	47
RCH_2CHO	RCH^-CHO	16	51
R_3CHOH	R_3CHO^-	16.5	47
R_3COH	R_3CO^-	17	47
RCONH_2	RCONH^-	17	52
RCOCH_2R	RCO^-CHR	19-20	53
		20	54, 55
		23	54, 55
ROOCCH_2R	ROOC^-CHR	24.5	40

TABLE 8.1 (Continued)

Acid	Base	Approximate pK_a (relative to water)	Ref.
RCH_2CN	$R\overset{\ominus}{C}HCN$	25	40, 56
$HC\equiv CH$	$HC\equiv C^-$	25	57
Ar_3CH	Ar_3C^-	31.5	54, 58
Ar_2CH_2	Ar_2CH^-	33.5	54, 58
H_2	H^-	35	59
NH_3	NH_2^-	38	60
$PhCH_3$	$PhCH_2^-$	40	61
$CH_2=CHCH_3$	$[CH_2=CH=CH_2]^-$	43	62
PhH	Ph^-	43	63
$CH_2=CH_2$	$CH_2=CH^-$	44	64
cyclo- C_3H_6	cyclo- $C_3H_5^-$	46	65
CH_4	CH_3^-	48	66
C_2H_6	$C_2H_5^-$	50	67
$(CH_3)_2CH_2$	$(CH_3)_2CH^-$	51	67
$(CH_3)_3CH$	$(CH_3)_3C^-$	—	68

¹⁶In this table we do not give pK_a values for individual compounds (with a few exceptions), only average values for functional groups. Extensive tables of pK values for many carboxylic and other acids and amines are given in Ref. 39. Values for more than 5500 organic acids are given in Serjeant; Dempsey *Ionisation Constants of Organic Acids in Aqueous Solution*; Pergamon: Elmsford, NY, 1979; Kortüm; Vogel; Andrussov *Dissociation Constants of Organic Acids in Aqueous Solution*; Butterworth: London, 1961. The index in the 1979 volume covers both volumes. Kortüm; Vogel; Andrussov *Pure Appl. Chem.* **1960**, *1*, 190-536 give values for 631 carboxylic acids and 110 phenols. Ref. 20 gives hundreds of values for very strong acids (very weak bases). Perrin *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworth: London, 1965, and Supplement, 1972 list pK values for more than 7000 amines and other bases. Collumcau *Bull. Soc. Chim. Fr.* **1968**, 5087-5112 gives pK values for about 800 acids and bases. Bordwell *Acc. Chem. Res.* **1988**, *21*, 456-463 gives values for more than 300 acids in dimethyl sulfoxide. For inorganic acids and bases, see Perrin, Ref. 42, *Pure Appl. Chem.* **1969**, *20*, 133-236.

¹⁷Carboxylic acids, esters, and amides are shown in this table to be protonated on the carbonyl oxygen. There has been some controversy on this point, but the weight of evidence is in that direction. See, for example, Katritzky; Jones *Chem. Ind. (London)* **1961**, 722; Ottenheim; van Raayen; Smidt; Groenewege; Veerkamp *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 1211; Stewart; Muenster *Can. J. Chem.* **1961**, *39*, 401; Smith; Yates *Can. J. Chem.* **1972**, *50*, 771; Benedetti; Di Blasio; Baine *J. Chem. Soc. Perkin Trans. 2* **1980**, 500; Ref. 8; Homer; Johnson, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 188-197. It has been shown that some amides protonate at nitrogen: see Perrin *Acc. Chem. Res.* **1989**, *22*, 268-275. For a review of alternative proton sites, see Liler *Adv. Phys. Org. Chem.* **1975**, *11*, 267-392.

¹⁸This value includes the CO_2 usually present. The value for H_2CO_3 alone is 3.9 (Ref. 21).

¹⁹Brouwer; van Doorn *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 895; Gold; Laali; Morris; Zdunek *J. Chem. Soc., Chem. Commun.* **1981**, 769; Sommer; Canivet; Schwartz; Rimmelin *Nouv. J. Chim.* **1981**, *5*, 45.

²⁰Arnett *Prog. Phys. Org. Chem.* **1963**, *1*, 223-403, pp. 324-325.

²¹Bell, Ref. 1.

²²Deno; Wisotsky *J. Am. Chem. Soc.* **1963**, *85*, 1735; Deno; Gaugler; Wisotsky *J. Org. Chem.* **1966**, *31*, 1967.

²³Levy; Cargioli; Racela *J. Am. Chem. Soc.* **1970**, *92*, 6238. See, however, Brouwer; van Doorn *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1010.

²⁴Stewart; Granger *Can. J. Chem.* **1961**, *39*, 2508.

²⁵Yates; Stewart *Can. J. Chem.* **1959**, *37*, 664; Stewart; Yates *J. Am. Chem. Soc.* **1958**, *80*, 6355.

²⁶Lee *Can. J. Chem.* **1970**, *48*, 1919.

²⁷Cerfontain; Koeberg-Telder; Kruk *Tetrahedron Lett.* **1975**, 3639.

²⁸Arnett; Wu *J. Am. Chem. Soc.* **1960**, *82*, 5660; Koeberg-Telder; Lambrechts; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1963**, *102*, 293.

²⁹Fischer; Grigor; Packer; Vaughan *J. Am. Chem. Soc.* **1961**, *83*, 4208.

³⁰Arnett; Wu *J. Am. Chem. Soc.* **1960**, *82*, 4999.

³¹Boyd *J. Phys. Chem.* **1963**, *67*, 737.

³²Arnett; Quirk; Burke *J. Am. Chem. Soc.* **1970**, *92*, 1260.

³³McTigue; Sime *Aust. J. Chem.* **1963**, *16*, 592.

³⁴Deno; Turner *J. Org. Chem.* **1966**, *31*, 1969.

³⁵Lee; Demchuk *Can. J. Chem.* **1987**, *65*, 1769; Chandler; Lee *Can. J. Chem.* **1990**, *68*, 1757.

³⁶For a discussion, see Campbell; Waite *J. Chem. Educ.* **1990**, *67*, 386.

³⁷Cox; Druet; Klausner; Modro; Wan; Yates *Can. J. Chem.* **1981**, *59*, 1568; Grant; McTigue; Ward *Aust. J. Chem.* **1983**, *36*, 2211.

when a given acid and base react without a solvent or, when possible, in water. In other solvents the order may be greatly different (see p. 272). In the gas phase, where solvation effects are completely or almost completely absent, acidity orders may also differ greatly.⁶⁹ For example, in the gas phase, toluene is a stronger acid than water and *t*-butoxide ion is a weaker base than methoxide ion⁷⁰ (see also pp. 270-272). It is also possible for the acidity order to change with temperature. For example, above 50°C the order of base strength is BuOH > H₂O > Bu₂O; from 1 to 50°C the order is BuOH > Bu₂O > H₂O; while below 1°C the order becomes Bu₂O > BuOH > H₂O.⁷¹

³⁸Bruckenstein; Kolthoff; in Kolthoff; Elving *Treatise on Analytical Chemistry*, vol. 1, pt. 1; Wiley: New York, 1959, pp. 432-433.

³⁹Brown; McDaniel; Häflinger, in Braude; Nachod *Determination of Organic Structures by Physical Methods*, vol. 1; Academic Press: New York, 1955, pp. 567-662.

⁴⁰Pearson; Dillon *J. Am. Chem. Soc.* **1953**, *75*, 2439.

⁴¹Crampton, in Patai *The Chemistry of the Thiol Group*, pt. 1; Wiley: New York, 1974, pp. 396-410.

⁴²Perrin *Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed.; Pergamon: Elmsford, NY, 1982.

⁴³Rochester, in Patai *The Chemistry of the Hydroxyl Group*, pt. 1; Wiley: New York, 1971, p. 374.

⁴⁴Cram *Chem. Eng. News* **1963**, *41*(No. 33, Aug. 19), 94.

⁴⁵Bowden; Stewart *Tetrahedron* **1965**, *21*, 261.

⁴⁶Hinc; Philips; Maxwell *J. Org. Chem.* **1970**, *35*, 3943. See also Ang; Lee *Aust. J. Chem.* **1977**, *30*, 521.

⁴⁷Reeve; Erikson; Aluotto *Can. J. Chem.* **1979**, *57*, 2747.

⁴⁸See also Mackay; Bohme *J. Am. Chem. Soc.* **1978**, *100*, 327; Olmstead; Margolin; Bordwell *J. Org. Chem.* **1980**, *45*, 3295.

⁴⁹Harned; Robinson *Trans. Faraday Soc.* **1940**, *36*, 973.

⁵⁰Streitwieser; Nebenzahl *J. Am. Chem. Soc.* **1976**, *98*, 2188.

⁵¹Guthrie; Cossar *Can. J. Chem.* **1986**, *64*, 2470.

⁵²Homer; Johnson. Ref. 17, pp. 238-240.

⁵³Tapuhi; Jencks *J. Am. Chem. Soc.* **1982**, *104*, 5758; Guthrie; Cossar; Klym *J. Am. Chem. Soc.* **1984**, *106*, 1351; Chiang; Kresge; Tang; Wirz *J. Am. Chem. Soc.* **1984**, *106*, 460.

⁵⁴Streitwieser; Ciuffarin; Hammons *J. Am. Chem. Soc.* **1967**, *89*, 63.

⁵⁵Streitwieser; Hollyhead; Pudjaatmaka; Owens; Kruger; Rubenstein; MacQuarrie; Brokaw; Chu; Niemeyer *J. Am. Chem. Soc.* **1971**, *93*, 5088.

⁵⁶For a review of the acidity of cyano compounds, see Hibbert, in Patai; Rappoport *The Chemistry of Triple-bonded Functional Groups*, pt. 1; Wiley: New York, 1983, pp. 699-736.

⁵⁷Cram. Ref. 11, p. 19. See also Dessy; Kitching; Psarras; Salinger; Chen; Chivers *J. Am. Chem. Soc.* **1966**, *88*, 460.

⁵⁸Streitwieser; Hollyhead; Sonnichsen; Pudjaatmaka; Chang; Kruger *J. Am. Chem. Soc.* **1971**, *93*, 5096.

⁵⁹Buncel; Menon *J. Am. Chem. Soc.* **1977**, *99*, 4457.

⁶⁰Buncel; Menon *J. Organomet. Chem.* **1977**, *141*, 1.

⁶¹Streitwieser; Ni *Tetrahedron Lett.* **1985**, *26*, 6317; Albrecht; Schneider *Tetrahedron* **1986**, *42*, 4729.

⁶²Boerth; Streitwieser *J. Am. Chem. Soc.* **1981**, *103*, 6443.

⁶³Streitwieser; Scannon; Niemeyer *J. Am. Chem. Soc.* **1972**, *94*, 7936.

⁶⁴Maskornick; Streitwieser *Tetrahedron Lett.* **1972**, 1625; Streitwieser; Boerth *J. Am. Chem. Soc.* **1978**, *100*, 755.

⁶⁵This value is calculated from results given in Streitwieser; Caldwell; Young *J. Am. Chem. Soc.* **1969**, *91*, 529. For a review of acidity and basicity of cyclopropanes, see Battiste; Coxon, in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley: New York, 1987, pp. 255-305.

⁶⁶This value is calculated from results given in Streitwieser; Taylor *J. Chem. Soc. D* **1970**, 1248.

⁶⁷These values are based on those given in Ref. 44 but are corrected to the newer scale of Streitwieser; Refs. 63 and 64.

⁶⁸Breslow and co-workers report a value of 71 [Breslow; Goodin *J. Am. Chem. Soc.* **1976**, *98*, 6076; Breslow; Grant *J. Am. Chem. Soc.* **1977**, *99*, 7745], but this was obtained by a different method, and is not comparable to the other values in Table 8.1. A more comparable value is about 53. See also Juan; Schwarz; Breslow *J. Am. Chem. Soc.* **1980**, *102*, 5741.

⁶⁹For a review of acidity and basicity scales in the gas phase and in solution, see Gal; Maria *Prog. Phys. Org. Chem.* **1990**, *17*, 159-238.

⁷⁰Brauman; Blair *J. Am. Chem. Soc.* **1970**, *92*, 5986; Bohme; Lee-Ruff; Young *J. Am. Chem. Soc.* **1972**, *94*, 4608, 5153.

⁷¹Gerrard; Macklen *Chem. Rev.* **1959**, *59*, 1105-1123. For other examples, see Calder; Barton *J. Chem. Educ.* **1971**, *48*, 338; Hamby *Rev. Pure Appl. Chem.* **1965**, *15*, 87-100, p. 88.

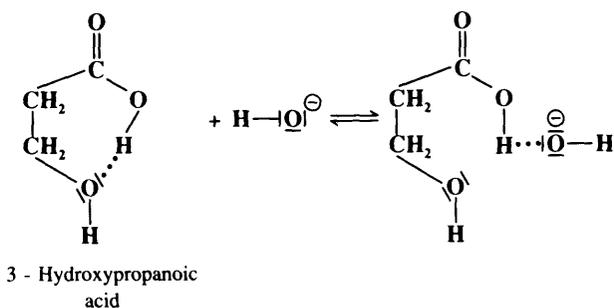
The Mechanism of Proton Transfer Reactions

Proton transfers between oxygen and nitrogen acids and bases are usually extremely fast.⁷² In the thermodynamically favored direction they are generally diffusion controlled.⁷³ In fact, a *normal acid* is defined⁷⁴ as one whose proton transfer reactions are completely diffusion controlled, except when the conjugate acid of the base to which the proton is transferred has a pK value very close (differs by < about 2 pK units) to that of the acid. The normal acid–base reaction mechanism consists of three steps:

1. $\text{HA} + |\text{B} \rightleftharpoons \text{AH} \cdots |\text{B}$
2. $\text{AH} \cdots |\text{B} \rightleftharpoons \text{A}|\cdots \text{HB}$
3. $\text{A}|\cdots \text{HB} \rightleftharpoons \text{A}| + \text{HB}$

The actual proton transfer takes place in the second step—the first step is formation of a hydrogen-bonded complex. The product of the second step is another hydrogen-bonded complex, which dissociates in the third step.

However, not all such proton transfers are diffusion controlled. For example, if an internal hydrogen bond exists in a molecule, reaction with an external acid or base is often much slower.⁷⁵ In a case such as this:



the OH^- ion can form a hydrogen bond with the acidic hydrogen only if the internal hydrogen bond breaks. Therefore only some of the collisions between OH^- ions and 3-hydroxypropanoic acid molecules result in proton transfer. In many collisions the OH^- ions will come away empty-handed, resulting in a lower reaction rate. Note that this affects only the rate, not the equilibrium. Another factor that can create lower rates is a molecular structure in which the acidic proton is protected within a molecular cavity (e.g., the in–in and out–in isomers shown on p. 133). See also the proton sponges mentioned on p. 268. Proton transfers between an acidic and a basic group within the same molecule can also be slow, if the two groups are too far apart for hydrogen bonding. In such cases participation of solvent molecules may be necessary.

⁷²For reviews of such proton transfers, see Hibbert *Adv. Phys. Org. Chem.* **1986**, 22, 113-212; Crooks, in Bamford; Tipper *Chemical Kinetics*, vol. 8; Elsevier: New York, 1977, pp. 197-250.

⁷³Kinetic studies of these very fast reactions were first carried out by Eigen. See Eigen *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 1-19 [*Angew. Chem.* **1963**, 75, 489-509].

⁷⁴See, for example, Hojatti; Kresge; Wang *J. Am. Chem. Soc.* **1987**, 109, 4023.

⁷⁵For an example of a slow proton transfer from F_3CCOOH to $(\text{PhCH}_2)_3\text{N}$, see Ritchie; Lu *J. Am. Chem. Soc.* **1989**, 111, 8542.

Proton transfers to or from a carbon atom⁷⁶ in most cases are much slower than those strictly between oxygen or nitrogen atoms. At least three factors can be responsible for this,⁷⁷ not all of them applying in every case:

1. Hydrogen bonding is very weak or altogether absent for carbon (Chapter 3).
2. Many carbon acids, upon losing the proton, form carbanions that are stabilized by resonance. Structural reorganization (movement of atoms to different positions within the molecule) may accompany this. Chloroform, HCN, and 1-alkynes do not form resonance-stabilized carbanions, and these⁷⁸ behave kinetically as normal acids.⁷⁹
3. There may be considerable reorganization of solvent molecules around the ion as compared to the neutral molecule.⁸⁰

In connection with factors 2 and 3, it has been proposed⁷⁷ that any factor that stabilizes the product (e.g., by resonance or solvation) lowers the rate constant if it develops late on the reaction coordinate, but increases the rate constant if it develops early. This is called the Principle of Imperfect Synchronization.

Measurements of Solvent Acidity⁸¹

When a solute is added to an acidic solvent it may become protonated by the solvent. If the solvent is water and the concentration of solute is not very great, then the pH of the solution is a good measure of the proton-donating ability of the solvent. Unfortunately, this is no longer true in concentrated solutions because activity coefficients are no longer unity. A measurement of solvent acidity is needed which works in concentrated solutions and applies to mixed solvents as well. The Hammett acidity function⁸² is a measurement that is used for acidic solvents of high dielectric constant.⁸³ For any solvent, including mixtures of solvents (but the proportions of the mixture must be specified), a value H_0 is defined as

$$H_0 = \text{p}K_{\text{BH}^+} - \log \frac{[\text{BH}^+]}{[\text{B}]}$$

H_0 is measured by using "indicators" that are weak bases (B) and so are partly converted, in these acidic solvents, to the conjugate acids BH^+ . Typical indicators are *o*-nitroanilinium ion, with a $\text{p}K$ in water of -0.29 , and 2,4-dinitroanilinium ion, with a $\text{p}K$ in water of -4.53 . For a given solvent, $[\text{BH}^+]/[\text{B}]$ is measured for one indicator, usually by spectrophotometric means. Then, using the known $\text{p}K$ in water ($\text{p}K_{\text{BH}^+}$) for that indicator, H_0 can be calculated for that solvent system. In practice, several indicators are used, so that an average H_0 is

⁷⁶For reviews of proton transfers to and from carbon, see Hibbert, in Bamford; Tipper, Ref. 72, pp. 97-196; Kreevoy *Isot. Org. Chem.* **1976**, 2, 1-31; Leffek *Isot. Org. Chem.* **1976**, 2, 89-125.

⁷⁷See Bernasconi *Tetrahedron* **1985**, 41, 3219.

⁷⁸Lin; Chiang; Dahlberg; Kresge *J. Am. Chem. Soc.* **1983**, 105, 5380; Bednar; Jencks *J. Am. Chem. Soc.* **1985**, 107, 7117, 7126, 7135; Kresge; Powell *J. Org. Chem.* **1986**, 51, 822; Formosinho; Gal *J. Chem. Soc., Perkin Trans. 2* **1987**, 1655.

⁷⁹Not all 1-alkynes behave as normal acids; see Aroella; Arrowsmith; Hojatti; Kresge; Powell; Tang; Wang *J. Am. Chem. Soc.* **1987**, 109, 7198.

⁸⁰See Bernasconi; Terrier *J. Am. Chem. Soc.* **1987**, 109, 7115; Kurz *J. Am. Chem. Soc.* **1989**, 111, 8631.

⁸¹For fuller treatments, see Hammett *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970, pp. 263-313; Jones *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University Press: Cambridge, 1984, pp. 83-93; Arnett; Scorrano *Adv. Phys. Org. Chem.* **1976**, 13, 83-153.

⁸²Hammett; Deyrup *J. Am. Chem. Soc.* **1932**, 54, 2721.

⁸³For a monograph on acidity functions, see Rochester, Ref. 10. For reviews, see Ref. 81; Cox; Yates *Can. J. Chem.* **1983**, 61, 2225-2243; Boyd, in Coetzee; Ritchie *Solute-Solvent Interactions*; Marcel Dekker: New York, 1969, pp. 97-218; Vinnik *Russ. Chem. Rev.* **1966**, 35, 802-817; Liler, Ref. 10, pp. 26-58.

taken. Once H_0 is known for a given solvent system, pK_a values in it can be calculated for any other acid–base pair.

The symbol h_0 is defined as

$$h_0 = \frac{a_{H^+} f_I}{f_{HI^+}}$$

where a_{H^+} is the activity of the proton and f_I and f_{HI^+} are the activity coefficients of the indicator and conjugate acid of the indicator,⁸⁴ respectively. H_0 is related to h_0 by

$$H_0 = -\log h_0$$

so that H_0 is analogous to pH and h_0 to $[H^+]$, and indeed in dilute aqueous solution $H_0 = \text{pH}$.

H_0 reflects the ability of the solvent system to donate protons, but it can be applied only to acidic solutions of high dielectric constant, mostly mixtures of water with acids such as nitric, sulfuric, perchloric, etc. It is apparent that the H_0 treatment is valid only when f_I/f_{HI^+} is independent of the nature of the base (the indicator). Since this is so only when the bases are structurally similar, the treatment is limited. Even when similar bases are compared, many deviations are found.⁸⁵ Other acidity scales⁸⁶ have been set up, among them H_- for bases with a charge of -1 , H_R for aryl carbinols,⁸⁷ H_C for bases that protonate on carbon,⁸⁸ and H_A for unsubstituted amides.⁸⁹ It is now clear that there is no single acidity scale that can be applied to a series of solvent mixtures, irrespective of the bases employed.⁹⁰

Although most acidity functions have been applied only to acidic solutions, some work has also been done with strongly basic solutions.⁹¹ The H_- function, which is used for highly acidic solutions when the base has a charge of -1 , can also be used for strongly basic solvents, in which case it measures the ability of these solvents to abstract a proton from a neutral acid BH.⁹² When a solvent becomes protonated, its conjugate acid is known as a *lyonium ion*.

Another approach to the acidity function problem was proposed by Bunnett and Olsen,⁹³ who derived the equation

$$\log \frac{[SH^+]}{[S]} + H_0 = \phi(H_0 + \log [H^+]) + pK_{SH^+}$$

⁸⁴For a review of activity coefficient behavior of indicators in acid solutions, see Yates; McClelland *Prog. Phys. Org. Chem.* **1974**, *11*, 323-420.

⁸⁵For example, see Kresge; Barry; Charles; Chiang *J. Am. Chem. Soc.* **1962**, *84*, 4343; Katritzky; Waring; Yates *Tetrahedron* **1963**, *19*, 465; Arnett; Mach *J. Am. Chem. Soc.* **1964**, *86*, 2671; Jorgenson; Hartter *J. Am. Chem. Soc.* **1963**, *85*, 878; Krecvov; Baughman *J. Am. Chem. Soc.* **1973**, *95*, 8178; Garcia; Leal; Herrero; Palacios *J. Chem. Soc., Perkin Trans. 2* **1988**, 1759; Ref. 32.

⁸⁶For lengthy tables of many acidity scales, with references, see Cox; Yates, Ref. 83. For an equation that is said to combine the vast majority of acidity functions, see Zalewski; Sarkice; Geltz *J. Chem. Soc., Perkin Trans. 2* **1983**, 1059.

⁸⁷Deno; Jaruzelski; Schriesheim *J. Am. Chem. Soc.* **1955**, *77*, 3044; Deno; Berkheimer; Evans; Peterson *J. Am. Chem. Soc.* **1959**, *81*, 2344.

⁸⁸Reagan *J. Am. Chem. Soc.* **1969**, *91*, 5506.

⁸⁹Yates; Stevens; Katritzky *Can. J. Chem.* **1964**, *42*, 1957; Yates; Riordan *Can. J. Chem.* **1965**, *43*, 2328; Edward; Wong *Can. J. Chem.* **1977**, *55*, 2492; Liler; Marković *J. Chem. Soc., Perkin Trans. 2* **1982**, 551.

⁹⁰Hammett, Ref. 81, p. 278; Rochester, Ref. 10, p. 21.

⁹¹For another approach to solvent basicity scales, see Catalán; Gómez; Couto; Laynez *J. Am. Chem. Soc.* **1990**, *112*, 1678.

⁹²For reviews, see Rochester *Q. Rev., Chem. Soc.* **1966**, *20*, 511-525; Rochester, Ref. 10, pp. 234-264; Bowden *Chem. Rev.* **1966**, *66*, 119-131 (the last review is reprinted in Coetzee and Ritchie, Ref. 83, pp. 186-215).

⁹³Bunnett; Olsen *Can. J. Chem.* **1966**, *44*, 1899, 1917; Bunnett; McDonald; Olsen *J. Am. Chem. Soc.* **1974**, *96*, 2855.

where S is a base that is protonated by an acidic solvent. Thus the slope of a plot of $\log ([\text{SH}^+]/[\text{S}] + H_0)$ against $H_0 + \log [\text{H}^+]$ is the parameter ϕ , while the intercept is the $\text{p}K_a$ of the lyonium ion SH^+ (referred to infinite dilution in water). The value of ϕ expresses the response of the equilibrium $\text{S} + \text{H}^+ \rightleftharpoons \text{SH}^+$ to changing acid concentration. A negative ϕ indicates that the log of the ionization ratio $[\text{SH}^+]/[\text{S}]$ increases, as the acid concentration increases, more rapidly than $-H_0$. A positive ϕ value indicates the reverse. The Bunnett–Olsen equation given above is a linear free-energy relationship (see p. 281) that pertains to acid-base equilibria. A corresponding equation that applies to kinetic data is

$$\log k_{\text{a}} + H_0 = \phi(H_0 + \log [\text{H}^+]) + \log k_2^{\circ}$$

where k_{a} is the pseudo-first-order rate constant for a reaction of a weakly basic substrate taking place in an acidic solution and k_2° is the second-order rate constant at infinite dilution in water. In this case ϕ characterizes the response of the reaction rate to changing acid concentration of the solvent. The Bunnett–Olsen treatment has also been applied to basic media, where, in a group of nine reactions in concentrated NaOMe solutions, no correlation was found between reaction rates and either H_- or stoichiometric base concentration but where the rates were successfully correlated by a linear free-energy equation similar to those given above.⁹⁴

A treatment partially based on the Bunnett–Olsen one is that of Bagno, Scorrano, and More O'Ferrall,⁹⁵ which formulates medium effects (changes in acidity of solvent) on acid–base equilibria. An appropriate equilibrium is chosen as reference, and the acidity dependence of other reactions compared with it, by use of the linear free-energy equation

$$\log \frac{K'}{K_0} = m^* \log \frac{K}{K_0}$$

where the K values are the equilibrium constants for the following:

K for the reaction under study in any particular medium

K' for the reference reaction in the same medium

K_0 for the reaction under study in a reference solvent

K'_0 for the reference reaction in the same reference solvent

and m^* is the slope of the relationship [corresponding to $(1 - \phi)$ of the Bunnett–Olsen treatment]. This equation has been shown to apply to many acid–base reactions.

Another type of classification system was devised by Bunnett⁹⁶ for reactions occurring in moderately concentrated acid solutions. $\log k_{\text{a}} + H_0$ is plotted against $\log a_{\text{H}_2\text{O}}$, where K_{a} is the pseudo-first-order rate constant for the protonated species and $a_{\text{H}_2\text{O}}$ is the activity of water. Most such plots are linear or nearly so. According to Bunnett, the slope of this plot w tells something about the mechanism. Where w is between -2.5 and 0 , water is not involved in the rate-determining step; where w is between 1.2 and 3.3 , water is a nucleophile in the rate-determining step; where w is between 3.3 and 7 , water is a proton-transfer agent. These rules hold for acids in which the proton is attached to oxygen or nitrogen.

⁹⁴More O'Ferrall *J. Chem. Soc., Perkin Trans. 2* **1972**, 976.

⁹⁵Bagno; Scorrano; More O'Ferrall *Rev. Chem. Intermed.* **1987**, *7*, 313-352. See also Marziano; Cimino; Passerini *J. Chem. Soc., Perkin Trans. 2* **1973**, 1915; Lucchini; Modena; Scorrano; Cox; Yates *J. Am. Chem. Soc.* **1982**, *104*, 1958; Sampoli; De Santis; Marziano *J. Chem. Soc., Chem. Commun.* **1985**, 110; Cox *Acc. Chem. Res.* **1987**, *20*, 27-31.

⁹⁶Bunnett *J. Am. Chem. Soc.* **1961**, *83*, 4956, 4968, 4973, 4978.

Acid and Base Catalysis⁹⁷

Many reactions are catalyzed by acids, bases, or both. In such cases the catalyst is involved in a fundamental way in the mechanism. Nearly always the first step of such a reaction is a proton transfer between the catalyst and the substrate.

Reactions can be catalyzed by acid or base in two different ways, called *general* and *specific catalysis*. If the rate of an acid-catalyzed reaction run in a solvent S is proportional to $[\text{SH}^+]$, the reaction is said to be subject to *specific acid catalysis*, the acid being the lyonium ion SH^+ . The acid that is put into the solvent may be stronger or weaker than SH^+ , but the rate is proportional only to the $[\text{SH}^+]$ that is actually present in the solution (derived from $\text{S} + \text{HA} \rightleftharpoons \text{SH}^+ + \text{A}^-$). The identity of HA makes no difference except insofar as it determines the position of equilibrium and hence the $[\text{SH}^+]$. Most measurements have been made in water, where SH^+ is H_3O^+ .

In *general acid catalysis*, the rate is increased not only by an increase in $[\text{SH}^+]$ but also by an increase in the concentration of other acids (e.g., in water by phenols or carboxylic acids). These other acids increase the rate even when $[\text{SH}^+]$ is held constant. In this type of catalysis the strongest acids catalyze best, so that, in the example given, an increase in the phenol concentration catalyzes the reaction much less than a similar increase in $[\text{H}_3\text{O}^+]$. This relationship between acid strength of the catalyst and its catalytic ability can be expressed by the *Brønsted catalysis equation*⁹⁸

$$\log k = \alpha \log K_a + C$$

where k is the rate constant for a reaction catalyzed by an acid of ionization constant K_a . According to this equation, when $\log k$ is plotted against $\log K_a$ for catalysis of a given reaction by a series of acids, a straight line should be obtained with slope α and intercept C . Although straight lines are obtained in many cases, this is not always the case. The relationship usually fails when acids of different types are compared. For example, it is much more likely to hold for a group of substituted phenols than for a collection of acids that contains both phenols and carboxylic acids. The Brønsted equation is another linear free-energy relationship (see p. 281).

Analogously, there are *general* and *specific* (S^- from an acidic solvent SH) *base-catalyzed reactions*. The Brønsted law for bases is

$$\log k = \beta \log K_b + C$$

The Brønsted equations relate a rate constant k to an equilibrium constant K_a . In Chapter 6 we saw that the Marcus equation also relates a rate term (in that case ΔG^\ddagger) to an equilibrium term ΔG° . When the Marcus treatment is applied to proton transfers⁹⁹ between a carbon and an oxygen (or a nitrogen), the simplified¹⁰⁰ equation (p. 216)

$$\Delta G^\ddagger = \Delta G_{\text{int}}^\ddagger + \frac{1}{2} \Delta G^\circ + \frac{(\Delta G^\circ)^2}{16 \Delta G_{\text{int}}^\ddagger}$$

⁹⁷For reviews, see Stewart, Ref. 1, pp. 251-305; Hammett, Ref. 81, pp. 315-345; Willi, in Bamford; Tipper, Ref. 72, pp. 1-95; Jones, Ref. 81, pp. 72-82; Bell, Ref. 1, pp. 159-193; Jencks *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969, pp. 163-242; Bender *Mechanisms of Homogeneous Catalysis from Protons to Proteins*; Wiley: New York, 1971, pp. 19-144.

⁹⁸For reviews, see Klumpp *Reactivity in Organic Chemistry*; Wiley: New York, 1982, pp. 167-179; Bell, in Chapman; Shorter *Correlation Analysis in Chemistry: Recent Advances*; Plenum Press: 1978, pp. 55-84; Kresge *Chem. Soc. Rev.* **1973**, 2, 475-503.

⁹⁹For applications of Marcus theory to proton transfers, see Marcus *J. Phys. Chem.* **1968**, 72, 891; Kreevoy; Konasewich *Adv. Chem. Phys.* **1971**, 21, 243; Kresge *Chem. Soc. Rev.* **1973**, 2, 475-503.

¹⁰⁰Omitting the work terms.

where

$$\Delta G_{\text{int}}^* = \frac{1}{2} (\Delta G_{\text{O},\text{O}}^* + \Delta G_{\text{C},\text{C}}^*)$$

can be further simplified: Because proton transfers between oxygen and oxygen (or nitrogen and nitrogen) are much faster than those between carbon and carbon, $\Delta G_{\text{O},\text{O}}^*$ is much smaller than $\Delta G_{\text{C},\text{C}}^*$ and we can write¹⁰¹

$$\Delta G^* = \frac{1}{2} \Delta G_{\text{C},\text{C}}^* + \frac{1}{2} \Delta G^\circ + \frac{(\Delta G^\circ)^2}{8 \Delta G_{\text{C},\text{C}}^*}$$

Thus, if the carbon part of the reaction is kept constant and only the A of HA is changed (where A is an oxygen or nitrogen moiety), then ΔG^* is dependent only on ΔG° . Differentiation of this equation yields the Brønsted α :

$$\frac{d\Delta G^*}{d\Delta G^\circ} = \alpha = \frac{1}{2} \left(1 + \frac{\Delta G^\circ}{2 \Delta G_{\text{C},\text{C}}^*} \right)$$

The Brønsted law is therefore a special case of the Marcus equation.

A knowledge of whether a reaction is subject to general or specific acid catalysis supplies information about the mechanism. For any acid-catalyzed reaction we can write



If the reaction is catalyzed only by the specific acid SH^+ , it means that step 1 is rapid and step 2 is rate-controlling, since an equilibrium has been rapidly established between A and the strongest acid present in the solution, namely, SH^+ (since this is the strongest acid that can be present in S). On the other hand, if step 2 is faster, there is no time to establish equilibrium and the rate-determining step must be step 1. This step is affected by all the acids present, and the rate reflects the sum of the effects of each acid (general acid catalysis). General acid catalysis is also observed if the slow step is the reaction of a hydrogen-bond complex $\text{A} \cdots \text{HB}$, since each complex reacts with a base at a different rate. A comparable discussion can be used for general and specific base catalysis.¹⁰² Further information can be obtained from the values α and β in the Brønsted catalysis equations, since these are approximate measures of the extent of proton transfer in the transition state. In most cases values of α and β are between 1 and 0. A value of α or β near 0 is generally taken to mean that the transition state resembles the reactants; i.e., the proton has been transferred very little when the transition state has been reached. A value of α or β near 1 is taken to mean the opposite; i.e., in the transition state the proton has been almost completely transferred. However, cases are known in which these generalizations are not followed,¹⁰³ and their theoretical basis has been challenged.¹⁰⁴ In general, the proton in the transition state lies closer to the weaker base.

¹⁰¹Albery *Annu. Rev. Phys. Chem.* **1980**, *31*, 227-263, p. 244.

¹⁰²For discussions of when to expect general or specific acid or base catalysis, see Jencks *Acc. Chem. Res.* **1976**, *9*, 425-432; Stewart; Srinivasan *Acc. Chem. Res.* **1978**, *11*, 271-277; Guthrie *J. Am. Chem. Soc.* **1980**, *102*, 5286.

¹⁰³See, for example, Bordwell; Boyle *J. Am. Chem. Soc.* **1972**, *94*, 3907; Davies *J. Chem. Soc., Perkin Trans. 2* **1974**, 1018; Agmon *J. Am. Chem. Soc.* **1980**, *102*, 2164; Murray; Jencks *J. Am. Chem. Soc.* **1988**, *110*, 7561.

¹⁰⁴Pross; Shaik *New J. Chem.* **1989**, *13*, 427; Lewis, *J. Phys. Org. Chem.* **1990**, *3*, 1.

where

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¹⁰¹Albery *Annu. Rev. Phys. Chem.* **1980**, *31*, 227-263, p. 244.

¹⁰²For discussions of when to expect general or specific acid or base catalysis, see Jencks *Acc. Chem. Res.* **1976**, *9*, 425-432; Stewart; Srinivasan *Acc. Chem. Res.* **1978**, *11*, 271-277; Guthrie *J. Am. Chem. Soc.* **1980**, *102*, 5286.

¹⁰³See, for example, Bordwell; Boyle *J. Am. Chem. Soc.* **1972**, *94*, 3907; Davies *J. Chem. Soc., Perkin Trans. 2* **1974**, 1018; Agmon *J. Am. Chem. Soc.* **1980**, *102*, 2164; Murray; Jencks *J. Am. Chem. Soc.* **1988**, *110*, 7561.

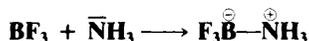
¹⁰⁴Pross; Shaik *New J. Chem.* **1989**, *13*, 427; Lewis, *J. Phys. Org. Chem.* **1990**, *3*, 1.

Lewis Acids and Bases. Hard and Soft Acids and Bases

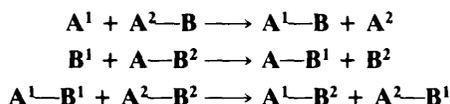
At about the same time that Brønsted proposed his acid–base theory, Lewis put forth a broader theory. A base in the Lewis theory is the same as in the Brønsted one, namely, a compound with an available pair of electrons, either unshared or in a π orbital. A *Lewis acid*, however, is any species with a vacant orbital.¹⁰⁵ In a Lewis acid–base reaction the unshared pair of the base forms a covalent bond with the vacant orbital of the acid, as represented by the general equation



in which charges are not shown, since they may differ. A specific example is



In the Brønsted picture, the acid is a proton donor, but in the Lewis picture the proton itself is the acid since it has a vacant orbital. A Brønsted acid becomes, in the Lewis picture, the compound that gives up the actual acid. The advantage of the Lewis theory is that it correlates the behavior of many more processes. For example, $AlCl_3$ and BF_3 are Lewis acids because they have only six electrons in the outer shell and have room for eight. $SnCl_4$ and SO_3 have eight, but their central elements, not being in the first row of the periodic table, have room for ten or twelve. Other Lewis acids are simple cations, like Ag^+ . The simple reaction $A + \bar{B} \rightarrow A-B$ is not very common in organic chemistry, but the scope of the Lewis picture is much larger because reactions of the types



which are very common in organic chemistry, are also Lewis acid–base reactions. In fact, all reactions in which a covalent bond is formed through one species contributing a filled and the other a vacant orbital may be regarded as Lewis acid–base reactions.

When a Lewis acid combines with a base to give a negative ion in which the central atom has a higher-than-normal valence, the resulting salt is called an *ate complex*.¹⁰⁶ Examples are

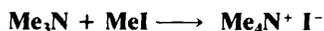


Ate complex



Ate complex

Ate complexes are analogous to the onium salts formed when a Lewis base expands its valence, e.g.,



Onium salt

¹⁰⁵For a monograph on Lewis acid–base theory, see Jensen *The Lewis Acid–Base Concept*; Wiley: New York, 1980. For a discussion of the definitions of Lewis acid and base, see Jensen *Chem. Rev.* **1978**, *78*, 1-22.

¹⁰⁶For a review of ate complexes, see Wittig *Q. Rev., Chem. Soc.* **1966**, *20*, 191-210.

Far fewer quantitative measurements have been made of Lewis acid strength compared to that of Brønsted acids.¹⁰⁷ A simple table of Lewis acidities based on some quantitative measurement (such as that given for Brønsted acids in Table 8.1) is not feasible because Lewis acidity depends on the nature of the base. Qualitatively, the following approximate sequence of acidity of Lewis acids of the type MX_n has been suggested, where X is a halogen atom or an inorganic radical: $BX_3 > AlX_3 > FeX_3 > GaX_3 > SbX_5 > SnX_4 > AsX_5 > ZnX_2 > HgX_2$.

The facility with which an acid–base reaction takes place depends of course on the strengths of the acid and the base. But it also depends on quite another quality, called the *hardness* or *softness* of the acid or base.¹⁰⁸ Hard and soft acids and bases have these characteristics:

Soft bases. The donor atoms are of low electronegativity and high polarizability and are easy to oxidize. They hold their valence electrons loosely.

Hard bases. The donor atoms are of high electronegativity and low polarizability and are hard to oxidize. They hold their valence electrons tightly.

Soft acids. The acceptor atoms are large, have low positive charge, and contain unshared pairs of electrons (*p* or *d*) in their valence shells. They have high polarizability and low electronegativity.

Hard acids. The acceptor atoms are small, have high positive charge, and do not contain unshared pairs in their valence shells. They have low polarizability and high electronegativity.

A qualitative listing of the hardness of some acids and bases is given in Table 8.2.¹⁰⁹ The treatment has also been made quantitative,¹¹⁰ with the following operational definition:

$$\eta = \frac{I - A}{2}$$

In this equation η , the *absolute hardness*, is half the difference between *I*, the ionization potential, and *A*, the electron affinity. The softness, σ , is the reciprocal of η . Values of η for some molecules and ions are given in Table 8.3.¹¹¹ Note that the proton, which is involved in all Brønsted acid–base reactions, is the hardest acid listed, with $\eta = \infty$ (it has no ionization potential). The above equation cannot be applied to anions, because electron affinities cannot be measured for them. Instead, the assumption is made that η for an anion X^- is the same as that for the radical X^\bullet .¹¹² Other methods are also needed to apply the treatment to polyatomic cations.¹¹²

¹⁰⁷For reviews of the quantitative aspects of Lewis acidity, see Satchell; Satchell *Q. Rev., Chem. Soc.* **1971**, 25, 171-199; *Chem. Rev.* **1969**, 69, 251-278. See also Maria; Gal *J. Phys. Chem.* **1985**, 89, 1296; Larson; McMahon *J. Am. Chem. Soc.* **1985**, 107, 766; Larson; Szulejko; McMahon *J. Am. Chem. Soc.* **1988**, 110, 7604; Sandström; Persson; Persson *Acta Chem. Scand.* **1990**, 44, 653; Laszlo; Teston-Henry *Tetrahedron Lett.* **1991**, 32, 3837.

¹⁰⁸Pearson *J. Am. Chem. Soc.* **1963**, 85, 3533; *Science* **1966**, 151, 172; Pearson; Songstad *J. Am. Chem. Soc.* **1967**, 89, 1827. For a monograph on the concept, see Ho *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977. For reviews, see Pearson, *J. Chem. Educ.* **1987**, 64, 561-567; Ho *Tetrahedron* **1985**, 41, 1-86; *J. Chem. Educ.* **1978**, 55, 355-360; *Chem. Rev.* **1975**, 75, 1-20; Pearson, in Chapman; Shorter *Advances in Linear Free-Energy Relationships*; Plenum Press: New York, 1972, pp. 281-319; Pearson *Surv. Prog. Chem.* **1969**, 5, 1-52 [portions of this article slightly modified also appear in Pearson *J. Chem. Educ.* **1968**, 45, 581-587, 643-648]; Garnovskii; Osipov; Bulgarevich *Russ. Chem. Rev.* **1972**, 41, 341-359; Scyden-Penne *Bull. Soc. Chim. Fr.* **1968**, 3871-3878. For a collection of papers, see Pearson *Hard and Soft Acids and Bases*; Dowden, Hutchinson, and Ross: Stroudsburg, PA, 1973.

¹⁰⁹Taken from larger listings in Pearson, Ref. 108.

¹¹⁰Parr; Pearson *J. Am. Chem. Soc.* **1983**, 105, 7512; Pearson *Inorg. Chem.* **1988**, 27, 734; *J. Org. Chem.* **1989**, 54, 1423. See also Orsky; Whitehead *Can. J. Chem.* **1987**, 65, 1970.

¹¹¹Note that there is not always a strict correlation between the values in Table 8.3 and the categories of Table 8.2.

¹¹²Pearson *J. Am. Chem. Soc.* **1988**, 110, 7684.

TABLE 8.2 Hard and soft acids and bases¹⁰⁹

Hard bases			Soft bases			Borderline bases		
H ₂ O	OH ⁻	F ⁻	R ₂ S	RSH	RS ⁻	ArNH ₂	C ₅ H ₅ N	
AcO ⁻	SO ₃ ²⁻	Cl ⁻	I ⁻	R ₃ P	(RO) ₃ P	N ₃ ⁻	Br ⁻	
CO ₃ ²⁻	NO ₃ ⁻	ROH	CN ⁻	RCN	CO	NO ₂ ⁻		
RO ⁻	R ₂ O	NH ₃	C ₂ H ₄	C ₆ H ₆				
RNH ₂			H ⁻	R ⁻				

Hard acids			Soft acids			Borderline acids		
H ⁺	Li ⁺	Na ⁺	Cu ⁺	Ag ⁺	Pd ²⁺	Fe ²⁺	Co ²⁺	Cu ²⁺
K ⁺	Mg ²⁺	Ca ²⁺	Pt ²⁺	Hg ²⁺	BH ₃	Zn ²⁺	Sn ²⁺	Sb ³⁺
Al ³⁺	Cr ²⁺	Fe ³⁺	GaCl ₃	I ₂	Br ₂	Bi ³⁺	BMe ₃	SO ₂
BF ₃	B(OR) ₃	AlMe ₃	CH ₂	carbenes		R ₃ C ⁺	NO ⁺	GaH ₃
AlCl ₃	AlH ₃	SO ₃				C ₆ H ₅ ⁺		
RCO ⁺	CO ₂							
HX (hydrogen-bonding molecules)								

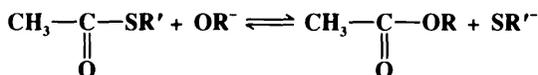
TABLE 8.3 Some absolute hardness values in electron volts¹¹⁰

Cations		Molecules		Anions ^b	
Ion	η	Compound	η	Ion	η
H ⁺	∞	HF	11.0	F ⁻	7.0
Al ³⁺	45.8	CH ₄	10.3	H ⁻	6.4
Li ⁺	35.1	BF ₃	9.7	OH ⁻	5.7
Mg ²⁺	32.6	H ₂ O	9.5	NH ₂ ⁻	5.3
Na ⁺	21.1	NH ₃	8.2	CN ⁻	5.1
Ca ²⁺	19.5	HCN	8.0	CH ₃ ⁻	4.9
K ⁺	13.6	(CH ₃) ₂ O	8.0	Cl ⁻	4.7
Zn ²⁺	10.9	CO	7.9	CH ₃ CH ₂ ⁻	4.4
Cr ³⁺	9.1	C ₂ H ₂	7.0	Br ⁻	4.2
Cu ²⁺	8.3	(CH ₃) ₃ N	6.3	C ₆ H ₅ ⁻	4.1
Pt ²⁺	8.0	H ₂ S	6.2	SH ⁻	4.1
Sn ²⁺	7.9	C ₂ H ₄	6.2	(CH ₃) ₂ CH ⁻	4.0
Hg ²⁺	7.7	(CH ₃) ₂ S	6.0	I ⁻	3.7
Fe ²⁺	7.2	(CH ₃) ₃ P	5.9	(CH ₃) ₃ C ⁻	3.6
Pd ²⁺	6.8	CH ₃ COCH ₃	5.6		
Cu ⁺	6.3	C ₆ H ₆	5.3		
		HI	5.3		
		C ₅ H ₅ N	5.0		
		C ₆ H ₅ OH	4.8		
		CH ₂ ^a	4.7		
		C ₆ H ₅ SH	4.6		
		Cl ₂	4.6		
		C ₆ H ₅ NH ₂	4.4		
		Br ₂	4.0		
		I ₂	3.4		

^aFor singlet state.^bThe same as for the corresponding radical.

Once acids and bases have been classified as hard or soft, a simple rule can be given: *hard acids prefer to bond to hard bases, and soft acids prefer to bond to soft bases (the HSAB principle)*.^{112a} The rule has nothing to do with acid or base *strength* but merely says that the product A—B will have extra stability if both A and B are hard or if both are soft. Another rule is that a soft Lewis acid and a soft Lewis base tend to form a covalent bond, while a hard acid and a hard base tend to bond ionically.

One application of the first rule given above is found in complexes between alkenes or aromatic compounds and metal ions (p. 80). Alkenes and aromatic rings are soft bases and should prefer to complex with soft acids. Thus, Ag^+ , Pt^{2+} , and Hg^{2+} complexes are common, but complexes of Na^+ , Mg^{2+} , or Al^{3+} are rare. Chromium complexes are also common, but in such complexes the chromium is in a low or zero oxidation state (which softens it) or attached to other soft ligands. In another application, we may look at this reaction:

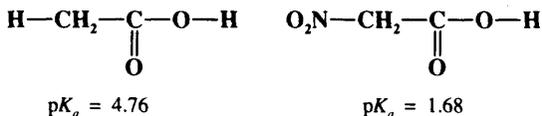


The HSAB principle predicts that the equilibrium should lie to the right, because the hard acid CH_3CO^+ should have a greater affinity for the hard base RO^- than for the soft base RS^- . Indeed, thiol esters are easily cleaved by OR^- or hydrolyzed by dilute base (OH^- is also a hard base).¹¹³ Another application of the rule is discussed on p. 349.¹¹⁴

The Effects of Structure on the Strengths of Acids and Bases¹¹⁵

The structure of a molecule can affect its acidity or basicity in a number of ways. Unfortunately, in most molecules two or more of these effects (as well as solvent effects) are operating, and it is usually very difficult or impossible to say how much each effect contributes to the acid or base strength.¹¹⁶ Small differences in acidity or basicity between similar molecules are particularly difficult to interpret. It is well to be cautious when attributing them to any particular effect.

1. Field effects. These were discussed on p. 17. As an example of the influence of field effects on acidity, we may compare the acidity of acetic acid and nitroacetic acid:



^{112a}For proofs of this principle, see Chattaraj; Lee; Parr *J. Am. Chem. Soc.* **1991**, *113*, 1855.

¹¹³Wolman, in Patai *The Chemistry of the Thiol Group*, pt. 2; Wiley: New York, 1974, p. 677; Maskill *The Physical Basis of Organic Chemistry*; Oxford University Press: Oxford, 1985, p. 159.

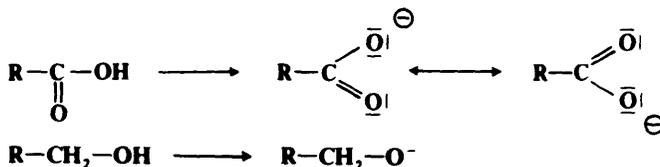
¹¹⁴See also Bochkov *J. Org. Chem. USSR* **1986**, *22*, 1830, 1837.

¹¹⁵For a monograph, see Hine *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New York, 1975. For reviews, see Taft *Prog. Phys. Org. Chem.* **1983**, *14*, 247-350; Petrov *Russ. Chem. Rev.* **1983**, *52*, 1144-1155 (NH acids); Bell, Ref. 1, pp. 86-110; Barlin; Perrin, in Bentley; Kirby *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (vol. 4 of Weissberger *Techniques of Chemistry*), pt. 1; Wiley: New York, 1972, pp. 611-676. For discussions, see Bolton; Hepler *Q. Rev., Chem. Soc.* **1971**, *25*, 521-532; Barlin; Perrin *Q. Rev., Chem. Soc.* **1966**, *20*, 75-101; Thiroit *Bull. Soc. Chim. Fr.* **1967**, 3559; Liler, Ref. 10, pp. 59-144. For a monograph on methods of estimating $\text{p}K$ values by analogy, extrapolation, etc., see Perrin; Dempsey; Serjeant *pK_a Prediction for Organic Acids and Bases*; Chapman and Hall: New York, 1981.

¹¹⁶The varying degrees by which the different factors that affect gas-phase acidities of 25 acids has been calculated: Taft; Koppel; Topsom; Anvia *J. Am. Chem. Soc.* **1990**, *112*, 2047.

The only difference in the structure of these molecules is the substitution of NO_2 for H. Since NO_2 is a strongly electron-withdrawing group, it withdraws electron density from the negatively charged COO^- group in the anion of nitroacetic acid (compared with the anion of acetic acid) and, as the $\text{p}K_a$ values indicate, nitroacetic acid is about 1000 times stronger than acetic acid.¹¹⁷ Any effect that results in electron withdrawal from a negatively charged center is a stabilizing effect because it spreads the charge. Thus, $-I$ groups increase the acidity of uncharged acids such as acetic because they spread the negative charge of the anion. However, $-I$ groups also increase the acidity of any acid, no matter what the charge. For example, if the acid has a charge of $+1$ (and its conjugate base is therefore uncharged), a $-I$ group destabilizes the positive center (by increasing and concentrating the positive charge) of the acid, a destabilization that will be relieved when the proton is lost. In general we may say that *groups that withdraw electrons by the field effect increase acidity and decrease basicity, while electron-donating groups act in the opposite direction*. Another example is the molecule $(\text{C}_6\text{F}_5)_3\text{CH}$, which has three strongly electron-withdrawing C_6F_5 groups and a $\text{p}K_a$ of 16,¹¹⁸ compared with Ph_3CH , with a $\text{p}K_a$ of 31.5 (Table 8.1), an acidity enhancement of about 10^{15} . Table 8.4 shows $\text{p}K_a$ values for some acids. An approximate idea of field effects can be obtained from this table. In the case of the chlorobutyric acids note how the effect decreases with distance. It must be remembered, however, that field effects are not the sole cause of the acidity differences noted and that in fact solvation effects may be more important in many cases (see pp. 269-272).¹¹⁹

2. Resonance effects. Resonance that stabilizes a base but not its conjugate acid results in the acid having a higher acidity than otherwise expected and vice versa. An example is found in the higher acidity of carboxylic acids compared with primary alcohols.



The RCOO^- ion is stabilized by resonance not available to the RCH_2O^- ion (or to RCOOH).¹²⁰ Note that the RCOO^- is stabilized not only by the fact that there are two equivalent canonical forms but also by the fact that the negative charge is spread over both oxygen atoms and is therefore less concentrated than in RCH_2O^- . The same effect is found in other compounds containing a $\text{C}=\text{O}$ or $\text{C}\equiv\text{N}$ group. Thus amides RCONH_2 are more acidic than amines RCH_2NH_2 ; esters $\text{RCH}_2\text{COOR}'$ than ethers $\text{RCH}_2\text{CH}_2\text{OR}'$; and ketones $\text{RCH}_2\text{COR}'$ than alkanes $\text{RCH}_2\text{CH}_2\text{R}'$ (Table 8.1). The effect is enhanced when two carbonyl groups are attached to the same carbon (because of additional resonance and spreading

¹¹⁷For a review of the enhancement of acidity by NO_2 , see Lewis, in Patai *The Chemistry of Functional Groups*, Supplement F, pt. 2; Wiley: New York, 1982, pp. 715-729.

¹¹⁸Filler; Wang *Chem. Commun.* **1968**, 287.

¹¹⁹For discussions, see Edward *J. Chem. Educ.* **1982**, 59, 354; Schwartz *J. Chem. Educ.* **1981**, 58, 778.

¹²⁰It has been contended that resonance delocalization plays only a minor role in the increased strength of carboxylic acids compared to alcohols, and the "... higher acidity of acids arises principally because the electrostatic potential of the acidic hydrogens is more positive in the neutral acid molecule ..."; Siggel; Thomas *J. Am. Chem. Soc.* **1986**, 108, 4360; Siggel; Streitwieser; Thomas *J. Am. Chem. Soc.* **1988**, 110, 8022; Thomas; Carroll; Siggel *J. Org. Chem.* **1988**, 53, 1812. For contrary views, see Exner *J. Org. Chem.* **1988**, 53, 1810; Dewar; Krull *J. Chem. Soc., Chem. Commun.* **1990**, 333; Perrin *J. Am. Chem. Soc.* **1991**, 113, 2865. See also Godfrey *Tetrahedron Lett.* **1990**, 31, 5181.

p-nitroaniline is weaker still, though the $-I$ effect should be less because of the greater distance. We can explain this result by taking into account the canonical form **A**. Because **A** contributes to the resonance hybrid,¹²¹ the electron density of the unshared pair is lower in *p*-nitroaniline than in *m*-nitroaniline, where a canonical form such as **A** is impossible. The basicity is lower in the para compound for two reasons, both caused by the same effect: (1) the unshared pair is less available for attack by a proton, and (2) when the conjugate acid is formed, the resonance stabilization afforded by **A** is no longer available because the previously unshared pair is now being shared by the proton. The acidity of phenols is affected by substituents in a similar manner.

In general, resonance effects lead to the same result as field effects. That is, here too, electron-withdrawing groups increase acidity and decrease basicity, and electron-donating groups act in the opposite manner. As a result of both resonance and field effects, charge dispersal leads to greater stability.

3. Periodic table correlations. When comparing Brønsted acids and bases that differ in the position of an element in the periodic table:

a. Acidity increases and basicity decreases in going from left to right across a row of the periodic table. Thus acidity increases in the order $\text{CH}_4 < \text{NH}_3 < \text{H}_2\text{O} < \text{HF}$, and basicity decreases in the order $\text{CH}_3^- > \text{NH}_2^- > \text{OH}^- > \text{F}^-$. This behavior can be explained by the increase in electronegativity upon going from left to right across the table. It is this effect that is responsible for the great differences in acidity between carboxylic acids, amides, and ketones: $\text{RCOOH} \gg \text{RCONH}_2 \gg \text{RCOCH}_3$.

b. Acidity increases and basicity decreases in going down a column of the periodic table, despite the decrease in electronegativity. Thus acidity increases in the order $\text{HF} < \text{HCl} < \text{HBr} < \text{HI}$ and $\text{H}_2\text{O} < \text{H}_2\text{S}$, and basicity decreases in the order $\text{NH}_3 > \text{PH}_3 > \text{AsH}_3$. This behavior is related to the size of the species involved. Thus, for example, F^- , which is much smaller than I^- , attracts a proton much more readily because its negative charge occupies a smaller volume and is therefore more concentrated (note that F^- is also much harder than I^- and is thus more attracted to the hard proton; see p. 263). This rule does not always hold for positively charged acids. Thus, although the order of acidity for the group 16 hydrides is $\text{H}_2\text{O} < \text{H}_2\text{S} < \text{H}_2\text{Se}$, the acidity order for the positively charged ions is $\text{H}_3\text{O}^+ > \text{H}_3\text{S}^+ > \text{H}_3\text{Se}^+$.¹²³

Lewis acidity is also affected by periodic table considerations. In comparing acid strengths of Lewis acids of the form MX_n :¹⁰⁷

c. Acids that require only one electron pair to complete an outer shell are stronger than those that require two. Thus GaCl_3 is stronger than ZnCl_2 . This results from the relatively smaller energy gain in adding an electron pair that does not complete an outer shell and from the buildup of negative charge if two pairs come in.

d. Other things being equal, the acidity of MX_n decreases in going down the periodic table because as the size of the molecule increases, the attraction between the positive nucleus and the incoming electron pair is weaker. Thus BCl_3 is a stronger acid than AlCl_3 .¹²⁴

4. Statistical effects. In a symmetrical diprotic acid, the first dissociation constant is twice as large as expected since there are two equivalent ionizable hydrogens, while the second constant is only half as large as expected because the conjugate base can accept a proton at two equivalent sites. So K_1/K_2 should be 4, and approximately this value is found

¹²¹See, however, Lipkowitz *J. Am. Chem. Soc.* **1982**, *104*, 2647; Krygowski; Maurin *J. Chem. Soc., Perkin Trans. 2* **1989**, 695.

¹²²Smith, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 161-204.

¹²³Taft, Ref. 115, pp. 250-254.

¹²⁴Note that Lewis acidity *decreases*, whereas Brønsted acidity *increases*, going down the table. There is no contradiction here when we remember that in the Lewis picture the actual acid in all Brønsted acids is the same, namely, the proton. In comparing, say, HI and HF, we are not comparing different Lewis acids but only how easily F^- and I^- give up the proton.

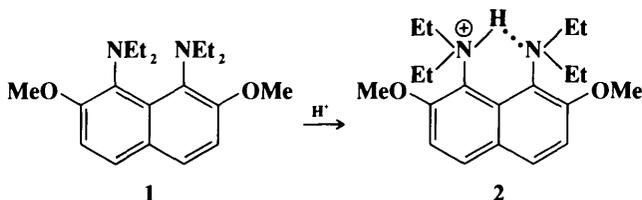
for dicarboxylic acids where the two groups are sufficiently far apart in the molecule that they do not influence each other. A similar argument holds for molecules with two equivalent basic groups.¹²⁵

5. Hydrogen bonding. Internal hydrogen bonding can greatly influence acid or base strength. For example, the pK for *o*-hydroxybenzoic acid is 2.98, while the value for the para isomer is 4.58. Internal hydrogen bonding between the OH and COO^- groups of the conjugate base of the ortho isomer stabilizes it and results in an increased acidity.

6. Steric effects. The proton itself is so small that direct steric hindrance is seldom encountered in proton transfers. Steric effects are much more common in Lewis acid–base reactions in which larger acids are used. Spectacular changes in the order of base strength have been demonstrated when the size of the acid was changed. Table 8.5 shows the order of base strength of simple amines when compared against acids of various size.¹²⁶ It can be seen that the usual order of basicity of amines (when the proton is the reference acid) can be completely inverted by using a large enough acid. The strain caused by formation of a covalent bond when the two atoms involved each have three large groups is called *face strain* or *F strain*.

Steric effects can indirectly affect acidity or basicity by affecting the resonance (see p. 37). For example, *o*-*t*-butylbenzoic acid is about 10 times as strong as the para isomer, because the carboxyl group is forced out of the plane by the *t*-butyl group. Indeed, virtually all ortho benzoic acids are stronger than the corresponding para isomers, regardless of whether the group on the ring is electron-donating or electron-withdrawing.

Steric effects can also be caused by other types of strain. 1,8-Bis(diethylamino)-2,7-dimethoxynaphthalene (**1**) is an extremely strong base for a tertiary amine (pK_a of the



conjugate acid = 16.3; compare *N,N*-dimethylaniline, $pK_a = 5.1$), but proton transfers to

TABLE 8.5 Bases listed in increasing order of base strength when compared with certain reference acids

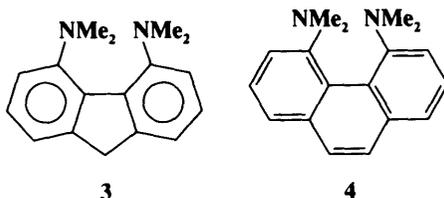
Increasing order of base strength ^a	Reference acid			
	H^+ or BMe_3	BMe_3	$\text{B}(\text{CMe}_3)_3$	
↓	NH_3	Et_3N	Me_3N	Et_3N
	Me_3N	NH_3	Me_2NH	Et_2NH
	MeNH_2	Et_2NH	NH_3	EtNH_2
	Me_2NH	EtNH_2	MeNH_2	NH_3

^aThe order of basicity (when the reference acids were boranes) was determined by the measurement of dissociation pressures.

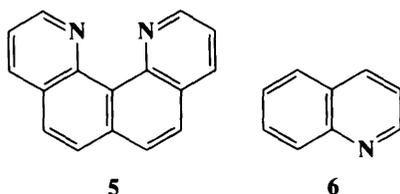
¹²⁵The effect discussed here is an example of a symmetry factor. For an extended discussion, see Ebersson, in Patai *The Chemistry of Carboxylic Acids and Esters*; Wiley: New York, 1969, pp. 211–293.

¹²⁶Brown *J. Am. Chem. Soc.* **1945**, 67, 378, 1452. Boranes in *Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972, pp. 53–64. See also Brown; Krishnamurthy; Hubbard *J. Am. Chem. Soc.* **1978**, 100, 3343.

and from the nitrogen are exceptionally slow; slow enough to be followed by a uv spectrophotometer.¹²⁷ **1** is severely strained because the two nitrogen lone pairs are forced to be near each other.¹²⁸ Protonation relieves the strain: one lone pair is now connected to a hydrogen, which forms a hydrogen bond to the other lone pair (shown in **2**). The same effects are found in 4,5-bis(dimethylamino)fluorene (**3**)¹²⁹ and 4,5-bis(dimethylamino)-

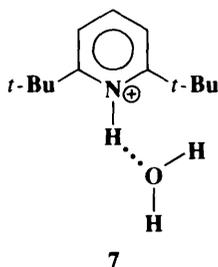


phenanthrene (**4**).¹³⁰ Compounds such as **1**, **3**, and **4** are known as *proton sponges*.¹³¹ Another type of proton sponge is quino[7,8-*h*]quinoline (**5**).¹³² Protonation of this compound also gives a stable monoprotonated ion similar to **2**, but the steric hindrance found in **1**, **3**, and



4 is absent. Therefore **5** is a much stronger base than quinoline (**6**) (pK_a values of the conjugate acids are 12.8 for **5** and 4.9 for **6**), but proton transfers are not abnormally slow.

Another type of steric effect is the result of an entropy effect. The compound 2,6-di-*t*-butylpyridine is a weaker base than either pyridine or 2,6-dimethylpyridine.¹³³ The reason is that the conjugate acid (**7**) is less stable than the conjugate acids of non-sterically



¹²⁷Alder; Goode; Miller; Hibbert; Hunte; Robbins *J. Chem. Soc., Chem. Commun.* **1978**, 89; Hibbert; Hunte *J. Chem. Soc., Perkin Trans. 2* **1963**, 1895; Barnett; Hibbert *J. Am. Chem. Soc.* **1984**, 106, 2080; Hibbert; Simpson *J. Chem. Soc., Perkin Trans. 2* **1987**, 243, 613.

¹²⁸For a review of the effect of strain on amine basicities, see Alder *Chem. Rev.* **1989**, 89, 1215-1223.

¹²⁹Staab; Saupe; Krieger *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 731 [*Angew. Chem.* 95, 748].

¹³⁰Saupe; Krieger; Staab *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 451 [*Angew. Chem.* 98, 460].

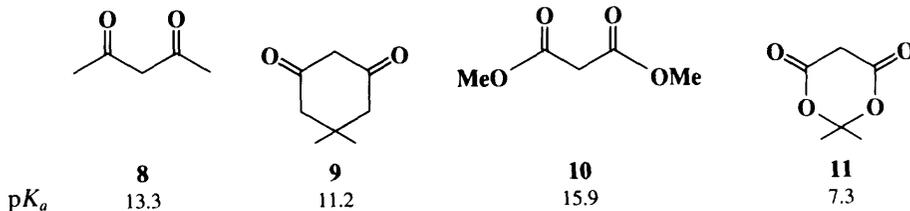
¹³¹For a review, see Staab; Saupe *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 865-879 [*Angew. Chem.* 895-909].

¹³²Zirnstein; Staab *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 460 [*Angew. Chem.* 99, 460]; Krieger; Newsom; Zirnstein; Staab *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 84 [*Angew. Chem.* 101, 72]. See also Schwesinger; Missfeldt; Peters; Schnering *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 1165 [*Angew. Chem.* 99, 1210]; Alder; Eastment; Hext; Moss; Orpen; White *J. Chem. Soc., Chem. Commun.* **1988**, 1528; Staab; Zirnstein; Krieger *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 86 [*Angew. Chem.* 101, 73].

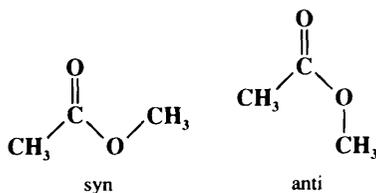
¹³³Brown; Kanner *J. Am. Chem. Soc.* **1953**, 75, 3865; **1966**, 88, 986.

hindered pyridines. In all cases the conjugate acids are hydrogen-bonded to a water molecule, but in the case of **7** the bulky *t*-butyl groups restrict rotations in the water molecule, lowering the entropy.¹³⁴

The conformation of a molecule can also affect its acidity. The following pK_a values were determined for these compounds:¹³⁵



Since ketones are stronger acids than carboxylic esters (Table 8.1), we are not surprised that **8** is a stronger acid than **10**. But cyclization of **8** to **9** increases the acidity by only 2.1 pK units while cyclization of **10** to **11** increases it by 8.6 units. Indeed, it has long been known that **11** (called Meldrum's acid) is an unusually strong acid for a 1,3-diester. In order to account for this very large cyclization effect, molecular orbital calculations were carried out two conformations of methyl acetate and of its enolate ion by two groups.¹³⁶ Both found



that loss of a proton is easier by about 5 kcal/mol (21 kJ/mol) for the syn than for the anti conformer of the ester. In an acyclic molecule like **10** the preferred conformations are anti, but in Meldrum's acid (**11**) the conformation on both sides is constrained to be syn.

7. Hybridization. An *s* orbital has a lower energy than a *p* orbital. Therefore the energy of a hybrid orbital is lower the more *s* character it contains. It follows that a carbanion at an *sp* carbon is more stable than a corresponding carbanion at an *sp*² carbon. Thus $\text{HC}\equiv\text{C}^-$, which has more *s* character in its unshared pair than $\text{CH}_2=\text{CH}^-$ or CH_3CH_2^- (*sp* vs. *sp*² vs. *sp*³, respectively), is a much weaker base. This explains the relatively high acidity of acetylenes and HCN. Another example is that alcohol and ether oxygens, where the unshared pair is *sp*³, are more strongly basic than carbonyl oxygens, where the unshared pair is *sp*² (Table 8.1).

The Effects of the Medium on Acid and Base Strength

Structural features are not the only factors that affect acidity or basicity. The same compound can have its acidity or basicity changed when the conditions are changed. The effect of

¹³⁴Meot-Ner; Sieck *J. Am. Chem. Soc.* **1983**, *105*, 2956; Hopkins; Jahagirdar; Moulik; Aue; Webb; Davidson; Pedley *J. Am. Chem. Soc.* **1984**, *106*, 4341; Meot-Ner; Smith *J. Am. Chem. Soc.* **1991**, *113*, 862, and references cited in these papers. See also Benoit; Fréchette; Lefebvre *Can. J. Chem.* **1988**, *66*, 1159.

¹³⁵Arnett; Harrelson *J. Am. Chem. Soc.* **1987**, *109*, 809.

¹³⁶Wang; Houk *J. Am. Chem. Soc.* **1988**, *110*, 1870; Wiberg; Laidig *J. Am. Chem. Soc.* **1988**, *110*, 1872.

temperature (p. 253) has already been mentioned. More important is the effect of the solvent, which can exert considerable influence on acid and base strengths by differential solvation.¹³⁷ If a base is more solvated than its conjugate acid, its stability is increased relative to the conjugate acid. For example, Table 8.5 shows that toward the proton, where steric effects are absent, methylamine is a stronger base than ammonia and dimethylamine is stronger still.¹³⁸ These results are easily explainable if one assumes that methyl groups are electron-donating. However, trimethylamine, which should be even stronger, is a weaker base than dimethylamine or methylamine. This apparently anomalous behavior can be explained by differential hydration.¹³⁹ Thus, NH_4^+ is much better hydrated (by hydrogen bonding to the water solvent) than NH_3 because of its positive charge.¹⁴⁰ It has been estimated that this effect contributes about 11 pK units to the base strength of ammonia.¹⁴¹ When methyl groups replace hydrogen, this difference in hydration decreases¹⁴² until, for trimethylamine, it contributes only about 6 pK units to the base strength.¹⁴¹ Thus two effects act in opposite directions, the field effect increasing the basicity as the number of methyl groups increases and the hydration effect decreasing it. When the effects are added, the strongest base is dimethylamine and the weakest is ammonia. If alkyl groups are electron-donating, one would expect that in the gas phase,¹⁴³ where the solvation effect does not exist, the basicity order of amines toward the proton should be $\text{R}_3\text{N} > \text{R}_2\text{NH} > \text{RNH}_2 > \text{NH}_3$, and this has indeed been confirmed, for $\text{R} = \text{Me}$ as well as $\text{R} = \text{Et}$ and Pr .¹⁴⁴ Aniline too, in the gas phase, is a stronger base than NH_3 ,¹⁴⁵ so its much lower basicity in aqueous solution ($\text{p}K_a$ of PhNH_3^+ 4.60 compared with 9.24 for aqueous NH_4^+) is caused by similar solvation effects and not by resonance and field electron-withdrawing effects of a phenyl group. Similarly, pyridine¹⁴⁶ and pyrrole¹⁴⁷ are both much less basic than NH_3 in aqueous solution (pyrrole¹⁴⁸ is neutral in aqueous solution) but *more* basic in the gas phase. These examples in particular

¹³⁷For reviews of the effects of solvent, see Epshtein; Iogansen *Russ. Chem. Rev.* **1990**, *59*, 134-151; Dyumaev; Korolev *Russ. Chem. Rev.* **1980**, *49*, 1021-1032. For a review of the effects of the solvent dimethyl sulfoxide, see Taft; Bordwell *Acc. Chem. Res.* **1988**, *21*, 463-469.

¹³⁸For a review of the basicity of amines, see Ref. 122.

¹³⁹Trotman-Dickenson *J. Chem. Soc.* **1949**, 1293; Pearson *J. Am. Chem. Soc.* **1948**, *70*, 204; Pearson; Williams *J. Am. Chem. Soc.* **1954**, *76*, 258; Hall *J. Am. Chem. Soc.* **1957**, *79*, 5441; Arnett; Jones; Taagepera; Henderson; Beauchamp; Holtz; Taft *J. Am. Chem. Soc.* **1972**, *94*, 4724; Aue; Webb; Bowers *J. Am. Chem. Soc.* **1972**, *94*, 4726; **1976**, *98*, 311, 318; Mucci; Domain; Benoit *Can. J. Chem.* **1980**, *58*, 953. See also Drago; Cundari; Ferris *J. Org. Chem.* **1989**, *54*, 1042.

¹⁴⁰For discussions of the solvation of ammonia and amines, see Jones; Arnett *Prog. Phys. Org. Chem.* **1974**, *11*, 263-420; Grunwald; Ralph *Acc. Chem. Res.* **1971**, *4*, 107-113.

¹⁴¹Condon *J. Am. Chem. Soc.* **1965**, *87*, 4481, 4485.

¹⁴²For two reasons: (1) the alkyl groups are poorly solvated by the water molecules, and (2) the strength of the hydrogen bonds of the BH^+ ions decreases as the basicity of B increases: Lau; Kebarle *Can. J. Chem.* **1981**, *59*, 151.

¹⁴³For reviews of acidities and basicities in the gas phase, see Liebman *Mol. Struct. Energ.* **1987**, *4*, 49-70; Dixon; Lias *Mol. Struct. Energ.* **1987**, *2*, 269-314; Bohme, in Patai, Ref. 117, pp. 731-762; Bartmess; McIver, in Bowers *Gas Phase Ion Chemistry*, vol. 2; Academic Press: New York, 1979, pp. 88-121; Kabachnik *Russ. Chem. Rev.* **1979**, *48*, 814-827; Kebarle *Annu. Rev. Phys. Chem.* **1977**, *28*, 445-476; Arnett *Acc. Chem. Res.* **1973**, *6*, 404-409. For a comprehensive table of gas-phase basicities, see Lias; Liebman; Levin *J. Phys. Chem. Ref. Data* **1984**, *13*, 695-808. See also the tables of gas-phase acidities and basicities in Meot-Ner; Kafafi *J. Am. Chem. Soc.* **1988**, *110*, 6297; Headley *J. Am. Chem. Soc.* **1987**, *109*, 2347; McMahon; Kebarle *J. Am. Chem. Soc.* **1985**, *107*, 2612; **1977**, *99*, 2222, 3399; Wolf; Staley; Koppel; Taagepera; McIver; Beauchamp; Taft *J. Am. Chem. Soc.* **1977**, *99*, 5417; Cumming; Kebarle *J. Am. Chem. Soc.* **1977**, *99*, 5818; **1978**, *100*, 1835; *Can. J. Chem.* **1978**, *56*, 1; Bartmess; Scott; McIver *J. Am. Chem. Soc.* **1979**, *101*, 6046; Fujio; McIver; Taft *J. Am. Chem. Soc.* **1981**, *103*, 4017; Lau; Nishizawa; Tse; Brown; Kebarle *J. Am. Chem. Soc.* **1981**, *103*, 6291.

¹⁴⁴Munson *J. Am. Chem. Soc.* **1965**, *87*, 2332; Brauman; Riveros; Blair *J. Am. Chem. Soc.* **1971**, *93*, 3914; Briggs; Yamdagni; Kebarle *J. Am. Chem. Soc.* **1972**, *94*, 5128; Aue; Webb; Bowers, Ref. 139.

¹⁴⁵Briggs; Yamdagni; Kebarle, Ref. 144; Dzidic *J. Am. Chem. Soc.* **1972**, *94*, 8333; Ikuta; Kebarle *Can. J. Chem.* **1983**, *61*, 97.

¹⁴⁶Taagepera; Henderson; Brownlee; Beauchamp; Holtz; Taft *J. Am. Chem. Soc.* **1972**, *94*, 1369; Taft; Taagepera; Summerhays; Mitsky *J. Am. Chem. Soc.* **1973**, *95*, 3811; Briggs; Yamdagni; Kebarle, Ref. 144.

¹⁴⁷Yamdagni; Kebarle *J. Am. Chem. Soc.* **1973**, *95*, 3504.

¹⁴⁸For a review of the basicity and acidity of pyrroles, see Catalan; Abboud; Elguero *Adv. Heterocycl. Chem.* **1987**, *41*, 187-274.

show how careful one must be in attributing relative acidities or basicities to any particular effect.

For simple alcohols the order of gas-phase *acidity* is completely reversed from that in aqueous solution. In solution the acidity is in the order $\text{H}_2\text{O} > \text{MeCH}_2\text{OH} > \text{Me}_2\text{CHOH} > \text{Me}_3\text{COH}$, but in the gas phase the order is precisely the opposite.¹⁴⁹ Once again solvation effects can be invoked to explain the differences. Comparing the two extremes, H_2O and Me_3COH , we see that the OH^- ion is very well solvated by water while the bulky Me_3CO^- is much more poorly solvated because the water molecules cannot get as close to the oxygen. Thus in solution H_2O gives up its proton more readily. When solvent effects are absent, however, the intrinsic acidity is revealed and Me_3COH is a stronger acid than H_2O . This result demonstrates that simple alkyl groups cannot be simply regarded as electron-donating. If methyl is an electron-donating group, then Me_3COH should be an intrinsically weaker acid than H_2O , yet it is stronger. A similar pattern is found with carboxylic acids, where simple aliphatic acids such as propanoic are stronger than acetic acid in the gas phase,¹⁵⁰ though weaker in aqueous solution (Table 8.4). The evidence in these and other cases¹⁵¹ is that alkyl groups can be electron-donating when connected to unsaturated systems but in other systems may have either no effect or may actually be electron-withdrawing. The explanation given for the intrinsic gas-phase acidity order of alcohols as well as the basicity order of amines is that alkyl groups, because of their polarizability, can spread both positive and negative charges.¹⁵² It has been calculated that even in the case of alcohols the field effects of the alkyl groups are still operating normally, but are swamped by the greater polarizability effects.¹⁵³ Polarizability effects on anionic centers are a major factor in gas-phase acid–base reactions.¹⁵⁴

It has been shown (by running reactions on ions that are solvated in the gas phase) that solvation by even one molecule of solvent can substantially affect the order of basicities.¹⁵⁵

An important aspect of solvent effects is the effect on the orientation of solvent molecules when an acid or base is converted to its conjugate. For example, consider an acid RCOOH converted to RCOO^- in aqueous solution. The solvent molecules, by hydrogen bonding, arrange themselves around the COO^- group in a much more orderly fashion than they had been arranged around the COOH group (because they are more strongly attracted to the negative charge). This represents a considerable loss of freedom and a decrease in entropy. Thermodynamic measurements show that for simple aliphatic and halogenated aliphatic acids in aqueous solution at room temperature, the entropy ($T\Delta S$) usually contributes much more to the total free-energy change ΔG than does the enthalpy ΔH .¹⁵⁶ Two examples are shown in Table 8.6.¹⁵⁷ Resonance and field effects of functional groups therefore affect the acidity of RCOOH in two distinct ways. They affect the enthalpy (electron-withdrawing

¹⁴⁹Baird *Can. J. Chem.* **1969**, *47*, 2306; Brauman; Blair, Ref. 70; Arnett; Small; McIver; Miller *J. Am. Chem. Soc.* **1974**, *96*, 5638; Blair; Isolani; Riveros *J. Am. Chem. Soc.* **1973**, *95*, 1057; McIver; Scott; Riveros *J. Am. Chem. Soc.* **1973**, *95*, 2706. The alkythiols behave similarly: gas-phase acidity increases with increasing group size while solution (aqueous) acidity decreases: Bartmess; McIver *J. Am. Chem. Soc.* **1977**, *99*, 4163.

¹⁵⁰For a table of gas-phase acidities of 47 simple carboxylic acids, see Caldwell; Renneboog; Kebarle *Can. J. Chem.* **1989**, *67*, 611.

¹⁵¹Brauman; Blair *J. Am. Chem. Soc.* **1971**, *93*, 4315; Kwart; Takeshita *J. Am. Chem. Soc.* **1964**, *86*, 1161; Fort; Schleyer *J. Am. Chem. Soc.* **1964**, *86*, 4194; Holtz; Stock *J. Am. Chem. Soc.* **1965**, *87*, 2404; Laurie; Muentzer *J. Am. Chem. Soc.* **1966**, *88*, 2883.

¹⁵²Brauman; Blair, Ref. 70; Munson, Ref. 144; Brauman; Riveros; Blair, Ref. 144; Huheey *J. Org. Chem.* **1971**, *36*, 204; Radom *Aust. J. Chem.* **1975**, *28*, 1; Aitken; Bahl; Bomben; Gimzewski; Nolan; Thomas *J. Am. Chem. Soc.* **1980**, *102*, 4873.

¹⁵³Taft; Taagepera; Abboud; Wolf; DeFrees; Hehre; Bartmess; McIver *J. Am. Chem. Soc.* **1978**, *100*, 7765. For a scale of polarizability parameters, see Hehre; Pau; Headley; Taft; Topsom *J. Am. Chem. Soc.* **1986**, *108*, 1711.

¹⁵⁴Bartmess; Scott; McIver *J. Am. Chem. Soc.* **1979**, *101*, 6056.

¹⁵⁵Bohme; Rakshit; Mackay *J. Am. Chem. Soc.* **1982**, *104*, 1100.

¹⁵⁶Bolton; Hepler, Ref. 115; Ref. 71. See also Wilson; Georgiadis; Bartmess *J. Am. Chem. Soc.* **1991**, *113*, 1762.

¹⁵⁷Bolton; Hepler, Ref. 115, p. 529; Hambly, Ref. 71, p. 92.

TABLE 8.6 Thermodynamic values for the ionizations of acetic and chloroacetic acids in H₂O at 25°C¹⁵⁷

Acid	p <i>K</i> _a	ΔG		ΔH		<i>T</i> ΔS	
		kcal/mol	kJ/mole	kcal/mole	kJ/mol	kcal/mol	kJ/mol
CH ₃ COOH	4.76	+6.5	+27	-0.1	-0.4	-6.6	-28
ClCH ₂ COOH	2.86	+3.9	+16	-1.1	-4.6	-5.0	-21
Cl ₂ CCOOH	0.65	+0.9	+3.8	+1.5	+6.3	+0.6	+2.5

groups increase acidity by stabilizing RCOO⁻ by charge dispersal), but they also affect the entropy (by lowering the charge on the COO⁻ group and by changing the electron-density distribution in the COOH group, electron-withdrawing groups alter the solvent orientation patterns around both the acid and the ion, and consequently change ΔS).

A change from a protic to an aprotic solvent can also affect the acidity or basicity, since there is a difference in solvation of anions by a protic solvent (which can form hydrogen bonds) and an aprotic one.¹⁵⁸ The effect can be extreme: in DMF, picric acid is stronger than HBr,¹⁵⁹ though in water HBr is far stronger. This particular result can be attributed to size. That is, the large ion (O₂N)₃C₆H₂O⁻ is better solvated by DMF than the smaller ion Br⁻.¹⁶⁰ The ionic strength of the solvent also influences acidity or basicity, since it has an influence on activity coefficients.

In summary, solvation can have powerful effects on acidity and basicity. In the gas phase the effects discussed in the previous section, especially resonance and field effects, operate unhindered by solvent molecules. As we have seen, electron-withdrawing groups generally increase acidity (and decrease basicity); electron-donating groups act in the opposite way. In solution, especially aqueous solution, these effects still largely persist (which is why p*K* values in Table 8.4 do largely correlate with resonance and field effects), but in general are much weakened, and occasionally reversed.¹¹⁹

¹⁵⁸For a review, see Parker *Q. Rev., Chem. Soc.* **1962**, *16*, 163-187.

¹⁵⁹Scars; Wolford; Dawson *J. Electrochem. Soc.* **1956**, *103*, 633.

¹⁶⁰Miller; Parker *J. Am. Chem. Soc.* **1961**, *83*, 117.

9

EFFECTS OF STRUCTURE ON REACTIVITY

When the equation for a reaction of, say, carboxylic acids, is written, it is customary to use the formula RCOOH , which implies that all carboxylic acids undergo the reaction. Since most compounds with a given functional group do give more or less the same reactions, the custom is useful, and the practice is used in this book. It allows a large number of individual reactions to be classified together and serves as an aid both for memory and understanding. Organic chemistry would be a huge morass of unconnected facts without the symbol R. Nevertheless, it must be borne in mind that a given functional group does not always react the same way, regardless of what molecule it is a part of. The reaction at the functional group is influenced by the rest of the molecule. This influence may be great enough to stop the reaction completely or to make it take an entirely different course. Even when two compounds with the same functional group undergo the same reaction, the rates and/or the positions of equilibrium are usually different, sometimes slightly, sometimes greatly, depending on the structures of the compounds. The greatest variations may be expected when additional functional groups are present.

The effects of structure on reactivity can be divided into three major types: field, resonance (or mesomeric), and steric.¹ In most cases two or all three of these are operating, and it is usually not easy to tell how much of the rate enhancement (or decrease) is caused by each of the three effects.

Resonance and Field Effects

It is often particularly difficult to separate resonance and field effects; they are frequently grouped together under the heading of *electrical effects*.² Field effects were discussed on pp. 17-19. Table 1.3 contains a list of some $+I$ and $-I$ groups. As for resonance effects, on p. 36 it was shown how the electron density distribution in aniline is not the same as it would be if there were no resonance interaction between the ring and the NH_2 group. Most groups that contain an unshared pair on an atom connected to an unsaturated system display a similar effect; i.e., the electron density on the group is less than expected, and the density on the unsaturated system is greater. Such groups are said to be electron-donating by the resonance effect ($+M$ groups). Alkyl groups, which do not have an unshared pair, are also $+M$ groups, presumably because of hyperconjugation.

On the other hand, groups that have a multiple-bonded electronegative atom directly connected to an unsaturated system are $-M$ groups. In such cases we can draw canonical

¹For a monograph, see Klumpp *Reactivity in Organic Chemistry*; Wiley: New York, 1982. For a general theoretical approach to organic reactivity, see Pross *Adv. Phys. Org. Chem.* **1985**, *21*, 99-196.

²For reviews of the study of electrical effects by ab initio mo methods, see Topsom *Prog. Phys. Org. Chem.* **1987**, *16*, 125-191. *Mol. Struct. Energ.* **1987**, *4*, 235-269.

forms in which electrons have been taken from the unsaturated system into the group, e.g.,

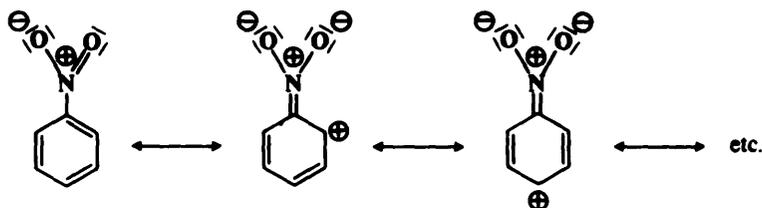
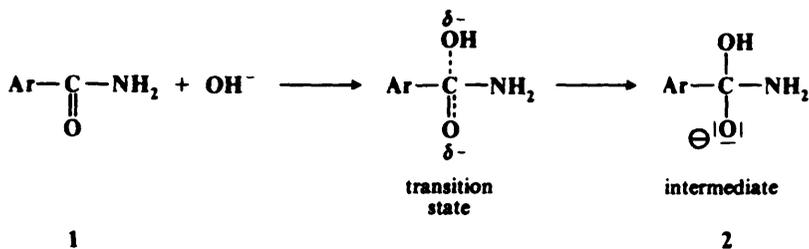


Table 9.1 contains a list of some $+M$ and $-M$ groups.

The resonance effect of a group, whether $+M$ or $-M$, operates only when the group is directly connected to an unsaturated system, so that, for example, in explaining the effect of the CH_3O group on the reactivity of the COOH in $\text{CH}_3\text{OCH}_2\text{CH}_2\text{COOH}$, only the field effect of the CH_3O need be considered. This is one way of separating the two effects. In *p*-methoxybenzoic acid both effects must be considered. The field effect operates through space, solvent molecules, or the σ bonds of a system, while the resonance effect operates through π electrons.

It must be emphasized once again that neither by the resonance nor by the field effect are any electrons actually being donated or withdrawn, though these terms are convenient (and we shall use them). As a result of both effects, the electron-density distribution is not the same as it would be without the effect (see pp. 18, 36). One thing that complicates the study of these effects on the reactivity of compounds is that a given group may have an effect in the transition state which is considerably more or less than it has in the unreacting molecule.

An example will show the nature of electrical effects (resonance and field) on reactivity. In the alkaline hydrolysis of aromatic amides (**0-11**), the rate-determining step is the attack of hydroxide ion at the carbonyl carbon:



In the transition state, which has a structure somewhere between that of the starting amide (**1**) and the intermediate (**2**), the electron density on the carbonyl carbon is increased. Therefore, electron-withdrawing groups ($-I$ or $-M$) on the aromatic ring will lower the free energy of the transition state (by spreading the negative charge). These groups have much less effect on the free energy of **1**. Since G is lowered for the transition state, but not substantially for **1**, ΔG^\ddagger is lowered and the reaction rate is increased (Chapter 6). Conversely, electron-donating groups ($+I$ or $+M$) should decrease the rate of this reaction. Of course, many groups are $-I$ and $+M$, and for these it is not always possible to predict which effect will predominate.

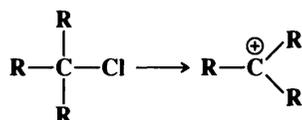
TABLE 9.1 Some groups with +M and -M effects, not listed in order of strength of effect
Ar appears in both lists because it is capable of both kinds of effect

+ M groups		-M groups	
O ⁻	SR	NO ₂	CHO
S ⁻	SH	CN	COR
NR ₂	Br	COOH	SO ₂ R
NHR	I	COOR	SO ₂ OR
NH ₂	Cl	CONH ₂	NO
NHCOR	F	CONHR	Ar
OR	R	CONR ₂	
OH	Ar		
OCOR			

Steric Effects

It occasionally happens that a reaction proceeds much faster or much slower than expected on the basis of electrical effects alone. In these cases it can often be shown that steric effects are influencing the rate. For example, Table 9.2 lists relative rates for the S_N2 ethanolysis of certain alkyl halides (see p. 294).³ All these compounds are primary bromides; the branching is on the second carbon, so that field-effect differences should be small. As Table 9.2 shows, the rate decreases with increasing β branching and reaches a very low value for neopentyl bromide. This reaction is known to involve an attack by the nucleophile from a position opposite to that of the bromine (see p. 294). The great decrease in rate can be attributed to *steric hindrance*, a sheer physical blockage to the attack of the nucleophile. Another example of steric hindrance is found in 2,6-disubstituted benzoic acids, which are difficult to esterify no matter what the resonance or field effects of the groups in the 2 or the 6 position. Similarly, once 2,6-disubstituted benzoic acids *are* esterified, the esters are difficult to hydrolyze.

Not all steric effects decrease reaction rates. In the hydrolysis of RCl by an S_N1 mechanism (see p. 298), the first step, which is rate-determining, involves ionization of the alkyl chloride to a carbocation:



The central carbon in the alkyl chloride is *sp*³-hybridized, with angles of about 109.5°, but

TABLE 9.2 Relative rates of reaction of RBr with ethanol³

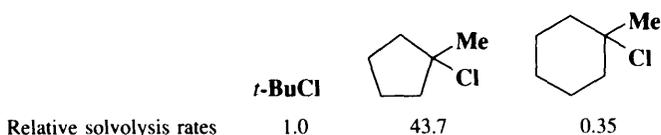
R	Relative rate
CH ₃	17.6
CH ₃ CH ₂	1
CH ₃ CH ₂ CH ₂	0.28
(CH ₃) ₂ CHCH ₂	0.030
(CH ₃) ₃ CCH ₂	4.2 × 10 ⁻⁶

³Hughes *Q. Rev., Chem. Soc.* **1948**, 2, 107-131.

when it is converted to the carbocation, the hybridization becomes sp^2 and the preferred angle is 120° . If the halide is tertiary and the three alkyl groups are large enough, they will be pushed together by the enforced tetrahedral angle, resulting in strain (see p. 163). This type of strain is called *B strain*⁴ (for back strain), and it can be relieved by ionization to the carbocation.⁵

The rate of ionization (and hence the solvolysis rate) of a molecule in which there is B strain is therefore expected to be larger than in cases where B strain is not present. Table 9.3 shows that this is so.⁶ Substitution of ethyl groups for the methyl groups of *t*-butyl chloride does not cause B strain; the increase in rate is relatively small, and the rate smoothly rises with the increasing number of ethyl groups. The rise is caused by normal field and resonance (hyperconjugation) effects. Substitution by one isopropyl group is not greatly different. But with the second isopropyl group the crowding is now great enough to cause B strain, and the rate is increased tenfold. Substitution of a third isopropyl group increases the rate still more. Another example where B strain increases solvolysis rates is found with the highly crowded molecules tri-*t*-butylcarbinol, di-*t*-butylneopentylcarbinol, *t*-butylideneopentylcarbinol, and trineopentylcarbinol, where rates of solvolysis of the *p*-nitrobenzoate esters are faster than that of *t*-butyl nitrobenzoate by factors of 13,000, 19,000, 68,000, and 560, respectively.⁷

Another type of strain, that can affect rates of cyclic compounds, is called *I strain* (internal strain).⁸ This type of strain results from changes in ring strain in going from a tetrahedral to a trigonal carbon or vice versa. For example, as mentioned above, S_N1 solvolysis of an alkyl halide involves a change in the bond angle of the central carbon from about 109.5° to about 120° . This change is highly favored in 1-chloro-1-methylcyclopentane because it relieves eclipsing strain (p. 156); thus this compound undergoes solvolysis in 80% ethanol at



25°C 43.7 times faster than the reference compound *t*-butyl chloride.⁹ In the corresponding cyclohexyl compound this factor is absent because the substrate does not have eclipsing

TABLE 9.3 Rates of hydrolysis of tertiary alkyl chlorides at 25°C in 80% aqueous ethanol⁶

Halide	Rate	Halide	Rate
Me₃CCl	0.033	Et₃CCl	0.099
Me₂EtCCl	0.055	Me₂(iso-Pr)CCl	0.029
MeEt₂CCl	0.086	Me(iso-Pr)₂CCl	0.45

⁴For a discussion, see Brown *Boranes in Organic Chemistry*, Cornell University Press: Ithaca, NY, 1972, pp. 114-121.

⁵For reviews of the effects of strain on reactivity, see Stirling *Tetrahedron* **1985**, *41*, 1613-1666. *Pure Appl. Chem.* **1984**, *56*, 1781-1796.

⁶Brown; Fletcher *J. Am. Chem. Soc.* **1949**, *71*, 1845.

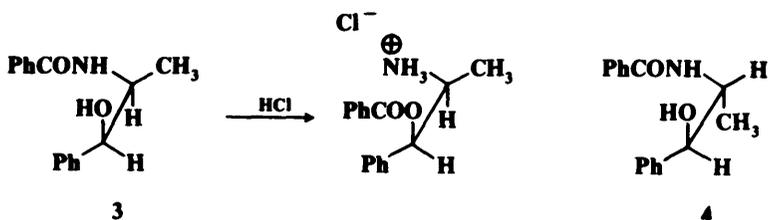
⁷Bartlett; Tidwell *J. Am. Chem. Soc.* **1968**, *90*, 4421.

⁸For a discussion, see Ref. 4, pp. 105-107, 126-128.

⁹Brown; Borkowski *J. Am. Chem. Soc.* **1952**, *74*, 1894. See also Brown; Ravindranathan; Peters; Rao; Rho *J. Am. Chem. Soc.* **1977**, *99*, 5373.

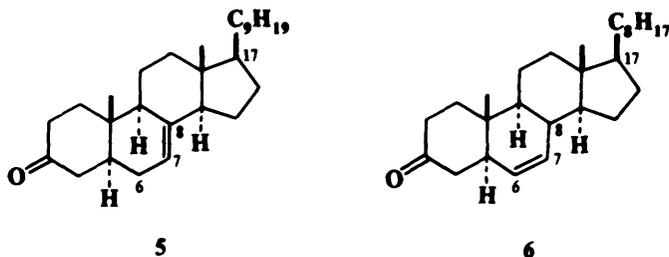
strain (p. 156), and this compound undergoes the reaction at about one-third the rate of *t*-butyl chloride. The reasons for this small decrease in rate are not clear. Corresponding behavior is found in the other direction, in changes from a trigonal to a tetrahedral carbon. Thus cyclohexanone undergoes addition reactions faster than cyclopentanone. Similar considerations apply to larger rings. Rings of 7 to 11 members exhibit eclipsing and transannular strain; and in these systems reactions in which a tetrahedral carbon becomes trigonal generally proceed faster than in open-chain systems.¹⁰

Conformational effects on reactivity can be considered under the heading of steric effects,¹¹ though in these cases we are considering not the effect of a group X and that of another group X' upon reactivity at a site Y but the effect of the conformation of the molecule. Many reactions fail entirely unless the molecules are able to assume the proper conformation. An example is the rearrangement of N-benzoylnorephedrine. The two dia-



stereomers of this compound behave very differently when treated with alcoholic HCl. In one of the isomers nitrogen-to-oxygen migration takes place, while the other does not react at all.¹² In order for the migration to take place, the nitrogen must be near the oxygen (*gauche* to it). When **3** assumes this conformation, the methyl and phenyl groups are anti to each other, which is a favorable position, but when **4** has the nitrogen *gauche* to the oxygen, the methyl must be *gauche* to the phenyl, which is so unfavorable that the reaction does not occur. Other examples are electrophilic additions to C=C double bonds (see p. 735) and E2 elimination reactions (see p. 983). Also, many examples are known where axial and equatorial groups behave differently.¹³

In steroids and other rigid systems, a functional group in one part of the molecule can strongly affect the rate of a reaction taking place at a remote part of the same molecule by altering the conformation of the whole skeleton. An example of this effect, called *conformational transmission*, is found in ergost-7-en-3-one (**5**) and cholest-6-en-3-one (**6**), where **6** condenses with benzaldehyde 15 times faster than **5**.¹⁴ The reaction site in both cases is



¹⁰See, for example, Schneider; Thomas *J. Am. Chem. Soc.* **1980**, *102*, 1424.

¹¹For reviews of conformational effects, see Green; Arad-Yellin; Cohen *Top. Stereochem.* **1986**, *16*, 131-218; Ōki *Acc. Chem. Res.* **1984**, *17*, 154-159; Seeman *Chem. Rev.* **1983**, *83*, 83-134. See also Ōki; Tsukahara; Moriyama; Nakamura *Bull. Chem. Soc. Jpn.* **1987**, *60*, 223, and other papers in this series.

¹²Fodor; Bruckner; Kiss; Ōhegyi *J. Org. Chem.* **1949**, *14*, 337.

¹³For a discussion, see Eliel *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962, pp. 219-234.

¹⁴Barton; McCapra; May; Thudium *J. Chem. Soc.* **1960**, 1297.

the carbonyl group, and the rate increases because moving the double bond from the 7 to the 6 position causes a change in conformation at the carbonyl group (the difference in the side chain at C-17 does not affect the rate).

Quantitative Treatments of the Effect of Structure on Reactivity¹⁵

Suppose a reaction is performed on a substrate molecule that can be represented as XGY, where Y is the site of the reaction, X a variable substituent, and G a skeleton group to which X and Y are attached, and we find that changing X from H to CH₃ results in a rate increase by a factor, say, 10. We would like to know just what part of the increase is due to each of the effects previously mentioned. The obvious way to approach such a problem is to try to find compounds in which one or two of the factors are absent or at least negligible. This is not easy to do acceptably because factors that seem negligible to one investigator do not always appear so to another. The first attempt to give numerical values was that of Hammett.¹⁶ For the cases of *m*- and *p*-XC₆H₄Y, Hammett set up the equation

$$\log \frac{k}{k_0} = \sigma \rho$$

where k_0 is the rate constant or equilibrium constant for X = H, k is the constant for the group X, ρ is a constant for a given reaction under a given set of conditions, and σ is a constant characteristic of the group X. The equation is called the *Hammett equation*.

The value of ρ was set at 1.00 for ionization of XC₆H₄COOH in water at 25°C. σ_m and σ_p values were then calculated for each group (for a group X, σ is different for the meta and para positions). Once a set of σ values was obtained, ρ values could be obtained for other reactions from the rates of just two X-substituted compounds, if the σ values of the X groups were known (in practice, at least four well-spaced values are used to calculate ρ because of experimental error and because the treatment is not exact). With the ρ value thus calculated and the known σ values for other groups, rates can be predicted for reactions that have not yet been run.

The σ values are numbers that sum up the total electrical effects (resonance plus field) of a group X when attached to a benzene ring. The treatment usually fails for the ortho position. The Hammett treatment has been applied to many reactions and to many functional groups and correlates quite well an enormous amount of data. Jaffé's review article¹⁶ lists ρ values for 204 reactions,¹⁷ many of which have different ρ values for different conditions.

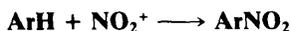
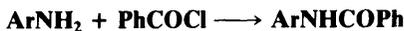
¹⁵For monographs, see Exner *Correlation Analysis of Chemical Data*; Plenum: New York, 1988; Johnson *The Hammett Equation*; Cambridge University Press: Cambridge, 1973; Shorter *Correlation Analysis of Organic Reactivity*; Wiley: New York, 1982; *Correlation Analysis in Organic Chemistry*; Clarendon Press: Oxford, 1973; Chapman: *Shorter Correlation Analysis in Chemistry: Recent Advances*; Plenum: New York, 1978; *Advances in Linear Free Energy Relationships*; Plenum: New York, 1972; Wells *Linear Free Energy Relationships*; Academic Press: New York, 1968. For reviews, see Connors *Chemical Kinetics*; VCH: New York, 1990, pp. 311-383; Lewis, in Bernasconi *Investigation of Rates and Mechanisms of Reactions* (vol. 6 of Weissberger *Techniques of Chemistry*), 4th ed.; Wiley: New York, 1986, pp. 871-901; Hammett, Ref. 2, pp. 347-390; Jones *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University Press: Cambridge, 1984, pp. 38-68; Charton, *CHEMTECH* **1974**, 502-511, **1975**, 245-255; Hine *Structural Effects in Organic Chemistry*; Wiley: New York, 1975, pp. 55-102; Afanas'ev *Russ. Chem. Rev.* **1971**, **40**, 216-232; Laurence; Wojtkowiak *Ann. Chim. (Paris)* **1970**, [14] **5**, 163-191. For a historical perspective, see Grunwald *CHEMTECH* **1984**, 698.

¹⁶For a review, see Jaffé *Chem. Rev.* **1953**, **53**, 191.

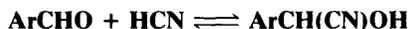
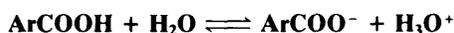
¹⁷Additional ρ values are given in Wells *Chem. Rev.* **1963**, **63**, 171-218 and van Bekkum; Verkade; Wepster *Recl. Trav. Chim. Pays-Bas* **1959**, **78**, 821-827.

Among them are reactions as disparate as the following:

Rate constants for



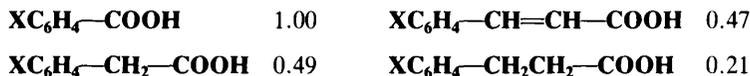
Equilibrium constants for



The Hammett equation has also been shown to apply to many physical measurements, including ir frequencies and nmr chemical shifts.¹⁸ The treatment is reasonably successful whether the substrates are attacked by electrophilic, nucleophilic, or free-radical reagents, the important thing being that the mechanism be the same *within* a given reaction series.

However, there are many reactions that do not fit the treatment. These are mostly reactions where the attack is directly on the ring and where the X group can enter into direct resonance interaction with the reaction site in the transition state (that is, the substrate is XY rather than XGY). For these cases, two new sets of σ values have been devised: σ^+ values (proposed by H. C. Brown) for cases in which an electron-donating group interacts with a developing positive charge in the transition state (this includes the important case of electrophilic aromatic substitutions; see Chapter 11), and σ^- values, where electron-withdrawing groups interact with a developing negative charge. Table 9.4 gives σ , σ^+ , and σ^- values for some common X groups.¹⁹ As shown in the table, σ is not very different from σ^+ for most electron-withdrawing groups. σ_m^- values are not shown in the table, since they are essentially the same as the σ_m values.

A positive value of σ indicates an electron-withdrawing group and a negative value an electron-donating group. The constant ρ measures the susceptibility of the reaction to electrical effects.²⁰ Reactions with a positive ρ are helped by electron-withdrawing groups and vice versa. The following ρ values for the ionization of some carboxylic acids illustrate this:²¹



¹⁸For a review of Hammett treatment of nmr chemical shifts, see Ewing, in Chapman; Shorter *Correlation Analysis in Chemistry: Recent Advances*; Plenum, New York, 1978, pp. 357-396.

¹⁹Unless otherwise noted, σ values are from Exner, in Chapman; Shorter, Ref. 18, pp. 439-540, and σ^+ values from Okamoto; Inukai; Brown *J. Am. Chem. Soc.* **1958**, *80*, 4969 and Brown; Okamoto *J. Am. Chem. Soc.* **1958**, *80*, 4979. σ^- values, except as noted, are from Jaffe. Ref. 16. Exner, pp. 439-540, has extensive tables giving values for more than 500 groups, as well as σ^+ , σ^- , σ_p , σ_m , and E_s values for many of these groups. Other large tables of the various sigma values are found in Hansch; Leo; Taft *Chem. Rev.* **1991**, *91*, 165-195. For tables of σ_p , σ_m , σ^+ , σ^- , and σ_R values of many groups containing Si, Ge, Sn, and Pb atoms, see Egorochkin; Razuvaev *Russ. Chem. Rev.* **1987**, *56*, 846-858. For values for heteroaromatic groups, see Mamaev; Shkurko; Baram *Adv. Heterocycl. Chem.* **1987**, *42*, 1-82.

²⁰For discussions of the precise significance of ρ , see Dubois; Ruasse; Argile *J. Am. Chem. Soc.* **1984**, *106*, 4840; Ruasse; Argile; Dubois *J. Am. Chem. Soc.* **1984**, *106*, 4846; Lee; Shim; Chung; Kim; Lee *J. Chem. Soc., Perkin Trans. 2* **1988**, 1919.

²¹Jones, Ref. 15, p. 42.

TABLE 9.4 σ , σ^+ , and σ^- values for some common groups¹⁹

Group	σ_p	σ_m	σ_p^+	σ_m^+	σ_p^-
O ⁻	-0.81 ³¹	-0.47 ³¹	-4.27 ³²	-1.15 ³²	
NMe ₂	-0.63	-0.10	-1.7		
NH ₂	-0.57	-0.09	-1.3	-0.16	
OH	-0.38 ²²	0.13 ²²	-0.92 ²³		
OMe	-0.28 ²²	0.10	-0.78	0.05	
CMe ₃	-0.15	-0.09	-0.26	-0.06	
Me	-0.14	-0.06	-0.31	-0.10 ²⁴	
H	0	0	0	0	0
Ph	0.05 ²⁵	0.05	-0.18	0 ²⁵	
COO ⁻	0.11 ³¹	0.02 ³¹	-0.41 ³²	-0.10 ³²	
F	0.15	0.34	-0.07	0.35	
Cl	0.24	0.37	0.11	0.40	
Br	0.26	0.37	0.15	0.41	
I	0.28 ²⁵	0.34	0.14	0.36	
N=NPh ²⁶	0.34	0.28	0.17		
COOH	0.44	0.35	0.42	0.32	0.73
COOR	0.44	0.35	0.48	0.37	0.68
COMe	0.47	0.36			0.87
CF ₃	0.53	0.46		0.57 ²⁴	
NH ₃ ⁺	0.60 ³¹	0.86 ³¹			
CN ²⁷	0.70	0.62	0.66	0.56	1.00
SO ₂ Me	0.73	0.64			
NO ₂	0.81	0.71	0.79	0.73 ²⁴	1.27
NMe ₃ ⁺	0.82 ²⁸	0.88 ²⁸	0.41	0.36	
N ₂ ⁺	1.93 ²⁹	1.65 ²⁹	1.88 ²⁹		3 ³⁰

This example shows that the insertion of a CH₂ or a CH=CH group diminishes electrical effects to about the same extent, while a CH₂CH₂ group diminishes them much more. A ρ greater than 1 would mean that the reaction is more sensitive to electrical effects than is the ionization of XC₆H₄COOH ($\rho = 1.00$).

Similar calculations have been made for compounds with two groups X and X' on one ring, where the σ values are sometimes additive and sometimes not,³³ for other ring systems such as naphthalene³⁴ and heterocyclic rings,³⁵ and for ethylenic and acetylenic systems.³⁶

²²Matsui; Ko; Hepler *Can. J. Chem.* **1974**, *52*, 2906.

²³de la Mare; Newman *Tetrahedron Lett.* **1982**, 1305 give this value as -1.6.

²⁴Amin; Taylor *Tetrahedron Lett.* **1978**, 267.

²⁵Sjöström; Wold *Chem. Scr.* **1976**, *9*, 200.

²⁶Byrne; Happer; Hartshorn; Powell *J. Chem. Soc., Perkin Trans. 2* **1987**, 1649.

²⁷For a review of directing and activating effects of C=O, C=C, C=N, and C=S groups, see Charton, in Patai *The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 239-298.

²⁸For a review of directing and activating effects of CN and C≡C groups, see Charton, in Patai: Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 1; Wiley: New York, 1983, pp. 269-323.

²⁹McDaniel; Brown *J. Org. Chem.* **1958**, *23*, 420.

³⁰Ustyniuk; Subbotin; Buchneva; Gruzdnova; Kazitsyna *Doklad. Chem.* **1976**, *227*, 175.

³¹Lewis; Johnson *J. Am. Chem. Soc.* **1959**, *81*, 2070.

³²Hine *J. Am. Chem. Soc.* **1960**, *82*, 4877.

³³Binev; Kuzmanova; Kaneti; Juchnovski *J. Chem. Soc., Perkin Trans. 2* **1982**, 1533.

³⁴Stone; Pearson *J. Org. Chem.* **1961**, *26*, 257.

³⁵Berliner; Winikov *J. Am. Chem. Soc.* **1959**, *81*, 1630; see also Wells; Ehrenson; Taft, Ref. 48.

³⁶For reviews, see Charton, in Chapman; Shorter, Ref. 18, pp. 175-268; Tomasik; Johnson *Adv. Heterocycl. Chem.* **1976**, *20*, 1-64.

³⁷For reviews of the application of the Hammett treatment to unsaturated systems, see Ford; Katritzky; Topsom, in Chapman; Shorter, Ref. 18, pp. 269-311; Charton *Prog. Phys. Org. Chem.* **1973**, *10*, 81-204.

The Hammett equation is a *linear free-energy relationship (LFER)*. This can be demonstrated as follows for the case of equilibrium constants (for rate constants a similar demonstration can be made with ΔG^\ddagger instead of ΔG). For each reaction, where X is any group,

$$\Delta G = -RT \ln K$$

For the unsubstituted case,

$$\Delta G_0 = -RT \ln K_0$$

The Hammett equation can be rewritten

$$\log K - \log K_0 = \sigma \rho$$

so that

$$\frac{-\Delta G}{2.3RT} + \frac{\Delta G_0}{2.3RT} = \sigma \rho$$

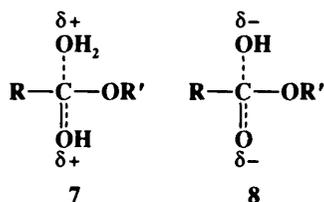
and

$$-\Delta G = \sigma \rho 2.3RT - \Delta G_0$$

For a given reaction under a given set of conditions, σ , R , T , and ΔG_0 are all constant, so that σ is linear with ΔG .

The Hammett equation is not the only LFER.³⁷ Some, like the Hammett equation, correlate structural changes in reactants, but the Grunwald–Winstein relationship (see p. 360) correlates changes in solvent and the Brønsted relation (see p. 258) relates acidity to catalysis. The Taft equation is a structure–reactivity equation that correlates only field effects.³⁸

Taft, following Ingold,³⁹ assumed that for the hydrolysis of carboxylic esters, steric and resonance effects will be the same whether the hydrolysis is catalyzed by acid or base (see the discussion of ester–hydrolysis mechanisms, reaction 0-10). Rate differences would therefore be caused only by the field effects of R and R' in RCOOR'. This is presumably a good system to use for this purpose because the transition state for acid-catalyzed hydrolysis (7) has a greater positive charge (and is hence destabilized by $-I$ and stabilized by $+I$ substituents) than the starting ester, while the transition state for base-catalyzed hydrolysis (8)



³⁷For a discussion of physicochemical preconditions for LFERs, see Exner *Prog. Phys. Org. Chem.* **1990**, *18*, 129-161.

³⁸For reviews of the separation of resonance and field effects, see Charton *Prog. Phys. Org. Chem.* **1981**, *13*, 119-251; Shorter *Q. Rev., Chem. Soc.* **1970**, *24*, 433-453; *Chem. Br.* **1969**, *5*, 269-274. For a review of field and inductive effects, see Reynolds *Prog. Phys. Org. Chem.* **1983**, *14*, 165-203. For a review of field effects on reactivity, see Grob *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 569-575 [*Angew. Chem.* **88**, 621-627].

³⁹Ingold *J. Chem. Soc.* **1930**, 1032.

⁴⁰For another set of field-effect constants, based on a different premise, see Draffehn; Ponsold *J. Prakt. Chem.* **1978**, 320, 249.

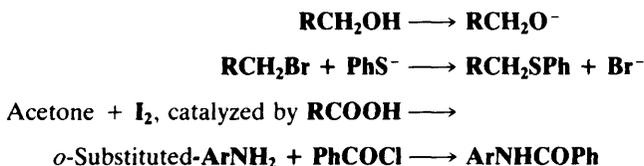
has a greater negative charge than the starting ester. Field effects of substituents X could therefore be determined by measuring the rates of acid- and base-catalyzed hydrolysis of a series XCH_2COOR' , where R' is held constant.³⁵ From these rate constants, a value σ_I could be determined by the equation⁴¹

$$\sigma_I \equiv 0.181 \left[\log \left(\frac{k}{k_0} \right)_B - \log \left(\frac{k}{k_0} \right)_A \right]$$

In this equation $(k/k_0)_B$ is the rate constant for basic hydrolysis of XCH_2COOR' divided by the rate constant for basic hydrolysis of CH_3COOR' , $(k/k_0)_A$ is the similar rate-constant ratio for acid catalysis, and 0.181 is an arbitrary constant. σ_I is a substituent constant for a group X, substituted at a saturated carbon, that reflects only field effects.⁴² Once a set of σ_I values was obtained, it was found that the equation

$$\log \frac{k}{k_0} = \rho_I \sigma_I$$

holds for a number of reactions, among them:⁴³



As with the Hammett equation, σ_I is constant for a given reaction under a given set of conditions. For very large groups the relationship may fail because of the presence of steric effects, which are not constant. The equation also fails when X enters into resonance with the reaction center to different extents in the initial and transition states. A list of some σ_I values is given in Table 9.5.⁴⁴ The σ_I values are about what we would expect for pure field-effect values (see p. 18) and are additive, as field effects (but not resonance or steric effects) would be expected to be. Thus, in moving a group one carbon down the chain, there is a decrease by a factor of 2.8 ± 0.5 (compare the values of R and RCH_2 in Table 9.5 for R = Ph and CH_3CO). An inspection of Table 9.5 shows that σ_I values for most groups are fairly close to the σ_m values (Table 9.4) for the same groups. This is not surprising, since σ_m values would be expected to arise almost entirely from field effects, with little contribution from resonance.

Since σ_p values represent the sum of resonance and field effects, these values can be divided into resonance and field contributions if σ_I is taken to represent the field-effect

⁴¹The symbol σ_f is also used in the literature; sometimes in place of σ_I , and sometimes to indicate only the field (not the inductive) portion of the total effect (p. 17).

⁴²There is another set of values (called σ^* values) that are also used to correlate field effects. These are related to σ_I values by $\sigma^* = \sigma_{f(X)} = 0.45\sigma_{f(XCH_2)}$. We discuss only σ_I , and not σ^* values.

⁴³Wells, Ref. 17, p. 196.

⁴⁴These values are from Bromilow; Brownlee; Lopez; Taft, Ref. 52, except that the values for NHAc, OH, and I are from Wells; Ehrenson; Taft, Ref. 48, the values for Ph and NMe_3^+ are from Ref. 51 and Taft; Deno; Skell, Ref. 47, and the value for CMe_3 is from Seth-Paul; de Meyer-van Duyse; Tollenaere *J. Mol. Struct.* **1973**, *19*, 811. The values for the CH_2Ph and CH_2COCH_3 groups were calculated from σ^* values by the formula given in footnote 42. For much larger tables of σ_I and σ_R values, see Charton, Ref. 38. See also Ref. 19 and Taylor; Wait *J. Chem. Soc., Perkin Trans. 2* **1986**, 1765.

TABLE 9.5 σ_I and σ_R° values for some groups⁴⁴

Group	σ_I	σ_R°	Group	σ_I	σ_R°
CMe ₃	-0.07	-0.17	OMe	0.27	-0.42
Me	-0.05	-0.13	OH	0.27	-0.44
H	0	0	I	0.39	-0.12
PhCH ₂	0.04		CF ₃	0.42	0.08
NMe ₂ ⁴⁵	0.06	-0.55	Br	0.44	-0.16
Ph	0.10	-0.10	Cl	0.46	-0.18
CH ₃ COCH ₂	0.10		F	0.50	-0.31
NH ₂	0.12	-0.50	CN	0.56	0.08
CH ₃ CO	0.20	0.16	SO ₂ Me	0.60	0.12
COOEt	0.20	0.16	NO ₂	0.65	0.15
NHAc	0.26	-0.22	NMe ₃ ⁺⁴⁶	0.86	

portion.⁴⁷ The resonance contribution σ_R^{48} is defined as

$$\sigma_R = \sigma_p - \sigma_I$$

As it stands, however, this equation is not very useful because the σ_R value for a given group, which should be constant if the equation is to have any meaning, is actually not constant but depends on the nature of the reaction.⁴⁹ In this respect, the σ_I values are much better. Although they vary with solvent in some cases, σ_I values are essentially invariant throughout a wide variety of reaction series. However, it is possible to overcome⁵⁰ the problem of varying σ_R values by using a special set of σ_R values, called σ_R° ,⁵¹ that measure the ability to delocalize π electrons into or out of an unperturbed or "neutral" benzene ring. Several σ_R° scales have been reported; the most satisfactory values are obtained from ¹³C chemical shifts of substituted benzenes.⁵² Table 9.5 lists some values of σ_R° , most of which were obtained in this way.⁵³

An equation such as

$$\log \frac{k}{k_0} = \rho_I \sigma_I + \rho_R \sigma_R^\circ$$

⁴⁴For σ_R° values for some other NR₂ groups, see Korzhenevskaya; Titov; Chotii; Chekhuta *J. Org. Chem. USSR* **1987**, 28, 1109.

⁴⁵Although we give a σ_I value for NMe₃⁺, (and F values for three charged groups in Table 9.6), it has been shown that charged groups (called polar substituents) cannot be included with uncharged groups (dipolar substituents) in one general scale of electrical substituent effects: Marriott; Reynolds; Topsom *J. Org. Chem.* **1985**, 50, 741.

⁴⁶Roberts; Moreland *J. Am. Chem. Soc.* **1953**, 75, 2167; Taft *J. Am. Chem. Soc.* **1957**, 79, 1045; *J. Phys. Chem.* **1960**, 64, 1805; Taft; Lewis *J. Am. Chem. Soc.* **1958**, 80, 2436; Taft; Deno; Skell *Annu. Rev. Phys. Chem.* **1958**, 9, 287-314, pp. 290-293.

⁴⁷For reviews of the σ_I and σ_R concept as applied to benzenes and naphthalenes, respectively, see Ehrenson; Brownlee; Taft *Prog. Phys. Org. Chem.* **1973**, 10, 1-80; Wells; Ehrenson; Taft *Prog. Phys. Org. Chem.* **1968**, 6, 147-322. See also Taft; Topsom *Prog. Phys. Org. Chem.* **1987**, 16, 1-83; Charton *Prog. Phys. Org. Chem.* **1987**, 16, 287-315.

⁴⁸Taft; Lewis *J. Am. Chem. Soc.* **1959**, 81, 5343; Reynolds; Dais; MacIntyre; Topsom; Marriott; von Nagy-Felsobuki; Taft *J. Am. Chem. Soc.* **1983**, 105, 378.

⁴⁹For a different way of overcoming this problem, see Happer; Wright *J. Chem. Soc., Perkin Trans. 2* **1979**, 694.

⁵⁰Taft; Ehrenson; Lewis; Glick *J. Am. Chem. Soc.* **1959**, 81, 5352.

⁵¹Bromilow; Brownlee; Lopez; Taft *J. Org. Chem.* **1979**, 44, 4766. See also Marriott; Topsom *J. Chem. Soc., Perkin Trans. 2* **1985**, 1045.

⁵²For a set of σ_R values for use in XY⁺ systems, see Charton *Mol. Struct. Energ.* **1987**, 4, 271-317.

which treats resonance and field effects separately, is known as a *dual substituent parameter equation*.⁵⁴

The only groups in Table 9.5 with negative values of σ_f are the alkyl groups methyl and *t*-butyl. There has been some controversy on this point.⁵⁵ One opinion is that σ_f values decrease in the series methyl, ethyl, isopropyl, *t*-butyl (respectively, -0.046 , -0.057 , -0.065 , -0.074).⁵⁶ Other evidence, however, has led to the belief that all alkyl groups have approximately the same field effect and that the σ_f values are invalid as a measure of the intrinsic field effects of alkyl groups.⁵⁷

Another attempt to divide σ values into resonance and field contributions⁵⁸ is that of Swain and Lupton, who have shown that the large number of sets of σ values (σ_m , σ_p , σ_p^- , σ_p^+ , σ_f , σ_R^+ , etc., as well as others we have not mentioned) are not entirely independent and that linear combinations of two sets of new values F (which expresses the field-effect contribution) and R (the resonance contribution) satisfactorily express 43 sets of values.⁵⁹ Each set is expressed as

$$\sigma = fF + rR$$

where f and r are weighting factors. Some F and R values for common groups are given in Table 9.6.⁶⁰ From the calculated values of f and r , Swain and Lupton calculated that the

TABLE 9.6 F and R values for some groups⁶⁰

Group	F	R	Group	F	R
COO ⁻	-0.27	0.40	OMe	0.54	-1.68
Me ₃ C	-0.11	-0.29	CF ₃	0.64	0.76
Et	-0.02	-0.44	I	0.65	-0.12
Me	-0.01	-0.41	Br	0.72	-0.18
H	0	0	Cl	0.72	-0.24
Ph	0.25	-0.37	F	0.74	-0.60
NH ₂	0.38	-2.52	NHCOCH ₃	0.77	-1.43
COOH	0.44	0.66	CN	0.90	0.71
OH	0.46	-1.89	NMe ₃ ⁺	1.54	
COOEt	0.47	0.67	N ₂ ⁺	2.36	2.81
COCH ₃	0.50	0.90			

⁵⁴There are also three-parameter equations. See, for example de Ligny and van Houwelingen *J. Chem. Soc., Perkin Trans. 2* **1987**, 559.

⁵⁵For a discussion, see Shorter, in Chapman; Shorter *Advances in Linear Free Energy Relationships*, Ref. 15, pp. 98-103.

⁵⁶For support for this point of view, see Levitt; Widing *Prog. Phys. Org. Chem.* **1976**, *12*, 119-157; Taft; Levitt *J. Org. Chem.* **1977**, *42*, 916; MacPhee; Dubois *Tetrahedron Lett.* **1978**, 2225; Screttas *J. Org. Chem.* **1979**, *44*, 3332; Hanson *J. Chem. Soc., Perkin Trans. 2* **1984**, 101.

⁵⁷For support for this point of view, see, for example, Ritchie *J. Phys. Chem.* **1961**, *65*, 2091; Bordwell; Drucker; McCollum *J. Org. Chem.* **1976**, *41*, 2786; Bordwell; Fried *Tetrahedron Lett.* **1977**, 1121; Charton *J. Am. Chem. Soc.* **1977**, *99*, 5687; *J. Org. Chem.* **1979**, *44*, 903; Adcock; Khor *J. Org. Chem.* **1978**, *43*, 1272; DeTar *J. Org. Chem.* **1980**, *45*, 5166; *J. Am. Chem. Soc.* **1980**, *102*, 7988.

⁵⁸Yukawa and Tsuno have still another approach, also involving dual parameters: Yukawa; Tsuno *Bull. Chem. Soc. Jpn.* **1959**, *32*, 971. For a review and critique of this method, see Shorter, in Chapman; Shorter, Ref. 18, pp. 119-173, pp. 126-144. This article also discusses the Swain-Lupton and Taft σ_f , σ_R approaches. For yet other approaches, see Afanas'ev *J. Org. Chem. USSR* **1981**, *17*, 373; *J. Chem. Soc., Perkin Trans. 2* **1984**, 1589; Ponec *Coll. Czech. Chem. Commun.* **1983**, *48*, 1564.

⁵⁹Swain; Lupton *J. Am. Chem. Soc.* **1968**, *90*, 4328; Swain; Unger; Rosenquist; Swain *J. Am. Chem. Soc.* **1983**, *105*, 492.

⁶⁰Taken from a much longer list in Swain; Unger; Rosenquist; Swain, Ref. 59. Long tables of R and F values are also given in Hansch; Leo; Taft, Ref. 19.

importance of resonance, % R , is 20% for σ_m , 38% for σ_p , and 62% for σ_p^+ .⁶¹ This is another dual substituent parameter approach.

Taft was also able to isolate steric effects.⁶² For the acid-catalyzed hydrolysis of esters in aqueous acetone, $\log(k/k_0)$ was shown to be insensitive to polar effects.⁶³ In cases where resonance interaction was absent, this value was proportional only to steric effects (and any others⁶⁴ that are not field or resonance). The equation is

$$\log \frac{k}{k_0} = E_s$$

Some E_s values are given in Table 9.7,⁶⁵ where hydrogen is taken as standard, with a value of 0.⁶⁶ This treatment is more restricted than those previously discussed, since it requires more assumptions, but the E_s values are approximately in order of the size of the groups. Charton has shown that E_s values for substituents of types CH_2X , CHX_2 , and CX_3 are linear functions of the van der Waals radii for these groups.⁶⁷

Two other steric parameters are independent of any kinetic data. Charton's v values are derived from van der Waals radii,⁶⁸ and Meyer's V^a values from the volume of the portion of the substituent that is within 0.3 nm of the reaction center.⁶⁹ The V^a values are obtained by molecular mechanics calculations based on the structure of the molecule. Table 9.7 gives v and V^a values for some groups.⁷⁰ As can be seen in the table, there is a fair, but not

TABLE 9.7 E_s , v , and V^a values for some groups⁶⁵

Group	E_s	v	$V^a \times 10^2$	Group	E_s	v	$V^a \times 10^2$
H	0	0		Cyclohexyl	-2.03	0.87	6.25
F	-0.46	0.27	1.22	iso-Bu	-2.17	0.98	5.26
CN	-0.51			sec-Bu	-2.37	1.02	6.21
OH	-0.55			CF ₃	-2.4	0.91	3.54
OMe	-0.55		3.39	<i>t</i> -Bu	-2.78	1.24	7.16
NH ₂	-0.61			NMe ₃ ⁺	-2.84		
Cl	-0.97	0.55	2.54	Neopentyl	-2.98	1.34	5.75
Me	-1.24	0.52	2.84	CCl ₃	-3.3	1.38	6.43
Et	-1.31	0.56	4.31	CBr ₃	-3.67	1.56	7.29
I	-1.4	0.78	4.08	(Me ₃ CCH ₂) ₂ CH	-4.42	2.03	
Pr	-1.6	0.68	4.78	Et ₃ C	-5.04	2.38	
iso-Pr	-1.71	0.76	5.74	Ph ₃ C	-5.92	2.92	

⁶¹The Swain-Lupton treatment has been criticized by Reynolds; Topsom *J. Org. Chem.* **1984**, *49*, 1989; Hoefnagel; Oosterbeek; Wepster *J. Org. Chem.* **1984**, *49*, 1993; and Charton *J. Org. Chem.* **1984**, *49*, 1997. For a reply to these criticisms, see Swain *J. Org. Chem.* **1984**, *49*, 2005. A study of the rates of dediazotiation reactions (**3-23**) was more in accord with the Taft and Charton (Ref. 38) σ_I and σ_R values than with the Swain-Lupton F and R values; Nakazumi; Kitao; Zollinger *J. Org. Chem.* **1987**, *52*, 2825.

⁶²For reviews of quantitative treatments of steric effects, see Gallo; Roussel; Berg *Adv. Heterocycl. Chem.* **1988**, *43*, 173-299; Gallo *Prog. Phys. Org. Chem.* **1983**, *14*, 115-163; Unger; Hansch *Prog. Phys. Org. Chem.* **1976**, *12*, 91-118.

⁶³Another reaction used for the quantitative measurement of steric effects is the aminolysis of esters (**0-55**); De Tar; Delahunty *J. Am. Chem. Soc.* **1983**, *105*, 2734.

⁶⁴It has been shown that E_s values include solvation effects; McClelland; Steenken *J. Am. Chem. Soc.* **1988**, *110*, 5860.

⁶⁵ E_s , v , and V^a values are taken from longer tables in respectively, Ref. 62, Charton *J. Am. Chem. Soc.* **1975**, *97*, 1552; *J. Org. Chem.* **1976**, *41*, 2217; and Ref. 69.

⁶⁶In Taft's original work, Me was given the value 0. The E_s values in Table 9.7 can be converted to the original values by adding 1.24.

⁶⁷Charton *J. Am. Chem. Soc.* **1969**, *91*, 615.

⁶⁸Charton, Ref. 65. See also Charton *J. Org. Chem.* **1978**, *43*, 3995; Idoux; Schreck *J. Org. Chem.* **1978**, *43*, 4002.

⁶⁹Meyer *J. Chem. Soc., Perkin Trans. 2* **1986**, 1567.

⁷⁰For a discussion of the various steric parameters, see DeTar, Ref. 57.

perfect, correlation among the E_s , v , and V^a values. Other sets of steric values, e.g., E_s' ,⁷¹ E_s^* ,⁷² Ω_s ,⁷³ and δ_s ,⁷⁴ have also been proposed.⁷⁰

Since the Hammett equation has been so successful in the treatment of the effects of groups in the meta and para positions, it is not surprising that attempts have been made to apply it to ortho positions also.⁷⁵ The effect on a reaction rate or equilibrium constant of a group in the ortho position is called the *ortho effect*.⁷⁶ Despite the many attempts made to quantify ortho effects, so far no set of values commands general agreement. However, the Hammett treatment is successful for ortho compounds when the group Y in *o*-XC₆H₄Y is separated from the ring; e.g., ionization constants of *o*-XC₆H₄OCH₂COOH can be successfully correlated.⁷⁷

Linear free-energy relationships can have mechanistic implications. If $\log(k/k_0)$ is linear with the appropriate σ , it is likely that the same mechanism operates throughout the series. If not, a smooth curve usually indicates a gradual change in mechanism, while a pair of intersecting straight lines indicates an abrupt change,⁷⁸ though nonlinear plots can also be due to other causes, such as complications arising from side reactions. If a reaction series follows σ^+ or σ^- better than σ it generally means that there is extensive resonance interaction in the transition state.⁷⁹

Information can also be obtained from the magnitude and sign of ρ . For example, a strongly negative ρ value indicates a large electron demand at the reaction center, from which it may be concluded that a highly electron-deficient center, perhaps an incipient carbocation, is involved. Conversely, a positive ρ value is associated with a developing negative charge in the transition state.⁸⁰ The $\sigma\rho$ relationship even applies to free-radical reactions, because free radicals can have some polar character (p. 679), though ρ values here are usually small (less than about 1.5) whether positive or negative. Reactions involving cyclic transition states (p. 206) also exhibit very small ρ values.

⁷¹MacPhee; Panaye; Dubois *Tetrahedron* **1978**, *34*, 3553, *J. Org. Chem.* **1980**, *45*, 1164; Dubois; MacPhee; Panaye *Tetrahedron Lett.* **1978**, 4099; *Tetrahedron* **1980**, *36*, 919. See also Datta; Sharma *J. Chem. Res. (S)* **1987**, 422.

⁷²Fellous; Luft *J. Am. Chem. Soc.* **1973**, *95*, 5593.

⁷³Komatsuzaki; Sakakibara; Hirota *Tetrahedron Lett.* **1989**, *30*, 3309, *Chem. Lett.* **1990**, 1913.

⁷⁴Beckhaus *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 593 [*Angew. Chem.* **90**, 633].

⁷⁵For reviews, see Fujita; Nishioka *Prog. Phys. Org. Chem.* **1976**, *12*, 49-89; Charton *Prog. Phys. Org. Chem.* **1971**, *8*, 235-317; Shorter, Ref. 55, pp. 103-110. See also Segura *J. Org. Chem.* **1985**, *50*, 1045; Robinson; Horton; Foshee; Jones; Hanissian; Slater *J. Org. Chem.* **1986**, *51*, 3535.

⁷⁶This is not the same as the ortho effect discussed on p. 514.

⁷⁷Charton *Can. J. Chem.* **1960**, *38*, 2493.

⁷⁸For a discussion, see Schreck *J. Chem. Educ.* **1971**, *48*, 103-107.

⁷⁹See, however, Gawley *J. Org. Chem.* **1981**, *46*, 4595.

⁸⁰For another method of determining transition state charge, see Williams *Acc. Chem. Res.* **1984**, *17*, 425-430.

PART TWO

In Part 2 of this book we shall be directly concerned with organic reactions and their mechanisms. The reactions have been classified into 10 chapters, based primarily on reaction type: substitutions, additions to multiple bonds, eliminations, rearrangements, and oxidation–reduction reactions. Five chapters are devoted to substitutions; these are classified on the basis of mechanism as well as substrate. Chapters 10 and 13 include nucleophilic substitutions at aliphatic and aromatic substrates, respectively. Chapters 12 and 11 deal with electrophilic substitutions at aliphatic and aromatic substrates, respectively. All free-radical substitutions are discussed in Chapter 14. Additions to multiple bonds are classified not according to mechanism, but according to the type of multiple bond. Additions to carbon–carbon multiple bonds are dealt with in Chapter 15; additions to other multiple bonds in Chapter 16. One chapter is devoted to each of the three remaining reaction types: Chapter 17, eliminations; Chapter 18, rearrangements; Chapter 19, oxidation–reduction reactions. This last chapter covers only those oxidation–reduction reactions that could not be conveniently treated in any of the other categories (except for oxidative eliminations).

Each chapter in Part 2 consists of two main sections. The first section of each chapter (except Chapter 19) deals with mechanism and reactivity. For each reaction type the various mechanisms are discussed in turn, with particular attention given to the evidence for each mechanism and to the factors that cause one mechanism rather than another to prevail in a given reaction. Following this, each chapter contains a section on reactivity, including, where pertinent, a consideration of orientation and the factors affecting it.

The second main section of each chapter is a treatment of the reactions belonging to the category indicated by the title of the chapter. It is not possible to discuss in a book of this nature all or nearly all known reactions. However, an attempt has been made to include all the important reactions of standard organic chemistry which can be used to prepare relatively pure compounds in reasonable yields. In order to present a well-rounded picture and to include some reactions that are traditionally discussed in textbooks, a number of reactions that do not fit into the above category have been included. The scope of the coverage is apparent from the fact that more than 90% of the individual preparations given in *Organic Syntheses* are treated. However, certain special areas have been covered only lightly or not at all. Among these are electrochemical and polymerization reactions, and the preparation and reactions of heterocyclic compounds, carbohydrates, steroids, and compounds containing phosphorus, silicon, arsenic, boron, and mercury. The basic principles involved in these areas are of course no different from those in the areas more fully treated. Even with these omissions, however, some 580 reactions are treated in this book.

Each reaction is discussed in its own numbered section.¹ These are numbered consec-

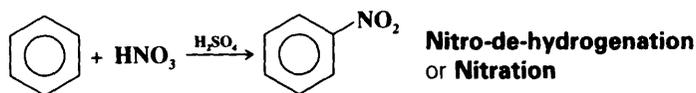
¹The classification of reactions into sections is, of course, to some degree arbitrary. Each individual reaction (for example, $\text{CH}_3\text{Cl} + \text{CN}^- \rightarrow \text{CH}_3\text{CN}$ and $\text{C}_2\text{H}_5\text{Cl} + \text{CN}^- \rightarrow \text{C}_2\text{H}_5\text{CN}$) is different, and custom generally decides how we group them together. Individual preferences also play a part. Some chemists would say that $\text{C}_6\text{H}_5\text{N}_2^+ + \text{CuCN} \rightarrow \text{C}_6\text{H}_5\text{CN}$ and $\text{C}_6\text{H}_5\text{N}_2^+ + \text{CuCl} \rightarrow \text{C}_6\text{H}_5\text{Cl}$ are examples of the "same" reaction. Others would say that they are not, but that $\text{C}_6\text{H}_5\text{N}_2^+ + \text{CuCl} \rightarrow \text{C}_6\text{H}_5\text{Cl}$ and $\text{C}_6\text{H}_5\text{N}_2^+ \rightarrow \text{CuBr} + \text{C}_6\text{H}_5\text{Br}$ are examples of the "same" reaction. No claim is made that the classification system used in this book is more valid than any other. For another way of classifying reactions, see Fujita *J. Chem. Soc., Perkin Trans. 2* **1988**, 597.

utively within a chapter. The *first* digit in each number is the *second* digit of the chapter number. Thus, reaction **6-1** is the first reaction of Chapter 16 and reaction **3-21** is the twenty-first reaction of Chapter 13. The second part of the reaction number has no other significance. The order in which the reactions are presented is not arbitrary but is based on an orderly outline that depends on the type of reaction. The placement of each reaction in a separate numbered section serves as an aid to both memory and understanding by setting clear boundary lines between one reaction and another, even if these boundary lines must be arbitrary, and by clearly showing the relationship of each reaction to all the others. Within each section, the scope and utility of the reaction are discussed and references are given to review articles, if any. If there are features of the mechanism that especially pertain to that reaction, these are also discussed within the section rather than in the first part of the chapter where the discussion of mechanism is more general.

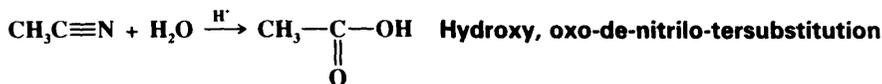
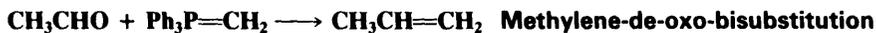
IUPAC Nomenclature for Transformations

There has long been a need for a method of naming reactions. As most students know well, many reactions are given the names of their discoverers or popularizers (e.g., Clemmensen, Diels–Alder, Prins, Wittig, Cope, Corey–Winter). This is useful as far as it goes, but each name must be individually memorized, and there are many reactions that do not have such names. The IUPAC Commission on Physical Organic Chemistry has produced a *system* for naming not reactions, but transformations (a reaction includes all reactants; a transformation shows only the substrate and product, omitting the reagents). The advantages of a systematic method are obvious. Once the system is known, no memorization is required; the name can be generated directly from the equation. The system includes rules for naming eight types of transformation: substitutions, additions, eliminations, attachments and detachments, simple rearrangements, coupling and uncoupling, insertions and extrusions, and ring opening and closing. We give here only the most basic rules for the first three of these types, which however will suffice for naming many transformations.² The complete rules give somewhat different names for speech-writing and indexing. In this book we give only the speech-writing names.

Substitutions. A name consists of the entering group, the syllable "de," and the leaving group. If the leaving group is hydrogen, it may be omitted (in all examples, the substrate is written on the left).



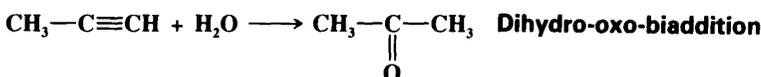
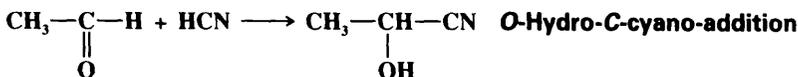
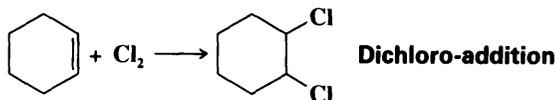
Multivalent substitutions are named by a modification of this system that includes suffixes such as "bisubstitution" and "tersubstitution."



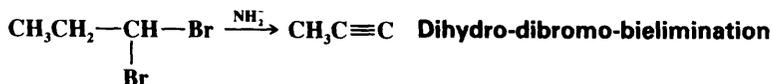
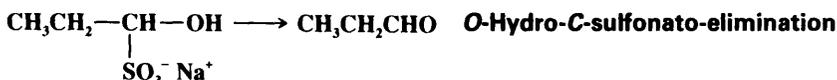
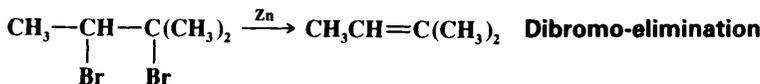
(Note: the nitrilo group is $\equiv\text{N}$.)

²For the complete rules, as so far published, see Jones; Bunnett *Pure Appl. Chem.* **1969**, *61*, 725-768.

Additions. For simple 1,2-additions, the names of both addends are given followed by the suffix "addition." The addends are named in order of priority in the Cahn-Ingold-Prelog system (p. 109), the lower-ranking addend coming first. Multivalent addition is indicated by "biaddition," etc.



Eliminations are named the same way as additions, except that "elimination" is used instead of "addition."



In the reaction sections of this book, we shall give IUPAC names for most transformations (these names will be printed in the same typeface used above), including examples of all eight types.³ As will become apparent, some transformations require more rules than we have given here.² However, it is hoped that the simplicity of the system will also be apparent.

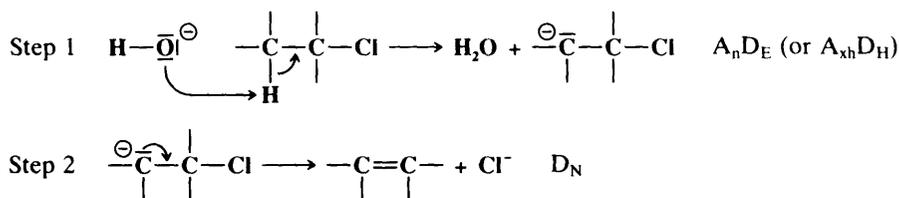
Two further notes: (1) Many transformations can be named using either of two reactants as the substrate. For example, the transformation **methylene-de-oxo-bisubstitution** above, can also be named **ethylidene-de-triphenylphosphorandiyl-bisubstitution**. In this book, unless otherwise noted, we will show only those names in which the substrate is considered to undergo the reactions indicated by the titles of the chapters. Thus the name we give to **1-12** ($\text{ArH} + \text{RCI} \rightarrow \text{ArR}$) is **alkyl-de-hydrogenation**, not **aryl-de-chlorination**, though the latter name is also perfectly acceptable under the IUPAC system. (2) The IUPAC rules recognize that some transformations are too complex to be easily fitted into the system, so they also include a list of names for some complex transformations, which are IUPAC approved, but nonsystematic (for some examples, see reactions **2-44**, **8-36**, **9-63**).

³For some examples, see: attachments (**8-29**, **9-28**), detachments (**9-48**, **9-56**), simple rearrangements (**8-7**, **8-31**), coupling (**0-86**, **9-35**), uncoupling (**9-9**, **9-61**), insertions (**2-20**, **8-9**), extrusions (**7-47**, **7-51**), ring opening (**0-18**, **0-49**), ring closing (**0-13**, **5-47**).

IUPAC System for Symbolic Representation of Mechanisms

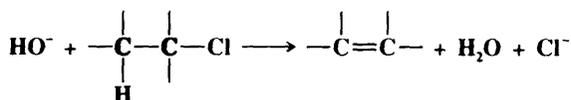
In addition to providing a system for naming transformations, the IUPAC Commission on Physical Organic Chemistry has also produced one for representing mechanisms.⁴ As we shall see in Part Two, many mechanisms (though by no means all) are commonly referred to by designations such as S_N2 , $AAC2$, $E1cB$, $S_{RN}1$, etc., many of them devised by C.K. Ingold and his co-workers. While these designations have been useful (and we shall continue to use them in this book), the sheer number of them can be confusing, especially since the symbols do not give a direct clue to what is happening. For example, there is no way to tell directly from the symbols how S_N2' is related to S_N2 (see p. 328). The IUPAC system is based on a very simple description of bond changes.⁵ The letter A represents formation of a bond (association); D the breaking of a bond (dissociation). These are *primitive changes*. The basic description of a mechanism consists of these letters, with subscripts to indicate where the electrons are going. In any mechanism the *core atoms* are defined as (a) the two atoms in a multiple bond that undergoes addition, or (b) the two atoms that will be in a multiple bond after elimination, or (c) the single atom at which substitution takes place.

As an example of the system, this is how an $E1cB$ mechanism (p. 991) would be represented:



Overall designation: $A_n D_E + D_N$ (or $A_{xh} D_H + D_N$)

In this case the overall reaction is:



and the core atoms are the two shaded carbons.

Step 1, First Symbol

A bond is being formed between O and H. Bond formation is represented by A. For this particular case the system gives two choices for subscript. In any process, the subscript is N if a core atom is forming a bond to a nucleophile (A_n) or breaking a bond to a nucleofuge (D_N). If a noncore atom is doing the same thing, lowercase n is used instead. Since H and O are non-core atoms, the lowercase n is used, and the formation of the O—H bond is designated by A_n . However, because involvement of H^+ is so common in organic mechanisms, the rules allow an alternative. The subscript H or h may replace N or n. The symbol xh denotes that the H^+ comes from or goes to an unspecified carrier atom X. Thus the

⁴Guthrie *Pure Appl. Chem.* **1989**, *61*, 23-56. For a briefer description, see Guthrie and Jencks *Acc. Chem. Res.* **1989**, *22*, 343-349.

⁵There are actually two IUPAC systems. The one we use in this book (Ref. 4) is intended for general use. A more detailed system, which describes every conceivable change happening in a system, and which is designed mostly for computer handling and storage, is given by Littler *Pure Appl. Chem.* **1989**, *61*, 57-81. The two systems are compatible; the Littler system uses the same symbols as the Guthrie system, but has additional symbols.

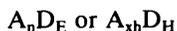
term A_{xh} means that a bond is being formed between H (moving without electrons) and an outside atom, in this case O. The same subscript, xh , would be used if the outside atom were any other nucleophilic atom, say, N or S.

Step 1, Second Symbol

A bond is being broken between C and H. The symbol is D. In any process, the subscript is E if a core atom is forming a bond to an electrophile (A_E) or breaking a bond to an electrofuge (D_E). Since C is a core atom, the symbol here is D_E . Alternatively, the symbol could be D_H . The rules allow A_H or D_H to replace A_E or D_E if the electrophile or electrofuge is H^+ . Because a core atom is involved in this primitive change the H in the subscript is capitalized.

Step 1, Combined Symbols

In step 1 two bond changes take place simultaneously. In such cases they are written together, with no space or punctuation:



Step 2

Only one bond is broken in this step and no bonds are formed. (The movement of a pair of unshared electrons into the C—C bond, forming a double bond, is not designated by any symbol. In this system bond multiplicity changes are understood without being specified.) Thus the symbol is D. The broken bond is between a core atom (C) and a nucleofuge (Cl), so the designation is D_N .

Overall Designation

This can be either $A_n D_N + D_N$ or $A_{xh} D_H + D_N$. The + symbol shows that there are two separate steps. If desired, rate-limiting steps can be shown by the symbol ‡. In this case, if the first step is the slow step [old designation (E1cB)], the designation would be $A_n D_E^\ddagger + D_N$ or $A_{xh} D_H^\ddagger + D_N$.

For most mechanisms (other than rearrangements), there will be only two A or D terms with uppercase subscripts, and the nature of the reaction can be immediately recognized by looking at them. If both are A, the reaction is an addition; if both are D (as in $A_n D_E + D_N$) it is an elimination. If one is A and the other D, the reaction is a substitution.

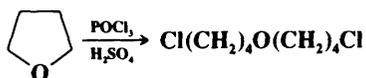
We have given here only a brief description of the system. Other IUPAC designations will be shown in Part Two, where appropriate. For more details, further examples, and additional symbols, see Ref. 4.

Organic Syntheses References

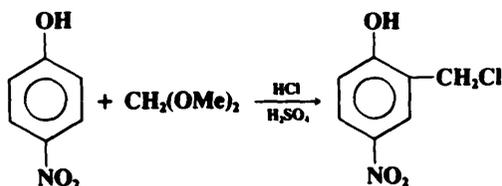
At the end of each numbered section there is a list of *Organic Syntheses* references (abbreviated OS). With the exception of a few very common reactions (**2-3**, **2-22**, **2-24**, and **2-38**) the list includes *all* OS references for each reaction. The volumes of OS that have been covered are Collective Volumes I to VII and individual volumes **66** to **69**. Where no OS references are listed at the end of a section, the reaction has not been reported in OS through volume **69**. These listings thus constitute a kind of index to OS.⁶ Certain ground

⁶Two indexes to *Organic Syntheses* have been published as part of the series. One of these, Liotta; Volmer *Organic Syntheses Reaction Guide*; Wiley: New York, 1991, which covers the series through volume 68, is described on p. 1257. The other, which covers the series through Collective Volume V, is Shriner; Shriner *Organic Syntheses Collective Volumes I, II, III, IV, V, Cumulative Indices*; Wiley: New York, 1976. For an older index to *Organic Syntheses* (through volume 45), see Sugawara; Nakai *Reaction Index of Organic Syntheses*; Wiley: New York, 1967.

rules were followed in assembling these lists. A reaction in which two parts of a molecule independently undergo simultaneous reaction is listed under both reactions. Similarly, if two reactions happen (or might happen) rapidly in succession without the isolation of an intermediate, the reactions are listed in both places. For example, at OS IV, 266 is



This reaction is treated as **0-68** followed by **0-16** and is listed in both places. However, certain reactions are not listed because they are trivial examples. An instance of this is the reaction found at OS III, 468:

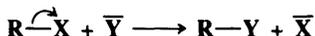


This is a chloromethylation reaction and is consequently listed at **1-24**. However, in the course of the reaction formaldehyde is generated from the acetal. This reaction is not listed at **0-6** (hydrolysis of acetals), because it is not really a preparation of formaldehyde.

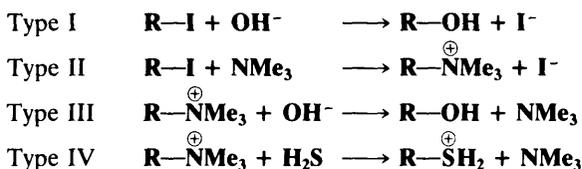
10

ALIPHATIC NUCLEOPHILIC SUBSTITUTION

In nucleophilic substitution the attacking reagent (the nucleophile) brings an electron pair to the substrate, using this pair to form the new bond, and the leaving group (the nucleofuge) comes away with an electron pair:



This equation says nothing about charges. Y may be neutral or negatively charged; RX may be neutral or positively charged; so there are four charge types, examples of which are



In all cases, Y must have an unshared pair of electrons, so that all nucleophiles are Lewis bases. When Y is the solvent, the reaction is called *solvolysis*. Nucleophilic substitution at an aromatic carbon is considered in Chapter 13.

Nucleophilic substitution at an alkyl carbon is said to *alkylate* the nucleophile. For example, the above reaction between RI and NMe₃ is an *alkylation* of trimethylamine. Similarly, nucleophilic substitution at an acyl carbon is an *acylation* of the nucleophile.

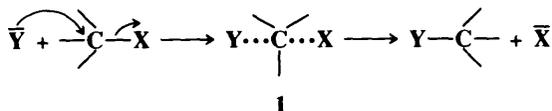
MECHANISMS

Several distinct mechanisms are possible for aliphatic nucleophilic substitution reactions, depending on the substrate, nucleophile, leaving group, and reaction conditions. In all of them, however, the attacking reagent carries the electron pair with it, so that the similarities are greater than the differences. Mechanisms that occur at a saturated carbon atom are considered first.¹ By far the most common are the S_N1 and S_N2 mechanisms.

¹For a monograph on this subject, see Hartshorn *Aliphatic Nucleophilic Substitution*; Cambridge University Press: Cambridge, 1973. For reviews, see Katritzky; Brycki *Chem. Soc. Rev.* **1990**, *19*, 83-105; Richard *Adv. Carbocation Chem.* **1989**, *1*, 121-169; Bazilevskii; Koldobskii; Tikhomirov *Russ. Chem. Rev.* **1986**, *55*, 948-965; de la Mare; Swedlund, in Patai *The Chemistry of the Carbon-Halogen Bond*, pt. 1; Wiley: New York, 1973, pp. 409-490. For some older books, see Thornton *Solvolysis Mechanisms*; Ronald Press: New York, 1964; Bunton *Nucleophilic Substitution at a Saturated Carbon Atom*; American Elsevier: New York, 1963; Streitwieser *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962.

The S_N2 Mechanism

S_N2 stands for *substitution nucleophilic bimolecular*. The IUPAC designation (p. 290) is A_ND_N. In this mechanism there is *backside attack*: the nucleophile approaches the substrate from a position 180° away from the leaving group. The reaction is a one-step process with no intermediate (see, however, pp. 297-298 and 305). The C—Y bond is formed as the C—X bond is broken:



The energy necessary to break the C—X bond is supplied by simultaneous formation of the C—Y bond. The position of the atoms at the top of the curve of free energy of activation can be represented as **1**. Of course the reaction does not stop here: this is the transition state. The group X must leave as the group Y comes in, because at no time can the carbon have more than eight electrons in its outer shell. When the transition state is reached, the central carbon atom has gone from its initial *sp*³ hybridization to an *sp*² state with an approximately perpendicular *p* orbital. One lobe of this *p* orbital overlaps with the nucleophile and the other with the leaving group. This is why a frontside S_N2 mechanism has never been observed. In a hypothetical frontside transition state, both the nucleophile and the leaving group would have to overlap with the same lobe of the *p* orbital. The backside mechanism involves the maximum amount of overlap throughout the course of the reaction. During the transition state the three nonreacting substituents and the central carbon are approximately coplanar. They will be exactly coplanar if both the entering and the leaving group are the same.

There is a large amount of evidence for the S_N2 mechanism. First there is the kinetic evidence. Since both the nucleophile and the substrate are involved in the rate-determining step (the only step, in this case), the reaction should be first order in each component, second order overall, and satisfy the rate expression

$$\text{Rate} = k[\text{RX}][\text{Y}] \quad (1)$$

This rate law has been found to apply. It has been noted that the 2 in S_N2 stands for bimolecular. It must be remembered that this is not always the same as second order (see p. 221). If a large excess of nucleophile is present—for example, if it is the solvent—the mechanism may still be bimolecular, though the experimentally determined kinetics will be first order:

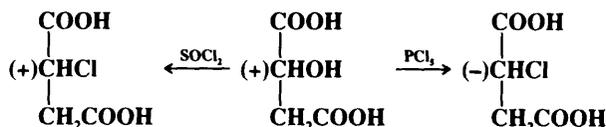
$$\text{Rate} = k[\text{RX}] \quad (2)$$

As previously mentioned (p. 223), such kinetics are called *pseudo-first order*.

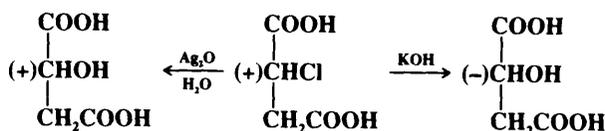
The kinetic evidence is a necessary but not a sufficient condition; we will meet other mechanisms that are also consistent with these data. Much more convincing evidence is obtained from the fact that the mechanism predicts inversion of configuration when substitution occurs at a chiral carbon and this has been observed many times. This inversion of configuration (see p. 111) is called the *Walden inversion* and was observed long before the S_N2 mechanism was formulated by Hughes and Ingold.²

²Cowdrey; Hughes; Ingold; Masterman; Scott *J. Chem. Soc.* **1937**, 1252. The idea that the addition of one group and removal of the other are simultaneous was first suggested by Lewis in *Valence and the Structure of Atoms and Molecules*; Chemical Catalog Company: New York, 1923, p. 113. The idea that a one-step substitution leads to inversion was proposed by Olsen *J. Chem. Phys.* **1933**, *1*, 418.

At this point it is desirable for us to see just how it was originally proved that a given substitution reaction proceeds with inversion of configuration, even before the mechanism was known. Walden presented a number of examples³ in which inversion *must* have taken place. For example, (+)-malic acid could be converted to (+)-chlorosuccinic acid by thionyl chloride and to (-)-chlorosuccinic acid by phosphorus pentachloride:

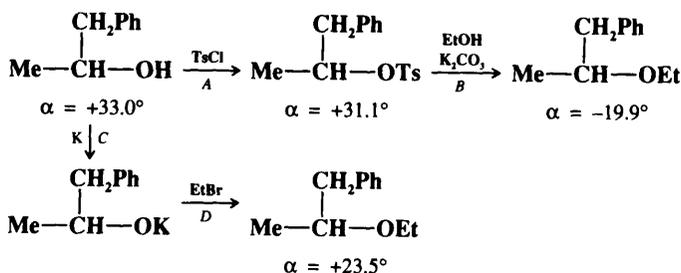


One of these must be an inversion and the other a retention of configuration, but the question is which is which? The signs of rotation are of no help in answering this question since, as we have seen (p. 108), rotation need not be related to configuration. Another example discovered by Walden is



Once again, one reaction and only one must be an inversion, but which?⁴ It may also be noticed [illustrated by the use of thionyl chloride on (+)-malic acid and treatment of the product with KOH] that it is possible to convert an optically active compound into its enantiomer.⁵

A series of experiments designed to settle the matter of exactly where inversion takes place was performed by Phillips, Kenyon, and co-workers. In 1923, Phillips carried out the following cycle:⁶



In this cycle, (+)-1-phenyl-2-propanol is converted to its ethyl ether by two routes, path *AB* giving the (-) ether, and path *CD* giving the (+) ether. Therefore, at least one of the four steps must be an inversion. It is extremely unlikely that there is inversion in step *A*,

³Walden *Ber.* **1893**, 26, 210, **1896**, 29, 133, **1899**, 32, 1855.

⁴For a discussion of these cycles, see Kryger; Rasmussen *Acta Chem. Scand.* **1972**, 26, 2349.

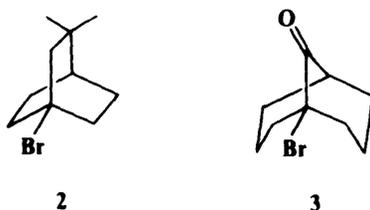
⁵The student may wonder just what the mechanism is in cases where retention of configuration is involved since it certainly is not simple $\text{S}_{\text{N}}2$. As we shall see later, the reaction between malic acid and thionyl chloride is an $\text{S}_{\text{N}}\text{i}$ process (p. 326), while a neighboring-group mechanism (p. 308) is involved in the treatment of chlorosuccinic acid with silver oxide.

⁶Phillips *J. Chem. Soc.* **1923**, 123, 44. For analyses of such cycles and general descriptions of more complex ones, see Garwood; Cram *J. Am. Chem. Soc.* **1970**, 92, 4575; Cram; Cram *Fortschr. Chem. Forsch.* **1972**, 31, 1-43.

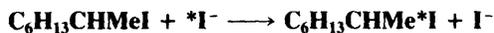
C, or *D*, since in all these steps the C—O bond is unbroken, and in none of them could the oxygen of the bond have come from the reagent. There is therefore a high probability that *A*, *C*, and *D* proceeded with retention, leaving *B* as the inversion. A number of other such cycles were carried out, always with nonconflicting results.⁷ These experiments not only definitely showed that certain specific reactions proceed with inversion, but also established the configurations of many compounds.

Walden inversion has been found at a primary carbon atom by the use of a chiral substrate containing a deuterium and a hydrogen atom at the carbon bearing the leaving group.⁸ Inversion of configuration has also been found for S_N2 reactions proceeding in the gas phase.⁹

Another kind of evidence for the S_N2 mechanism comes from compounds with potential leaving groups at bridgehead carbons. If the S_N2 mechanism is correct, these compounds should not be able to react by this mechanism, since the nucleophile cannot approach from the rear. Among the many known examples of unsuccessful reaction attempts at bridgeheads



under S_N2 conditions¹⁰ are treatment of the [2.2.2] system **2** with ethoxide ion¹¹ and treatment of the [3.3.1] system **3** with sodium iodide in acetone.¹² In these cases, open-chain analogs underwent the reactions readily. As a final example of evidence for the S_N2 mechanism, the reaction between optically active 2-octyl iodide and radioactive iodide ion may be mentioned:



We expect racemization in this reaction, since if we start with the pure *R* isomer, at first each exchange will produce an *S* isomer, but with increasing concentration of *S* isomer, it will begin to compete for I⁻ with the *R* isomer, until at the end a racemic mixture is left. The point investigated was a comparison of the rate of inversion with the rate of uptake of radioactive *I⁻. It was found¹³ that the rates were identical within experimental error:

Rate of inversion	$2.88 \pm 0.03 \times 10^{-5}$
Rate of exchange	$3.00 \pm 0.25 \times 10^{-5}$

⁷For example, see Kenyon; Phillips; Turley *J. Chem. Soc.* **1925**, 127, 399; Kenyon; Phillips; Taylor *J. Chem. Soc.* **1933**, 173; Kenyon; Phillips; Shutt *J. Chem. Soc.* **1935**, 1663.

⁸Streitwieser *J. Am. Chem. Soc.* **1953**, 75, 5014.

⁹Lieder; Brauman *J. Am. Chem. Soc.* **1974**, 96, 4028; Speranza; Angelini *J. Am. Chem. Soc.* **1980**, 102, 3115. For a review of nucleophilic displacements in the gas phase, see Riveros; José; Takashima *Adv. Phys. Org. Chem.* **1985**, 21, 197-240.

¹⁰For a review of bridgehead reactivity in nucleophilic substitution reactions, see Müller; Marcda, in Olah *Cage Hydrocarbons*; Wiley: New York, 1990, pp. 189-217. For a review of reactions at bridgehead carbons, see Fort; Schleyer *Adv. Alicyclic Chem.* **1966**, 1, 283-370.

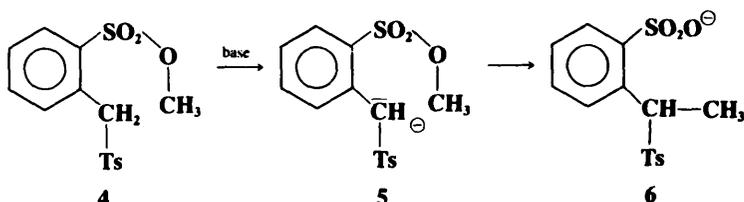
¹¹Doering; Levitz; Sayigh; Sprecher; Whelan *J. Am. Chem. Soc.* **1953**, 75, 1008. Actually, a slow substitution was observed in this case, but not by an S_N2 mechanism.

¹²Cope; Synerholm *J. Am. Chem. Soc.* **1950**, 72, 5228.

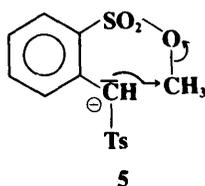
¹³Hughes; Juliusburger; Masterman; Topley; Weiss *J. Chem. Soc.* **1935**, 1525.

What was actually measured was the rate of racemization, which is twice the rate of inversion, since each inversion creates, in effect, two racemic molecules. The significance of this result is that it shows that every act of exchange is an act of inversion.

Eschenmoser and co-workers have provided strong evidence that the transition state in an S_N2 reaction must be linear.¹⁴ Base treatment of methyl α -tosyl-*o*-toluenesulfonate (**4**) gives the *o*-(1-tosylethyl)benzenesulfonate ion (**6**). The role of the base is to remove the α



proton to give the ion **5**. It might be supposed that the negatively charged carbon of **5** attacks the methyl group in an internal S_N2 process:



but this is not the case. Crossover experiments¹⁴ (p. 555) have shown that the negatively charged carbon attacks the methyl group of another molecule rather than the nearby one in the same molecule, that is, the reaction is intermolecular and not intramolecular, despite the more favorable entropy of the latter pathway (p. 211). The obvious conclusion is that intramolecular attack does not take place because complete linearity cannot be attained. This behavior is in sharp contrast to that in cases in which the leaving group is not constrained (p. 309), where intramolecular S_N2 mechanisms operate freely.

There is evidence, both experimental and theoretical, that there are intermediates in at least some S_N2 reactions in the gas phase, in charge type I reactions, where a negative ion nucleophile attacks a neutral substrate. Two energy minima, one before and one after the transition state appear in the reaction coordinate (Figure 10.1).¹⁵ These minima correspond to unsymmetrical ion-dipole complexes.¹⁶ Theoretical calculations also show such minima in certain solvents, e.g., DMF, but not in water.¹⁷

For a list of some of the more important reactions that operate by the S_N2 mechanism, see Table 10.7.

¹⁴Tenud; Farooq; Seibl; Eschenmoser *Helv. Chim. Acta* **1970**, *53*, 2059. See also King; McGarrity *J. Chem. Soc., Chem. Commun.* **1979**, 1140.

¹⁵Taken from Chandrasekhar; Smith; Jorgensen, Ref. 16.

¹⁶Olmstead; Brauman *J. Am. Chem. Soc.* **1977**, *99*, 4219; Pellerite; Brauman *J. Am. Chem. Soc.* **1980**, *102*, 5993; Wolfe; Mitchell; Schlegel *J. Am. Chem. Soc.* **1981**, *103*, 7692; Chandrasekhar; Smith; Jorgensen *J. Am. Chem. Soc.* **1985**, *107*, 154; Evanseck; Blake; Jorgensen *J. Am. Chem. Soc.* **1987**, *109*, 2349; Kozaki; Morihashi; Kikuchi *J. Am. Chem. Soc.* **1989**, *111*, 1547; Jorgensen *Acc. Chem. Res.* **1989**, *22*, 184-189.

¹⁷Chandrasekhar; Jorgensen *J. Am. Chem. Soc.* **1985**, *107*, 2974.

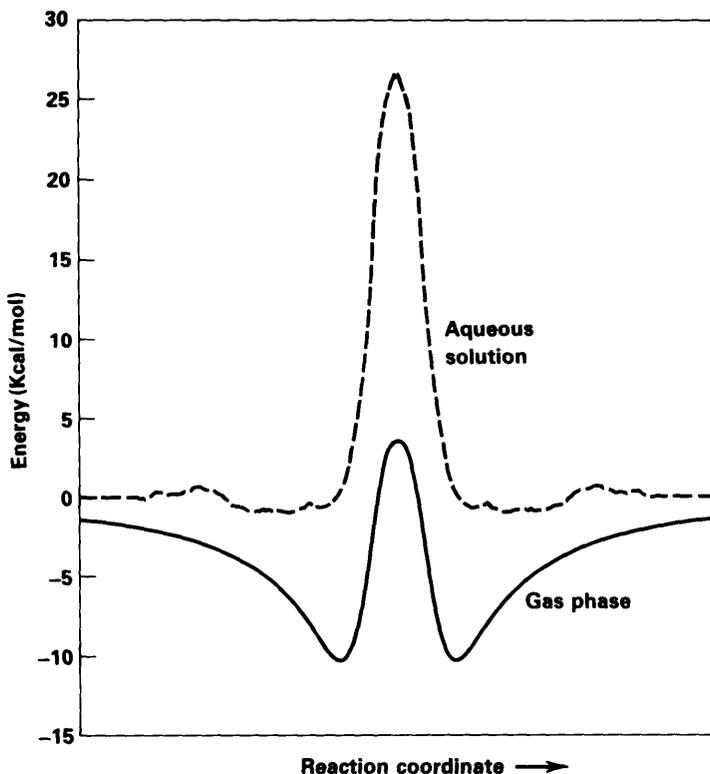


FIGURE 10.1 Free-energy profile for the gas phase (solid line) and aqueous solution (dashed line) S_N2 reaction between CH₃Cl and Cl⁻, from molecular orbital calculations.¹⁵

The S_N1 Mechanism

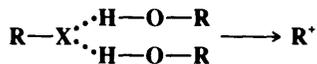
The most ideal version of the S_N1 mechanism (*substitutional nucleophilic unimolecular*) consists of two steps (once again, possible charges on the substrate and nucleophile are not shown):



The first step is a slow ionization of the substrate and is the rate-determining step. The second is a rapid reaction between the intermediate carbocation and the nucleophile. The ionization is always assisted by the solvent,¹⁸ since the energy necessary to break the bond is largely recovered by solvation of R⁺ and of X. For example the ionization of *t*-BuCl to *t*-Bu⁺ and Cl⁻ in the gas phase without a solvent requires 150 kcal/mol (630 kJ/mol). In the absence of a solvent such a process simply would not take place, except at very high temperatures. In water this ionization requires only 20 kcal/mol (84 kJ/mol). The difference

¹⁸For reviews of solvolysis, see Okamoto *Adv. Carbocation Chem.* **1989**, *1*, 171-218; Blandamer; Scott; Robertson *Prog. Phys. Org. Chem.* **1985**, *15*, 149-196; Robertson *Prog. Phys. Org. Chem.* **1967**, *4*, 213-280. For a review of the solvolytic cleavage of *t*-butyl substrates, see Dvorko; Ponomareva; Kulik *Russ. Chem. Rev.* **1984**, *53*, 547-560.

is solvation energy. In cases where the role of the solvent is solely to assist in departure of the leaving group from the frontside, that is, where there is a complete absence of backside (S_N2) participation by solvent molecules, the mechanism is called *limiting* S_N1 . There is kinetic and other evidence¹⁹ that in pulling X away from RX, two molecules of a protic solvent form weak hydrogen bonds with X

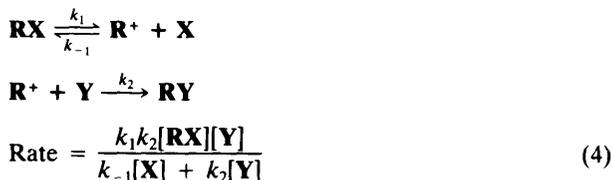


In the IUPAC system the S_N1 mechanism is $D_N + A_N$ or $D_N^\ddagger + A_N$ (where \ddagger denotes the rate-determining step). The IUPAC designations for the S_N1 and S_N2 mechanisms thus clearly show the essential differences between them: $A_N D_N$ indicates that bond breaking is concurrent with bond formation; $D_N + A_N$ shows that the former happens first.

In looking for evidence for the S_N1 mechanism the first thought is that it should be a first-order reaction following the rate law

$$\text{Rate} = k[\text{RX}] \quad (3)$$

Since the slow step involves only the substrate, the rate should be dependent only on the concentration of that. Although the solvent is necessary to assist in the process of ionization, it does not enter the rate expression, because it is present in large excess. However, the simple rate law given in Eq. (3) is not sufficient to account for all the data. Many cases are known where pure first-order kinetics are followed, but in many other cases more complicated kinetics are found. We can explain this by taking into account the reversibility of the first step. The X formed in this step competes with Y for the cation and the rate law must be modified as follows (see Chapter 6):



At the beginning of the reaction, when the concentration of X is very small, $k_{-1}[\text{X}]$ is negligible compared with $k_2[\text{Y}]$ and the rate law is reduced to Eq. (3). Indeed, S_N1 reactions generally do display simple first-order kinetics in their initial stages. Most kinetic studies of S_N1 reactions fall into this category. In the later stages of S_N1 solvolyses, $[\text{X}]$ becomes large and Eq. (4) predicts that the rate should decrease. This is found to be the case for diarylmethyl halides,²⁰ though not for *t*-butyl halides, which follow Eq. (3) for the entire reaction.²¹ An explanation for this difference is that *t*-butyl cations are less selective than the relatively stable diarylmethyl type (p. 169). Although halide ion is a much more powerful nucleophile than water, there is much more water available since it is the solvent.²² The selective diphenylmethyl cation survives many collisions with solvent molecules before combining with a reactive halide, but the less selective *t*-butyl ion cannot wait for a reactive but relatively rare halide ion and combines with the solvent.

¹⁹Blandamer; Burgess; Duce; Symons; Robertson; Scott *J. Chem. Res. (S)* **1982**, 130.

²⁰Benfey; Hughes; Ingold *J. Chem. Soc.* **1952**, 2488.

²¹Bateman; Hughes; Ingold *J. Chem. Soc.* **1940**, 960.

²²In the experiments mentioned, the solvent was actually "70%" or "80%" aqueous acetone. "80%" aqueous acetone consists of 4 vol of dry acetone and 1 vol of water.

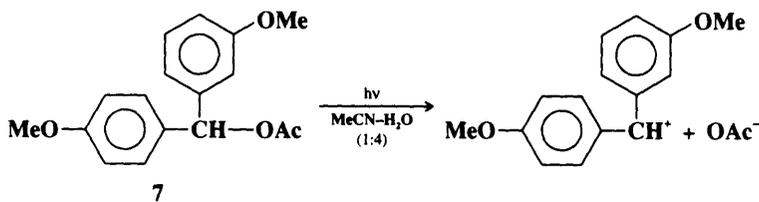
If the X formed during the reaction can decrease the rate, at least in some cases, it should be possible to *add* X from the outside and further decrease the rate in that way. This retardation of rate by addition of X is called *common-ion effect* or the *mass-law effect*. Once again, addition of halide ions decreases the rate for diphenylmethyl but not for *t*-butyl halides.

One factor that complicates the kinetic picture is the *salt effect*. An increase in ionic strength of the solution usually increases the rate of an S_N1 reaction (p. 359). But when the reaction is of charge type II, where both Y and RX are neutral, so that X is negatively charged (and most solvolyses are of this charge type), the ionic strength increases as the reaction proceeds and this increases the rate. This effect must be taken into account in studying the kinetics. Incidentally, the fact that the addition of outside ions *increases* the rate of most S_N1 reactions makes especially impressive the *decrease* in rate caused by the common ion.

It may be noted that the pseudo-first-order rate law for an S_N2 reaction in the presence of a large excess of Y [Eq. (2)] is the same as that for an ordinary S_N1 reaction [Eq. (3)]. It is thus not possible to tell these cases apart by simple kinetic measurements. However, we can often distinguish between them by the common-ion effect mentioned above. Addition of a common ion will not markedly affect the rate of an S_N2 reaction beyond the effect caused by other ions. Unfortunately, as we have seen, not all S_N1 reactions show the common-ion effect, and this test fails for *t*-butyl and similar cases.

Kinetic studies also provide other evidence for the S_N1 mechanism. If this mechanism operates essentially as shown on p. 298, the rate should be the same for a given substrate under a given set of conditions, *regardless of the identity of the nucleophile or its concentration*. In one experiment that demonstrates this, benzhydryl chloride (Ph₂CHCl) was treated in SO₂ with the nucleophiles fluoride ion, pyridine, and triethylamine at several concentrations of each nucleophile.²³ In each case the initial rate of the reaction was approximately the same when corrections were made for the salt effect. The same type of behavior has been shown in a number of other cases, even when the reagents are as different in their nucleophilicities (see p. 348) as H₂O and OH⁻.

It is normally not possible to detect the carbocation intermediate of an S_N1 reaction directly, because its lifetime is very short. However, in the case of 3,4'-dimethoxydiphenylmethyl acetate (7) and certain other substrates in polar solvents it was possible to initiate



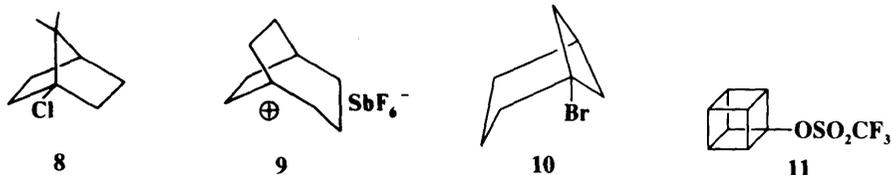
the reaction photolytically, and under these conditions the uv spectra of the intermediate carbocations could be obtained,²⁴ providing additional evidence for the S_N1 mechanism.

Further evidence for the S_N1 mechanism is that reactions run under S_N1 conditions fail or proceed very slowly at the bridgehead positions¹⁰ of [2.2.1] (norbornyl) systems²⁵ (e.g. 1-chloroapocamphane, 8). If S_N1 reactions require carbocations and if carbocations must

²³Bateman; Hughes; Ingold *J. Chem. Soc.* **1940**, 1011.

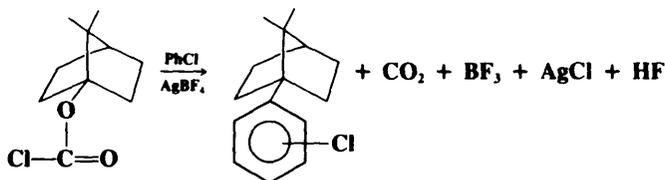
²⁴McClelland; Kanagasabapathy; Steenken *J. Am. Chem. Soc.* **1988**, *110*, 6913.

²⁵For a review, see Fort, in Olah; Schleyer *Carbonium Ions*, vol. 4; Wiley: New York, 1973, pp. 1783-1835.



be planar or nearly planar, then it is no surprise that bridgehead 1-norbornyl carbon atoms, which cannot assume planarity, do not become the seat of carbocations. As an example, **8**, boiled 21 hr with 30% KOH in 80% ethanol or 48 hr with aqueous ethanolic silver nitrate, gave no reaction in either case,²⁶ though analogous open-chain systems reacted readily. According to this theory, S_N1 reactions should be possible with larger rings, since near-planar carbocations might be expected there. This turns out to be the case. For example, [2.2.2] bicyclic systems undergo S_N1 reactions much faster than smaller bicyclic systems, though the reaction is still slower than with open-chain systems.²⁷ Proceeding to a still larger system, the bridgehead [3.2.2] cation **9** is actually stable enough to be kept in solution in SbF₅-SO₂ClF at temperatures below -50°C²⁸ (see also p. 345). Other small bridgehead systems that undergo S_N1 reactions are the [3.1.1] (e.g., **10**)²⁹ and the cubyl (e.g., **11**)³⁰ systems. Ab initio calculations show that the cubyl cation, though it cannot be planar, requires less energy to form than the 1-norbornyl cation.³¹

Certain nucleophilic substitution reactions that normally involve carbocations can take place at norbornyl bridgeheads³² (though it is not certain that carbocations are actually involved in all cases) if the leaving group used is of the type that cannot function as a nucleophile (and thus come back) once it has gone, e.g.,



In this example,³³ chlorobenzene is the nucleophile (see **1-12**).

Additional evidence for the S_N1 mechanism—in particular, for the intermediacy of carbocations—is that solvolysis rates of alkyl chlorides in ethanol parallel carbocation stabilities as determined by heats of ionization measured in superacid solutions (p. 166).³⁴

²⁶Bartlett; Knox *J. Am. Chem. Soc.* **1939**, *61*, 3184.

²⁷For synthetic examples, see Kraus; Hon *J. Org. Chem.* **1985**, *50*, 4605.

²⁸Olah; Liang; Wiseman; Chong *J. Am. Chem. Soc.* **1972**, *74*, 4927.

²⁹Della; Pigou; Tsanaktsidis *J. Chem. Soc., Chem. Commun.* **1987**, 833.

³⁰Eaton; Yang; Xiong *J. Am. Chem. Soc.* **1990**, *112*, 3225; Moriarty; Tuladhar; Penmasta; Awasthi *J. Am. Chem. Soc.* **1990**, *112*, 3228.

³¹Hrovat; Borden *J. Am. Chem. Soc.* **1990**, *112*, 3227.

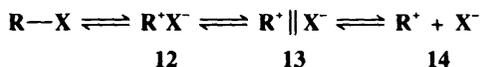
³²Ref. 26; Beak; Trancik *J. Am. Chem. Soc.* **1968**, *90*, 2714; Clive; Denyer *Chem. Commun.* **1971**, 1112; White; McGirk; Aufdermarsh; Tiwari; Todd *J. Am. Chem. Soc.* **1973**, *95*, 8107; Beak; Harris *J. Am. Chem. Soc.* **1974**, *96*, 6363.

³³For a review of reactions with the OCOCl leaving group, see Beak *Acc. Chem. Res.* **1976**, *9*, 230-236.

³⁴Arnett; Petro *J. Am. Chem. Soc.* **1978**, *100*, 5408; Arnett; Petro; Schleyer *J. Am. Chem. Soc.* **1979**, *101*, 522; Arnett; Pienta *J. Am. Chem. Soc.* **1980**, *102*, 3329; Arnett; Molter *Acc. Chem. Res.* **1985**, *18*, 339-346.

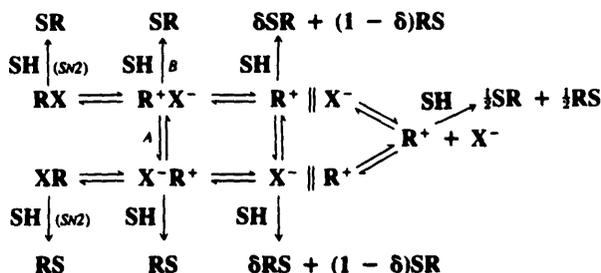
Ion Pairs in the S_N1 Mechanism³⁵

Like the kinetic evidence, the stereochemical evidence for the S_N1 mechanism is less clear-cut than it is for the S_N2 mechanism. If there is a free carbocation, it is planar (p. 172), and the nucleophile should attack with equal facility from either side of the plane, resulting in complete racemization. Although many first-order substitutions do give complete racemization, many others do not. Typically there is 5 to 20% inversion, though in a few cases, a small amount of retention of configuration has been found. These and other results have led to the conclusion that in many S_N1 reactions at least some of the products are not formed from free carbocations but rather from *ion pairs*. According to this concept,³⁶ S_N1 reactions proceed in this manner:



where **12** is an *intimate, contact, or tight* ion pair, **13** a *loose, or solvent-separated* ion pair, and **14** the dissociated ions (each surrounded by molecules of solvent).³⁷ The reaction in which the intimate ion pair recombines to give the original substrate is referred to as *internal return*. The reaction products can result from attack by the nucleophile at any stage. In the intimate ion pair **12**, R⁺ does not behave like the free cation of **14**. There is probably significant bonding between R⁺ and X⁻ and asymmetry may well be maintained.³⁸ X⁻ "solvates" the cation on the side from which it departed, while solvent molecules near **12** can only solvate it from the opposite side. Nucleophilic attack by a solvent molecule on **12** thus leads to inversion.

A complete picture of the possibilities for solvolysis reactions in a solvent SH (ignoring the possibilities of elimination or rearrangement—see Chapters 17 and 18) is the following,³⁹ though in any particular case it is unlikely that all these reactions occur:



In this scheme RS and SR represent enantiomers, etc., and δ represents some fraction. The following are the possibilities: (1) Direct attack by SH on RX gives SR (complete inversion) in a straight S_N2 process. (2) If the intimate ion pair R⁺X⁻ is formed, the solvent can attack at this stage. This can lead to total inversion if reaction A does not take place or to a combination of inversion and racemization if there is competition between A and B. (3) If the solvent-separated ion pair is formed, SH can attack here. The stereochemistry is not

³⁵For reviews of ion pairs in S_N reactions, see Beletskaya *Russ. Chem. Rev.* **1975**, *44*, 1067-1090; Harris *Prog. Phys. Org. Chem.* **1974**, *11*, 89-173; Raber; Harris; Schleyer, in *Szwarc Ions and Ion Pairs in Organic Reactions*, vol. 2: Wiley: New York, 1974, pp. 247-374.

³⁶Proposed by Winstein; Clippinger; Fainberg; Heck; Robinson *J. Am. Chem. Soc.* **1956**, *78*, 328.

³⁷For a review of the energy factors involved in the recombination of ion pairs, see Kessler; Feigel *Acc. Chem. Res.* **1982**, *15*, 2-8.

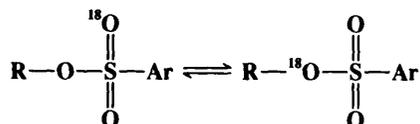
³⁸Fry; Lancelot; Lam; Harris; Bingham; Raber; Hall; Schleyer *J. Am. Chem. Soc.* **1970**, *92*, 2538.

³⁹Shiner; Fisher *J. Am. Chem. Soc.* **1971**, *93*, 2553.

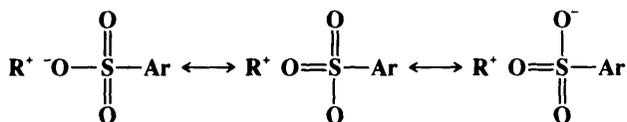
maintained as tightly and more racemization (perhaps total) is expected. (4) Finally, if free R^+ is formed, it is planar, and attack by SH gives complete racemization.

The ion-pair concept thus predicts that S_N1 reactions can display either complete racemization or partial inversion. The fact that this behavior is generally found is evidence that ion pairs are involved in many S_N1 reactions. There is much other evidence for the intervention of ion pairs:⁴⁰

1. The compound 2-octyl brosylate was labeled at the sulfone oxygen with ^{18}O and solvolyzed. The unreacted brosylate recovered at various stages of solvolysis had the ^{18}O considerably, though not completely, scrambled:⁴¹



In an intimate ion pair, the three oxygens become equivalent:



Similar results were obtained with several other sulfonate esters.⁴² The possibility must be considered that the scrambling resulted from ionization of one molecule of $ROSO_2Ar$ to R^+ and $ArSO_2O^-$ followed by attack by the $ArSO_2O^-$ ion on *another* carbocation or perhaps on a molecule of $ROSO_2Ar$ in an S_N2 process. However, this was ruled out by solvolyzing unlabeled substrate in the presence of labeled $HOSO_2Ar$. These experiments showed that there was some intermolecular exchange (3 to 20%), but not nearly enough to account for the amount of scrambling found in the original experiments. Similar scrambling was found in solvolysis of labeled carboxylic esters $R-^{18}O-COR'$, where the leaving group is $R'COO^-$.⁴³ In this case also, the external addition of $RCOO^-$ did not result in significant exchange. However, it has been proposed that the scrambling could result from a concerted process, not involving ion-pair intermediates, and there is some evidence for this view.⁴⁴

2. The *special salt effect*. The addition of $LiClO_4$ or $LiBr$ in the acetolysis of certain tosylates produced an initial steep rate acceleration that then decreased to the normal linear acceleration (caused by the ordinary salt effect).⁴⁵ This is interpreted as follows: the ClO_4^-

⁴⁰For further evidence beyond that given here, see Winstein; Baker; Smith *J. Am. Chem. Soc.* **1964**, *86*, 2072; Streitwieser; Walsh *J. Am. Chem. Soc.* **1965**, *87*, 3686; Sommer; Carey *J. Org. Chem.* **1967**, *32*, 800, 2473; Kwart; Irvine *J. Am. Chem. Soc.* **1969**, *91*, 5541; Harris; Becker; Fagan; Walden *J. Am. Chem. Soc.* **1974**, *96*, 4484; Bunton; Huang; Paik *J. Am. Chem. Soc.* **1975**, *97*, 6262; Humski; Sendjarević; Shiner *J. Am. Chem. Soc.* **1976**, *98*, 2865; Maskill; Thompson; Wilson *J. Chem. Soc., Chem. Commun.* **1981**, 1239; McManus; Safavy; Roberts *J. Org. Chem.* **1982**, *47*, 4388; Ref. 35; McLennan; Stein; Dobson *Can. J. Chem.* **1986**, *64*, 1201; Kinoshita; Komatsu; Ikai; Kashimura; Tanikawa; Hatanaka; Okamoto *J. Chem. Soc., Perkin Trans. 2* **1988**, 1875; Ronco; Petit; Guyon; Villa *Helv. Chim. Acta* **1988**, *71*, 648; Kevill; Kyong; Weitz *J. Org. Chem.* **1990**, *55*, 4304.

⁴¹Diaz; Lazdins; Winstein *J. Am. Chem. Soc.* **1968**, *90*, 1904.

⁴²Goering; Thies *J. Am. Chem. Soc.* **1968**, *90*, 2967, 2968; Goering; Jones *J. Am. Chem. Soc.* **1980**, *102*, 1628; Yukawa; Morisaki; Tsuji; Kim; Ando *Tetrahedron Lett.* **1981**, *22*, 5187; Chang; le Noble *J. Am. Chem. Soc.* **1983**, *105*, 3708; Paradisi; Bunnett *J. Am. Chem. Soc.* **1985**, *107*, 8223; Fujio; Sanematsu; Tsuno; Sawada; Takai *Tetrahedron Lett.* **1988**, *29*, 93.

⁴³Goering; Levy *J. Am. Chem. Soc.* **1962**, *84*, 3853. **1964**, *86*, 120; Goering; Hopf *J. Am. Chem. Soc.* **1971**, *93*, 1224.

⁴⁴Dietze; Wojciechowski *J. Am. Chem. Soc.* **1990**, *112*, 5240.

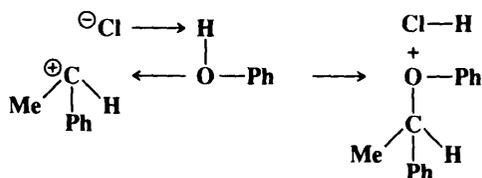
⁴⁵Ref. 36; Winstein; Klinedinst; Clippinger *J. Am. Chem. Soc.* **1961**, *83*, 4986; Cristol; Noreen; Nachtigall *J. Am. Chem. Soc.* **1972**, *94*, 2187.

(or Br^-) traps the solvent-separated ion pair to give $\text{R}^+ \parallel \text{ClO}_4^-$ which, being unstable under these conditions, goes to product. Hence, the amount of solvent-separated ion pair that would have returned to the starting material is reduced, and the rate of the overall reaction is increased. The special salt effect has been directly observed by the use of picosecond absorption spectroscopy.⁴⁶

3. We have previously discussed the possibilities of racemization or inversion of the product RS of a solvolysis reaction. However, the formation of an ion pair followed by internal return can also affect the stereochemistry of the substrate molecule RX. Cases have been found where internal return racemizes an original optically active RX, an example being solvolysis in aqueous acetone of α -*p*-anisylethyl *p*-nitrobenzoate,⁴⁷ while in other cases partial or complete retention is found, for example, solvolysis in aqueous acetone of *p*-chlorobenzhydryl *p*-nitrobenzoate.⁴⁸ Racemization of RX is presumably caused by the pathway: $\text{RX} \rightleftharpoons \text{R}^+\text{X}^- \rightleftharpoons \text{X}^-\text{R}^+ \rightleftharpoons \text{XR}$. Evidence for ion pairs is that, in some cases where internal return involves racemization, it has been shown that such racemization is faster than solvolysis. For example, optically active *p*-chlorobenzhydryl chloride racemizes about 30 times faster than it solvolyzes in acetic acid.⁴⁹

Molecular orbital calculations⁵⁰ made on *t*-BuCl show that the C—Cl distance in the intimate ion pair is 2.9 Å and the onset of the solvent-separated ion pair takes place at about 5.5 Å (compare the C—Cl bond length of 1.8 Å).

In a few cases, $\text{S}_{\text{N}}1$ reactions have been found to proceed with partial retention (20 to 50%) of configuration. Ion pairs have been invoked to explain some of these.⁵¹ For example, it has been proposed that the phenolysis of optically active α -phenylethyl chloride, in which the ether of net retained configuration is obtained, involves a four-center mechanism:



This conclusion is strengthened by the fact that partial retention was obtained in this system only with chloride or other neutral leaving groups; with leaving groups bearing a positive charge, which are much less likely to form hydrogen bonds with the solvent, no retention was found.⁵² Partial retention can also arise when the ion pair is shielded at the backside by an additive such as acetonitrile, acetone, or aniline.⁵³

The difference between the $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms is in the timing of the steps. In the $\text{S}_{\text{N}}1$ mechanism, first X leaves, then Y attacks. In the $\text{S}_{\text{N}}2$ case, the two things happen simultaneously. One could imagine a third possibility: first the attack of Y and then the removal of X. This is not possible at a saturated carbon, since it would mean more than

⁴⁶Simon; Peters *J. Am. Chem. Soc.* **1982**, *104*, 6142.

⁴⁷Goering; Briody; Sandrock *J. Am. Chem. Soc.* **1970**, *92*, 7401.

⁴⁸Goering; Briody; Levy *J. Am. Chem. Soc.* **1963**, *85*, 3059.

⁴⁹Winstein; Gall; Hojo; Smith *J. Am. Chem. Soc.* **1960**, *82*, 1010. See also Shiner; Hartshorn; Vogel *J. Org. Chem.* **1973**, *38*, 3604.

⁵⁰Jorgensen; Buckner; Huston; Rosky *J. Am. Chem. Soc.* **1987**, *109*, 1891.

⁵¹Okamoto; Yamada; Nitta; Shingu *Bull. Chem. Soc. Jpn.* **1966**, *39*, 299; Okamoto; Takeuchi; Inoue *J. Chem. Soc., Perkin Trans. 2* **1980**, 842; Okamoto *Pure Appl. Chem.* **1984**, *56*, 1797-1808. For a similar mechanism with amine nucleophiles, see Lee; Kim; Kang; Lee *J. Org. Chem.* **1988**, *53*, 2678; Lee; Kim; Lee; Kim *J. Phys. Org. Chem.* **1989**, *2*, 35.

⁵²Okamoto; Kinoshita; Shingu *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1545.

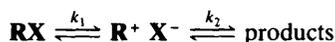
⁵³Okamoto; Nitta; Dohi; Shingu *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3220; Kinoshita; Ueno; Ikai; Fujiwara; Okamoto *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3273; Kinoshita et al., Ref. 40.

eight electrons in the outer shell of carbon. However, this type of mechanism is possible and indeed occurs at other types of substrate (p. 331; Chapter 13).

Mixed S_N1 and S_N2 Mechanisms

Some reactions of a given substrate under a given set of conditions display all the characteristics of S_N2 mechanisms; other reactions seem to proceed by S_N1 mechanisms, but cases are found that cannot be characterized so easily. There seems to be something in between, a mechanistic "borderline" region.⁵⁴ At least two broad theories have been devised to explain these phenomena. One theory holds that intermediate behavior is caused by a mechanism that is neither "pure" S_N1 nor "pure" S_N2, but some "in-between" type. According to the second theory, there is no intermediate mechanism at all, and borderline behavior is caused by simultaneous operation, in the same flask, of both the S_N1 and S_N2 mechanisms; that is, some molecules react by the S_N1, while others react by the S_N2 mechanism.

One formulation of the intermediate-mechanism theory is that of Sneen.⁵⁵ The formulation is in fact very broad and applies not only to borderline behavior but to all nucleophilic substitutions at a saturated carbon.⁵⁶ According to Sneen, all S_N1 and S_N2 reactions can be accommodated by one basic mechanism (the *ion-pair mechanism*). The substrate first ionizes to an intermediate ion pair which is then converted to products:



The difference between the S_N1 and S_N2 mechanisms is that in the former case the *formation* of the ion pair (k_1) is rate-determining, while in the S_N2 mechanism its *destruction* (k_2) is rate-determining. Borderline behavior is found where the rates of formation and destruction of the ion pair are of the same order of magnitude.⁵⁷ However, a number of investigators have asserted that these results could also be explained in other ways.⁵⁸

There is evidence for the Sneen formulation where the leaving group has a positive charge. In this case there is a cation-molecule pair ($RX^+ \rightarrow R^+ X$)⁵⁹ instead of the ion pair that would be present if the leaving group were uncharged. Katritzky, le Noble, and co-workers found that when such a reaction was run at varying high pressures, there was a minimum in the plot of rate constant vs. pressure.⁶⁰ A minimum of this sort usually indicates a change in mechanism, and the interpretation in this case was that the normal S_N2 mechanism operates at higher pressures and the cation-molecule mechanism at lower pressures.

⁵⁴For an essay on borderline mechanisms in general, see Jencks *Chem. Soc. Rev.* **1982**, *10*, 345-375.

⁵⁵Weiner; Sneen *J. Am. Chem. Soc.* **1965**, *87*, 292; Sneen; Larsen *J. Am. Chem. Soc.* **1969**, *91*, 362, 6031; Sneen; Felt; Dickason *J. Am. Chem. Soc.* **1973**, *95*, 638; Sneen *Acc. Chem. Res.* **1973**, *6*, 46-53.

⁵⁶Including substitution at an allylic carbon; see Sneen; Bradley *J. Am. Chem. Soc.* **1972**, *94*, 6975; Sneen; Carter *J. Am. Chem. Soc.* **1972**, *94*, 6990; Bordwell; Mecca *J. Am. Chem. Soc.* **1975**, *97*, 123, 127; Bordwell; Wiley; Mecca *J. Am. Chem. Soc.* **1975**, *97*, 132; Kevill; Degenhardt *J. Am. Chem. Soc.* **1979**, *101*, 1465.

⁵⁷For evidence for this point of view, see Ref. 55; Sneen; Carter; Kay *J. Am. Chem. Soc.* **1966**, *88*, 2594; Sneen; Robbins *J. Am. Chem. Soc.* **1972**, *94*, 7868; Graczyk; Taylor *J. Am. Chem. Soc.* **1974**, *96*, 3255; Peeters; Anteunis *J. Org. Chem.* **1975**, *40*, 312; Pross; Aronovitch; Koren *J. Chem. Soc., Perkin Trans. 2* **1978**, *197*; Blandamer; Robertson; Scott; Vrieling *J. Am. Chem. Soc.* **1980**, *102*, 2585; Stein; Tencer; Moffatt; Dawe; Sweet *J. Org. Chem.* **1980**, *45*, 3539; Stein; Moffatt *Can. J. Chem.* **1985**, *63*, 3433; Stein *Can. J. Chem.* **1987**, *65*, 363.

⁵⁸See, for example, Gregory; Kohnstam; Queen; Reid *Chem. Commun.* **1971**, 797; Kurz; Harris *J. Am. Chem. Soc.* **1970**, *92*, 4117; Raber; Harris; Hall; Schleyer *J. Am. Chem. Soc.* **1971**, *93*, 4821; McLennan *J. Chem. Soc., Perkin Trans. 2* **1972**, 1577, **1974**, 481, *Acc. Chem. Res.* **1976**, *9*, 281-287, *Tetrahedron Lett.* **1975**, 4689; McLennan; Martin *Tetrahedron Lett.* **1973**, 4215; Raaen; Juhlke; Brown; Collins *J. Am. Chem. Soc.* **1974**, *96*, 5928; Gregoriou *Tetrahedron Lett.* **1974**, 233, **1976**, 4605, 4767; Queen; Matts *Tetrahedron Lett.* **1975**, 1503; Stein *J. Org. Chem.* **1976**, *41*, 519; Stephan *Bull. Soc. Chim. Fr.* **1977**, 779; Katritzky; Musumarra; Sakizadeh *J. Org. Chem.* **1981**, *46*, 3831. For a reply to some of these objections, see Sneen; Robbins, Ref. 57. For a discussion, see Klumpp *Reactivity in Organic Chemistry*; Wiley: New York, 1982, pp. 442-450.

⁵⁹For ion-molecule pairs in other solvolysis reactions, see Thibblin *J. Chem. Soc., Perkin Trans. 2* **1987**, 1629.

⁶⁰Katritzky; Sakizadeh; Gabrielsen; le Noble *J. Am. Chem. Soc.* **1984**, *106*, 1879.

An alternative view that also favors an intermediate mechanism is that of Schleyer and co-workers,⁶¹ who believe that the key to the problem is varying degrees of nucleophilic solvent assistance to ion-pair formation. They have proposed an S_N2 (intermediate) mechanism.⁶²

Among the experiments that have been cited for the viewpoint that borderline behavior results from simultaneous S_N1 and S_N2 mechanisms is the behavior of 4-methoxybenzyl chloride in 70% aqueous acetone.⁶³ In this solvent, hydrolysis (that is, conversion to 4-methoxybenzyl alcohol) occurs by an S_N1 mechanism. When azide ions are added, the alcohol is still a product, but now 4-methoxybenzyl azide is another product. Addition of azide ions increases the rate of ionization (by the salt effect) but *decreases* the rate of hydrolysis. If more carbocations are produced but fewer go to the alcohol, then some azide must be formed by reaction with carbocations—an S_N1 process. However, the rate of ionization is always *less* than the total rate of reaction, so some azide must also form by an S_N2 mechanism.⁶³ Thus, the conclusion is that S_N1 and S_N2 mechanisms operate simultaneously.⁶⁴

Some nucleophilic substitution reactions that seem to involve a "borderline" mechanism actually do not. Thus, one of the principal indications that a "borderline" mechanism is taking place has been the finding of partial racemization and partial inversion. However, Weiner and Sneen have demonstrated that this type of stereochemical behavior is quite consistent with a strictly S_N2 process. These workers studied the reaction of optically active 2-octyl brosylate in 75% aqueous dioxane, under which conditions inverted 2-octanol was obtained in 77% optical purity.⁶⁵ When sodium azide was added, 2-octyl azide was obtained along with the 2-octanol, *but the latter was now 100% inverted*. It is apparent that, in the original case, 2-octanol was produced by two different processes: an S_N2 reaction leading to inverted product, and another process in which some intermediate leads to racemization or retention. When azide ions were added, they scavenged this intermediate, so that the entire second process now went to produce azide, while the S_N2 reaction, unaffected by addition of azide, still went on to give inverted 2-octanol. What is the nature of the intermediate in the second process? At first thought we might suppose that it is a carbocation, so that this would be another example of simultaneous S_N1 and S_N2 reactions. However, solvolysis of 2-octyl brosylate in pure methanol or of 2-octyl methanesulfonate in pure water, in the absence of azide ions, gave methyl 2-octyl ether or 2-octanol, respectively, *with 100% inversion of configuration*, indicating that the mechanism in these solvents was pure S_N2. Since methanol and water are more polar than 75% aqueous dioxane and since an increase in polarity of solvent increases the rate of S_N1 reactions at the expense of S_N2 (p. 356), it is extremely unlikely that any S_N1 process could occur in 75% aqueous dioxane. The intermediate in the second process is thus not a carbocation. What it is is suggested by the fact that, in the absence of azide ions, the amount of inverted 2-octanol decreased with an

⁶¹Bentley; Schleyer *J. Am. Chem. Soc.* **1976**, *98*, 7658; Bentley; Bowen; Morten; Schleyer *J. Am. Chem. Soc.* **1981**, *103*, 5466.

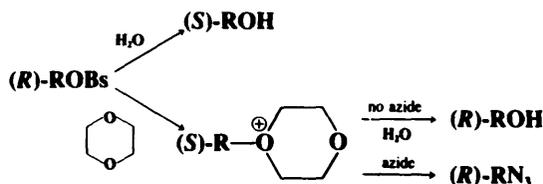
⁶²For additional evidence for this view, see Laureillard; Casadevall; Casadevall *Tetrahedron* **1984**, *40*, 4921. *Helv. Chim. Acta* **1984**, *67*, 352; McLennan *J. Chem. Soc., Perkin Trans. 2* **1981**, 1316. For evidence against the S_N2(intermediate) mechanism, see Allen; Kanagasabapathy; Tidwell *J. Am. Chem. Soc.* **1985**, *107*, 4513; Fărcașiu; Jähme; Rüdhardt *J. Am. Chem. Soc.* **1985**, *107*, 5717; Dietze; Jencks *J. Am. Chem. Soc.* **1986**, *108*, 4549; Dietze; Hariri; Khattak *J. Org. Chem.* **1989**, *54*, 3317; Coles; Maskill *J. Chem. Soc., Perkin Trans. 2* **1987**, 1083; Richard; Amyes; Vontor *J. Am. Chem. Soc.* **1991**, *113*, 5871.

⁶³Kohnstam; Queen; Shillaker *Proc. Chem. Soc.* **1959**, 157; Amyes; Richard *J. Am. Chem. Soc.* **1990**, *112*, 9507. For other evidence supporting the concept of simultaneous mechanisms, see Pocker *J. Chem. Soc.* **1959**, 3939, 3944; Casapieri; Swart *J. Chem. Soc.* **1961**, 4342. **1963**, 1254; Ceccon; Papa; Fava *J. Am. Chem. Soc.* **1966**, *88*, 4643; Okamoto; Uchida; Saitō; Shingu *Bull. Chem. Soc. Jpn.* **1966**, *39*, 307; Guinot; Lamaty *Chem. Commun.* **1967**, 960; Queen *Can. J. Chem.* **1979**, *57*, 2646; Katritzky; Musumarra; Sakizadeh; El-Shafie; Jovanovic *Tetrahedron Lett.* **1980**, *21*, 2697; Richard; Rothenberg; Jencks *J. Am. Chem. Soc.* **1984**, *106*, 1361; Richard; Jencks *J. Am. Chem. Soc.* **1984**, *106*, 1373, 1383; Katritzky; Brycki *J. Phys. Org. Chem.* **1988**, *1*, 1; Stein *Can. J. Chem.* **1989**, *67*, 297.

⁶⁴These data have also been explained as being in accord with the ion-pair mechanism: Sneen; Larsen *J. Am. Chem. Soc.* **1969**, *91*, 6031.

⁶⁵Weiner; Sneen *J. Am. Chem. Soc.* **1965**, *87*, 287.

increasing percentage of dioxane in the solvent. Thus the intermediate is an oxonium ion formed by an S_N2 attack by *dioxane*. This ion is not a stable product but reacts with water in another S_N2 process to produce 2-octanol with retained configuration. The entire process can be shown as follows:



That part of the original reaction that resulted in retention of configuration⁶⁶ is thus seen to stem from two successive S_N2 reactions and not from any “borderline” behavior.⁶⁷

SET Mechanisms

In certain reactions where nucleophilic substitutions would seem obviously indicated, there is evidence that radicals and/or radical ions are actually involved.⁶⁸ The first step in such a process is transfer of an electron from the nucleophile to the substrate to form a radical anion:



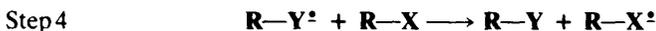
Mechanisms that begin this way are called *SET (single electron transfer) mechanisms*.⁶⁹ Once formed, the radical ion cleaves:



The radicals formed in this way can go on to product by reacting with the Y^\bullet produced in Step 1 or with the original nucleophilic ion $\bar{\text{Y}}^-$, in which case an additional step is necessary:



or



In the latter case, the radical ion R-X^\bullet is formed by Step 4 as well as by Step 1, so that a chain reaction (p. 678) can take place.

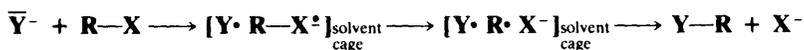
⁶⁶According to this scheme, the configuration of the isolated RN_3 should be retained. It was, however, largely inverted, owing to a competing S_N2 reaction where N_3^- directly attacks ROBs .

⁶⁷For other examples, see Streitwieser; Walsh; Wolfe *J. Am. Chem. Soc.* **1965**, *87*, 3682; Streitwieser; Walsh *J. Am. Chem. Soc.* **1965**, *87*, 3686; Beronius; Nilsson; Holmgren *Acta Chem. Scand.* **1972**, *26*, 3173. See also Knier; Jencks *J. Am. Chem. Soc.* **1980**, *102*, 6789.

⁶⁸Kerber; Urry; Kornblum *J. Am. Chem. Soc.* **1965**, *87*, 4520; Kornblum; Michel; Kerber *J. Am. Chem. Soc.* **1966**, *88*, 5660, 5662; Russell; Danen *J. Am. Chem. Soc.* **1966**, *88*, 5663; Bank; Noyd *J. Am. Chem. Soc.* **1973**, *95*, 8203; Ashby; Goel; Park *Tetrahedron Lett.* **1981**, *22*, 4209. For discussions of the relationship between S_N2 and SET mechanisms, see Lewis *J. Am. Chem. Soc.* **1989**, *111*, 7576; Shaik *Acta Chem. Scand.* **1990**, *44*, 205-221.

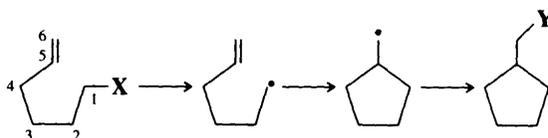
⁶⁹For reviews, see Savéant *Adv. Phys. Org. Chem.* **1990**, *26*, 1-130; Rossi; Pierini; Palacios *J. Chem. Educ.* **1989**, *66*, 720; Ashby *Acc. Chem. Res.* **1988**, *21*, 414-421; Chanon; Tobe *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 1-23 [*Angew. Chem.* **94**, 27-49]. See also Pross *Acc. Chem. Res.* **1985**, *18*, 212-219; Chanon *Acc. Chem. Res.* **1987**, *20*, 214-221.

One type of evidence for an SET mechanism is the finding of some racemization. A totally free radical would of course result in a completely racemized product RY, but it has been suggested⁷⁰ that inversion can also take place in some SET processes. The suggestion is that in Step 1 the Y⁻ still approaches from the back side, even though an ordinary S_N2 mechanism will not follow, and that the radical R[•], once formed, remains in a solvent cage with Y[•] still opposite X⁻, so that Steps 1, 2, and 3 can lead to inversion.



Reactions with SET mechanisms typically show predominant, though not 100%, inversion.

Other evidence cited⁷¹ for SET mechanisms has been detection of radical or radical ion intermediates by esr⁷² or CIDNP; the finding that such reactions can take place at 1-norbornyl bridgeheads;⁷³ and the formation of cyclic side products when the substrate has a double bond in the 5,6 position (such substrates are called *radical probes*).



Free radicals with double bonds in this position are known to cyclize readily (p. 744).⁷⁴

The SET mechanism is chiefly found where X = I or NO₂ (see 0-94). A closely related mechanism, the S_{RN}1, takes place with aromatic substrates (Chapter 13).⁷⁵ In that mechanism the initial attack is by an electron donor, rather than a nucleophile.

The mechanisms so far considered can, in theory at least, operate on any type of saturated (or for that matter unsaturated) substrate. There are other mechanisms that are more limited in scope.

The Neighboring-Group Mechanism⁷⁶

It is occasionally found with certain substrates that (1) the rate of reaction is greater than expected, and (2) the configuration at a chiral carbon is *retained* and not inverted or racemized. In these cases there is usually a group with an unshared pair of electrons β to the leaving group (or sometimes farther away). The mechanism operating in such cases is called the *neighboring-group mechanism* and consists essentially of two S_N2 substitutions, each

⁷⁰Ashby; Pham *Tetrahedron Lett.* **1987**, 28, 3183; Daasbjerg; Lund; Lund *Tetrahedron Lett.* **1989**, 30, 493.

⁷¹See also Chanon; Tobe, Ref. 69; Fuhlendorff; Lund; Lund; Pedersen *Tetrahedron Lett.* **1987**, 28, 5335.

⁷²See, for example Russell; Pecoraro *J. Am. Chem. Soc.* **1979**, 101, 3331.

⁷³Santiago; Morris; Rossi *J. Chem. Soc., Chem. Commun.* **1988**, 220.

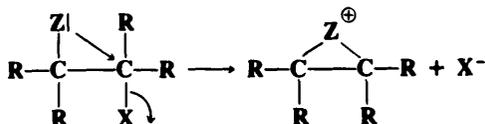
⁷⁴For criticisms of this method for demonstrating SET mechanisms, see Newcomb; Kaplan *Tetrahedron Lett.* **1988**, 29, 3449; Newcomb; Kaplan; Curran *Tetrahedron Lett.* **1988**, 29, 3451; Newcomb; Curran *Acc. Chem. Res.* **1988**, 21, 206-214; Newcomb *Acta Chem. Scand.* **1990**, 44, 299. For replies to the criticism, see Ashby *Acc. Chem. Res.* **1988**, 21, 414-421; Ashby; Pham; Amrollah-Madjdabadi *J. Org. Chem.* **1991**, 56, 1596.

⁷⁵In this book we make the above distinction between the SET and S_{RN}1 mechanisms. However, many workers use the designation SET to refer to the S_{RN}1, the chain version of the SET, or both.

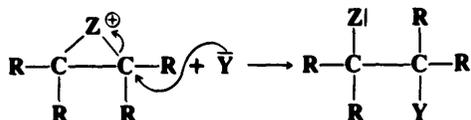
⁷⁶For a monograph, see Capon; McManus *Neighboring Group Participation*, vol. 1; Plenum: New York, 1976.

causing an inversion so the net result is retention of configuration.⁷⁷ In the first step of this reaction the neighboring group acts as a nucleophile, pushing out the leaving group but still retaining attachment to the molecule. In the second step the external nucleophile displaces the neighboring group by a backside attack:

Step 1



Step 2



The reaction obviously must go faster than if Y were attacking directly, since if the latter process were faster, it would be happening. The neighboring group Z is said to be lending *anchimeric assistance*. The rate law followed in the neighboring-group mechanism is the first-order law shown in Eq. (2) or (3); that is, Y does not take part in the rate-determining step.

The reason attack by Z is faster than that by Y is that the group Z is more available. In order for Y to react, it must collide with the substrate, but Z is immediately available by virtue of its position. A reaction between the substrate and Y involves a large decrease in entropy of activation (ΔS^\ddagger), since the reactants are far less free in the transition state than before. Reaction of Z involves a much smaller loss of ΔS^\ddagger (see p. 211).⁷⁸

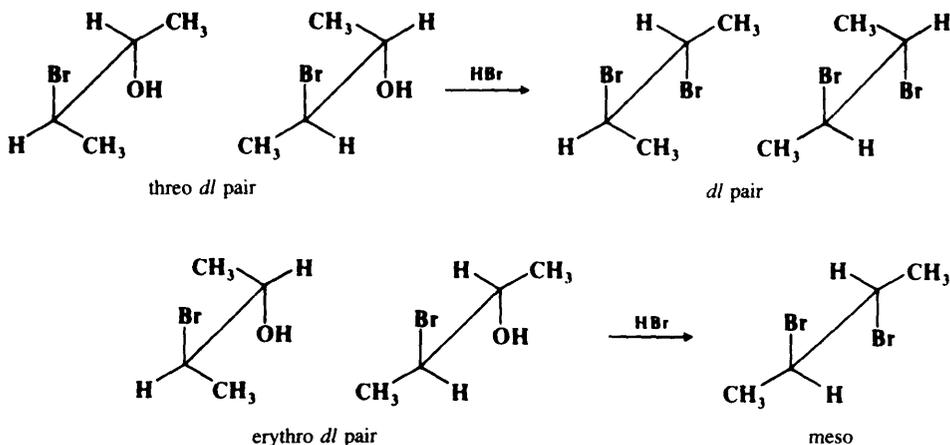
It is not always easy to determine when a reaction rate has been increased by anchimeric assistance. In order to be certain, it is necessary to know what the rate would be without participation by the neighboring group. The obvious way to examine this question is to compare the rates of the reaction with and without the neighboring group, for example, $\text{HOCH}_2\text{CH}_2\text{Br}$ vs. $\text{CH}_3\text{CH}_2\text{Br}$. However, this will certainly not give an accurate determination of the extent of participation, since the steric and field effects of H and OH are not the same. Furthermore, no matter what the solvent, the shell of solvent molecules that surrounds the polar protic OH group must differ greatly from that which surrounds the nonpolar H. Because of these considerations, it is desirable to have a large increase in the rate, preferably more than fiftyfold, before a rate increase is attributed to neighboring-group participation.

The first important evidence for the existence of this mechanism was the demonstration that retention of configuration can occur if the substrate is suitable. It was shown that the *threo dl* pair of 3-bromo-2-butanol when treated with HBr gave *dl*-2,3-dibromobutane, while the *erythro* pair gave the *meso* isomer:⁷⁹

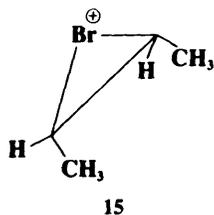
⁷⁷There is evidence that this kind of process can happen intermolecularly (e.g., $\text{RX} + \text{Z}^- \rightarrow \text{RZ} + \text{X}^-$). In this case Z^- acts as a catalyst for the reaction $\text{RX} + \text{Y}^- \rightarrow \text{RY}$: McCortney; Jacobson; Vreeke; Lewis *J. Am. Chem. Soc.* **1990**, *112*, 3554.

⁷⁸For a review of the energetics of neighboring-group participation, see Page *Chem. Soc. Rev.* **1973**, *2*, 295-323.

⁷⁹Winstein; Lucas *J. Am. Chem. Soc.* **1939**, *61*, 1576, 2845.

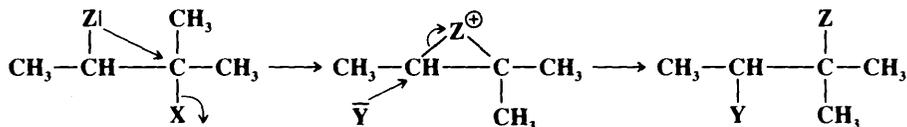


This indicated that retention had taken place. Note that both products are optically inactive and so cannot be told apart by differences in rotation. The meso and *dl* dibromides have different boiling points and indexes of refraction and were identified by these properties. Even more convincing evidence was that either of the two threo isomers alone gave not just one of the enantiomeric dibromides, but the *dl* pair. The reason for this is that the intermediate present after the attack by the neighboring group (**15**) is symmetrical, so the external



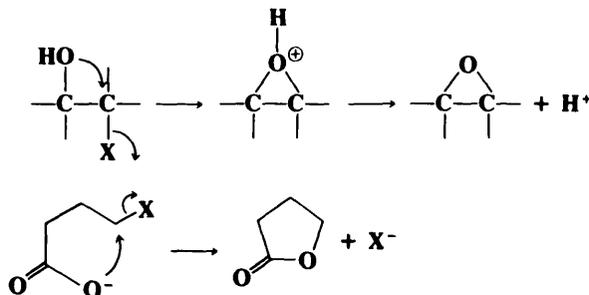
nucleophile Br^- can attack both carbon atoms equally well. **15** is a bromonium ion, the existence of which has been demonstrated in several types of reactions.

Although **15** is symmetrical, intermediates in most neighboring-group mechanisms are not, and it is therefore possible to get not a simple substitution product but a rearrangement. This will happen if Y attacks not the carbon atom from which X left, but the one to which Z was originally attached:

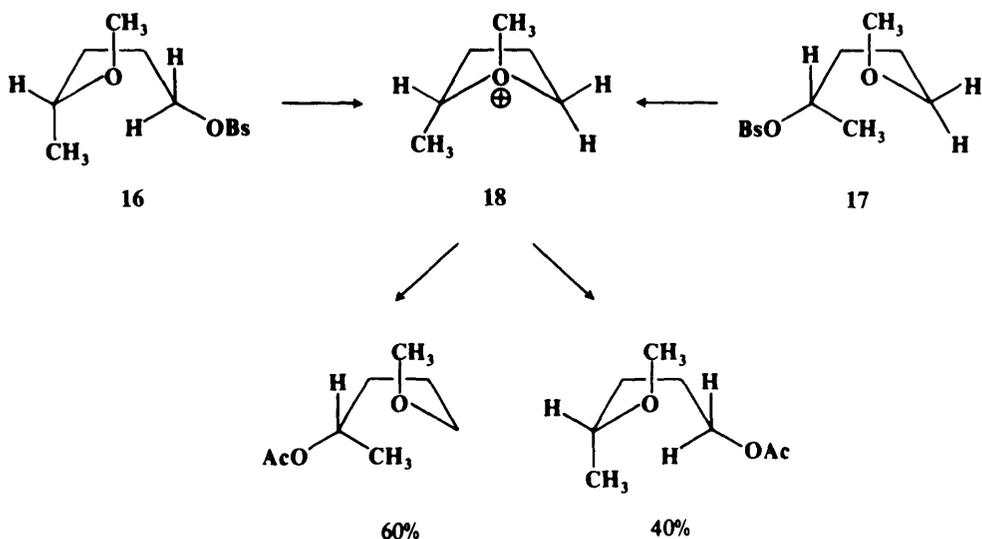


In such cases substitution and rearrangement products are often produced together. For a discussion of rearrangements, see Chapter 18.

Another possibility is that the intermediate may be stable or may find some other way to stabilize itself. In such cases, Y never attacks at all and the product is cyclic. These are simple internal $\text{S}_{\text{N}}2$ reactions. Two examples are formation of epoxides and lactones:



The fact that acetolysis of both 4-methoxy-1-pentyl brosylate (**16**) and 5-methoxy-2-pentyl brosylate (**17**) gave the same mixture of products is further evidence for participation by a



neighboring group.⁸⁰ In this case the intermediate **18** is common to both substrates.

The neighboring-group mechanism operates only when the ring size is right for a particular type of Z. For example, for $\text{MeO}(\text{CH}_2)_n\text{OBs}$, neighboring-group participation was important for $n = 4$ or 5 (corresponding to a five- or six-membered intermediate) but not for $n = 2, 3$, or 6 .⁸¹ However, optimum ring size is not the same for all reactions, even with a particular Z. In general, the most rapid reactions occur when the ring size is three, five, or six, depending on the reaction type. The likelihood of four-membered ring neighboring-group participation is increased when there are alkyl groups α or β to the neighboring group.⁸²

The following are some of the more important neighboring groups: COO^- (but not COOH), COOR , COAr , OCOR ,⁸³ OR , OH , O^- ,⁸⁴ NH_2 , NHR , NR_2 , NHCOR , SH , SR ,

⁸⁰Allred; Winstein *J. Am. Chem. Soc.* **1967**, *89*, 3991, 3998.

⁸¹Winstein; Allred; Heck; Glick *Tetrahedron* **1958**, *3*, 1; Allred; Winstein *J. Am. Chem. Soc.* **1967**, *89*, 4012.

⁸²Eliel; Clawson; Knox *J. Org. Chem.* **1985**, *50*, 2707; Eliel; Knox *J. Am. Chem. Soc.* **1985**, *107*, 2946.

⁸³For an example of OCOR as a neighboring group where the ring size is seven-membered, see Wilen; Delguzzo; Saferstein *Tetrahedron* **1987**, *43*, 5089.

⁸⁴For a review of oxygen functions as neighboring groups, see Perst *Oxonium Ions in Organic Chemistry*; Verlag Chemie: Deerfield Beach, FL, 1971, pp. 100-127. There is evidence that the oxygen in an epoxy group can also act as a neighboring group: Francl; Hansell; Patel; Swindell *J. Am. Chem. Soc.* **1990**, *112*, 3535.

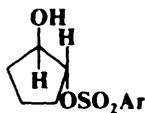
S⁻,⁸⁵ I, Br, and Cl. The effectiveness of halogens as neighboring groups decreases in the order I > Br > Cl.⁸⁶ Cl is a very weak neighboring group and can be shown to act in this way only when the solvent does not interfere. For example, when 5-chloro-2-hexyl tosylate is solvolyzed in acetic acid, there is little participation by the Cl, but when the solvent is changed to trifluoroacetic acid, which is much less nucleophilic, neighboring-group participation by the Cl becomes the major reaction pathway.⁸⁷ Thus, Cl acts as a neighboring group *only when there is need for it* (for other examples of the *principle of increasing electron demand*, see below; p. 315).

A number of intermediates of halogen participation (halonium ions),⁸⁸ e.g., **19** and **20**, have been prepared as stable salts in SbF₅-SO₂ or SbF₅-SO₂ClF solutions.⁸⁹ Some have even



been crystallized. Attempts to prepare four-membered homologs of **19** and **20** were not successful.⁹⁰ There is no evidence that F can act as a neighboring group.⁸⁶

The principle that a neighboring group lends assistance in proportion to the need for such assistance also applies to differences in leaving-group ability. Thus, *p*-NO₂C₆H₄SO₂O (the nosylate group) is a better leaving group than *p*-MeC₆H₄SO₂O (the tosylate group). Experiments have shown that the OH group in *trans*-2-hydroxycyclopentyl arenesulfonates:



acts as a neighboring group when the leaving group is tosylate but not when it is nosylate, apparently because the nosylate group leaves so rapidly that it does not require assistance.⁹¹

Neighboring-Group Participation by π and σ Bonds. Nonclassical Carbocations⁹²

For all the neighboring groups listed in the preceding section, the nucleophilic attack is made by an atom with an unshared pair of electrons. In this section we consider neighboring-

⁸⁵For a review of sulfur-containing neighboring groups, see Block *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978, pp. 141-145.

⁸⁶Peterson *Acc. Chem. Res.* **1971**, *4*, 407-413, and references cited therein.

⁸⁷Peterson; Bopp; Chevli; Curran; Dillard; Kamat *J. Am. Chem. Soc.* **1967**, *89*, 5902. See also Reich; Reich *J. Am. Chem. Soc.* **1974**, *96*, 2654.

⁸⁸For a monograph, see Olah *Halonium Ions*; Wiley: New York, 1975. For a review, see Koster, in Patai; Rappoport *The Chemistry of Functional Groups. Supplement D*, pt. 2; Wiley: New York, 1983, pp. 1265-1351.

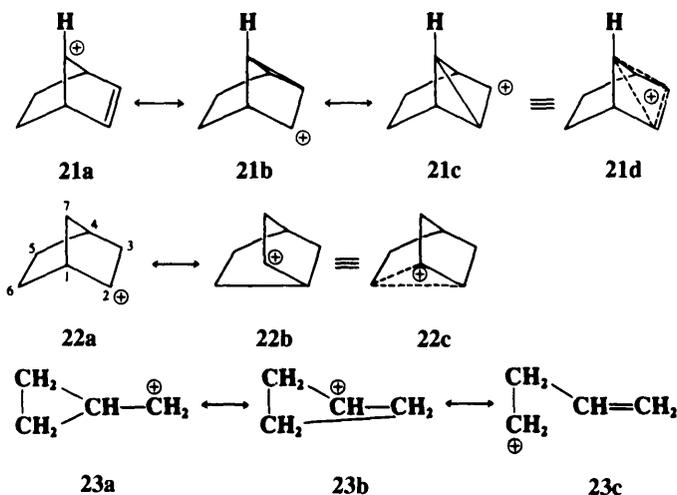
⁸⁹See, for example Olah; Bollinger *J. Am. Chem. Soc.* **1967**, *89*, 4744, **1968**, *90*, 947; Olah; Peterson *J. Am. Chem. Soc.* **1968**, *90*, 4675; Peterson; Clifford; Slama *J. Am. Chem. Soc.* **1970**, *92*, 2840; Bonazza; Peterson *J. Org. Chem.* **1973**, *38*, 1015; Henrichs; Peterson *J. Am. Chem. Soc.* **1973**, *95*, 7449; *J. Org. Chem.* **1976**, *41*, 362; Olah; Liang; Staral *J. Am. Chem. Soc.* **1974**, *96*, 8112; Vančik; Percač; Sunko *J. Chem. Soc., Chem. Commun.* **1991**, 807.

⁹⁰Olah; Bollinger; Mo; Brinich *J. Am. Chem. Soc.* **1972**, *94*, 1164.

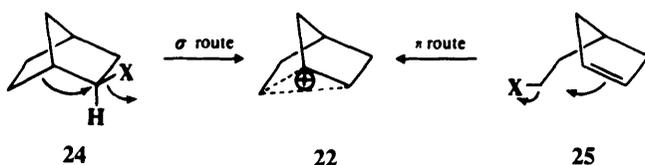
⁹¹Haupt; Smith *Tetrahedron Lett.* **1974**, 4141.

⁹²For monographs, see Olah; Schleyer *Carbonium Ions*, vol. 3; Wiley: New York, 1972; Bartlett *Nonclassical Ions*; W.A. Benjamin: New York, 1965. For reviews, see Barkhash *Top. Curr. Chem.* **1984**, *116/117*, 1-265; Kirmse *Top. Curr. Chem.* **1979**, *80*, 125-311, pp. 196-288; McManus; Pittman, in McManus *Organic Reactive Intermediates*; Academic Press: New York, 1973, pp. 302-321; Bethell; Gold *Carbonium Ions*; Academic Press: New York, 1967; pp. 222-282. For a related review, see Prakash; Iyer *Rev. Chem. Intermed.* **1988**, *9*, 65-116.

group participation by C=C π bonds and C—C and C—H σ bonds. There has been a great deal of controversy over whether such bonds can act as neighboring groups and about the existence and structure of the intermediates involved. These intermediates are called *nonclassical* (or *bridged*) carbocations. In classical carbocations (Chapter 5) the positive charge is localized on one carbon atom or delocalized by resonance involving an unshared pair of electrons or a double or triple bond in the allylic position. In a nonclassical carbocation, the positive charge is delocalized by a double or triple bond that is not in the allylic position or by a single bond. Examples are the 7-norbornenyl cation (**21**), the norbornyl cation (**22**),



and the cyclopropylmethyl cation (**23**). **21** is called a *homoallylic* carbocation, because in **21a** there is one carbon atom between the positively charged carbon and the double bond. Many of these carbocations can be produced in more than one way if the proper substrates are chosen. For example, **22** can be generated by the departure of a leaving group from **24**



or from **25**.⁹³ The first of these pathways is called the σ route to a nonclassical carbocation, because participation of a σ bond is involved. The second is called the π route.⁹⁴ The argument against the existence of nonclassical carbocations is essentially that the structures **21a**, **21b**, **21c** (or **22a**, **22b**, etc.) are not canonical forms but real structures and that there is rapid equilibration among them.

In discussing nonclassical carbocations we must be careful to make the distinction between neighboring-group participation and the existence of nonclassical carbocations.⁹⁵ If a nonclassical carbocation exists in any reaction, then an ion with electron delocalization, as shown

⁹³Lawton *J. Am. Chem. Soc.* **1961**, *83*, 2399; Bartlett; Bank; Crawford; Schmid *J. Am. Chem. Soc.* **1965**, *88*, 1288.

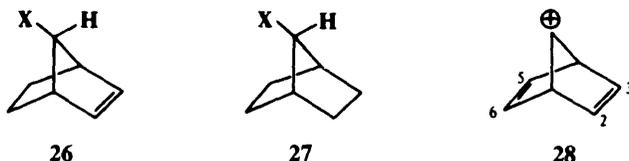
⁹⁴Winstein; Carter *J. Am. Chem. Soc.* **1961**, *83*, 4485.

⁹⁵This was pointed out by Cram *J. Am. Chem. Soc.* **1964**, *86*, 3767.

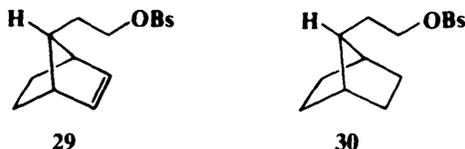
in the above examples, is a discrete reaction intermediate. If a carbon-carbon double or single bond participates in the departure of the leaving group to form a carbocation, it may be that a nonclassical carbocation is involved, but there is no necessary relation. In any particular case either or both of these possibilities can be taking place.

In the following pages we consider some of the evidence bearing on the questions of the participation of π and σ bonds and on the existence of nonclassical carbocations,⁹⁶ though a thorough discussion is beyond the scope of this book.⁷⁸

1. $C=C$ as a neighboring group.⁹⁷ The most striking evidence that $C=C$ can act as a neighboring group is that acetolysis of **26**-OTs is 10^{11} times faster than that of **27**-OTs and proceeds with retention of configuration.⁹⁸ The rate data alone do not necessarily prove that



acetolysis of **26**-OTs involves a nonclassical intermediate (**21d**), but it is certainly strong evidence that the $C=C$ group assists in the departure of the OTs. Evidence that **21** is indeed a nonclassical ion comes from an nmr study of the relatively stable norbornadienyl cation (**28**). The spectrum shows that the 2 and 3 protons are not equivalent to the 5 and 6 protons.⁹⁹ Thus there is interaction between the charged carbon and one double bond, which is evidence for the existence of **21d**.¹⁰⁰ In the case of **26** the double bond is geometrically fixed in an especially favorable position for backside attack on the carbon bearing the leaving group (hence the very large rate enhancement), but there is much evidence that other double bonds in the homoallylic position,¹⁰¹ as well as in positions farther away,¹⁰² can also lend anchimeric assistance, though generally with much lower rate ratios. One example of the latter is the compound β -(*syn*-7-norbornenyl)ethyl brosylate (**29**) which at 25°C undergoes



⁹⁶The arguments against nonclassical ions are summed up in Brown *The Nonclassical Ion Problem*; Plenum: New York, 1977. This book also includes rebuttals by Schleyer. See also Brown *Pure Appl. Chem.* **1982**, *54*, 1783-1796.

⁹⁷For reviews, see Story; Clark, in Olah; Schleyer, Ref. 92, vol. 3, 1972, pp. 1007-1060; Richey, in Zabicky *The Chemistry of Alkenes*, vol. 2; Wiley: New York, 1970, pp. 77-101.

⁹⁸Winstein; Shatavsky *J. Am. Chem. Soc.* **1956**, *78*, 592.

⁹⁹Story; Saunders *J. Am. Chem. Soc.* **1962**, *84*, 4876; Story; Snyder; Douglass; Anderson; Kornegay *J. Am. Chem. Soc.* **1963**, *85*, 3630. For a discussion, see Story; Clark, Ref. 97, pp. 1026-1041. See also Lustgarten; Brookhart; Winstein *J. Am. Chem. Soc.* **1972**, *94*, 2347.

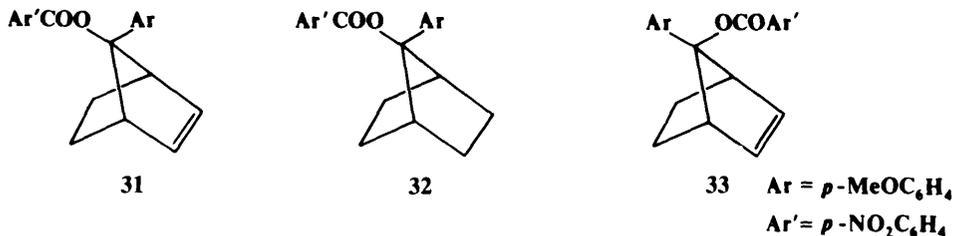
¹⁰⁰For further evidence for the nonclassical nature of **21**, see Winstein; Ordroneau *J. Am. Chem. Soc.* **1960**, *82*, 2084; Brookhart; Diaz; Winstein *J. Am. Chem. Soc.* **1966**, *88*, 3135; Richey; Lustgarten *J. Am. Chem. Soc.* **1966**, *88*, 3136; Gassman; Patton *J. Am. Chem. Soc.* **1969**, *91*, 2160; Richey; Nichols; Gassman; Fentiman; Winstein; Brookhart; Lustgarten *J. Am. Chem. Soc.* **1970**, *92*, 3783; Gassman; Doherty *J. Am. Chem. Soc.* **1982**, *104*, 3742; Laube *J. Am. Chem. Soc.* **1989**, *111*, 9224.

¹⁰¹For examples, see Shoppee *J. Chem. Soc.* **1946**, 1147; LeBel; Huber *J. Am. Chem. Soc.* **1963**, *85*, 3193; Closson; Kwiatkowski *Tetrahedron* **1965**, *21*, 2779; Cristol; Nachtigall *J. Am. Chem. Soc.* **1968**, *90*, 7132; Masamune; Takada; Nakatsuka; Vukov; Cain *J. Am. Chem. Soc.* **1969**, *91*, 4322; Hess *J. Am. Chem. Soc.* **1969**, *91*, 5657; Brown; Peters; Ravindranathan *J. Am. Chem. Soc.* **1975**, *97*, 7449; Lambert; Finzel *J. Am. Chem. Soc.* **1983**, *105*, 1954; Schleyer; Bentley; Koch; Kos; Schwarz *J. Am. Chem. Soc.* **1987**, *109*, 6953.

¹⁰²For examples, see LeNy *C. R. Acad. Sci.* **1960**, *251*, 1526; Goering; Closson *J. Am. Chem. Soc.* **1961**, *83*, 3511; Bartlett; Trahanovsky; Bolon; Schmid *J. Am. Chem. Soc.* **1965**, *87*, 1314; Bly; Swindell *J. Org. Chem.* **1965**, *30*, 10; Marvell; Sturmer; Knutson *J. Org. Chem.* **1968**, *33*, 2991; Cogdell *J. Org. Chem.* **1972**, *37*, 2541; Ferber; Gream *Aust. J. Chem.* **1981**, *34*, 1051; Kronja; Polla; Borčić *J. Chem. Soc., Chem. Commun.* **1983**, 1044; Orlović; Borčić; Humski; Kronja; Imper; Polla; Shiner *J. Org. Chem.* **1991**, *56*, 1874; Ref. 94.

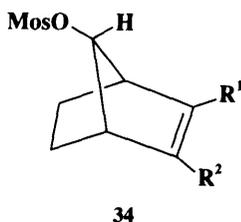
acetolysis about 140,000 times faster than the saturated analog **30**.¹⁰³ Triple bonds¹⁰⁴ and allenes¹⁰⁵ can also act as neighboring groups.

We have already seen evidence that participation by a potential neighboring group can be reduced or eliminated if an outside nucleophile is present that is more effective than the neighboring group in attacking the central carbon (p. 312), or if a sufficiently good leaving group is present (p. 312). In another example of the principle of increasing electron demand, Gassman and co-workers have shown that neighboring-group participation can also be reduced if the stability of the potential carbocation is increased. They found that the presence of a *p*-anisyl group at the 7 position of **26** and **27** exerts a powerful leveling effect on the rate differences. Thus, solvolysis in acetone–water at 85°C of **31** was only about 2.5 times



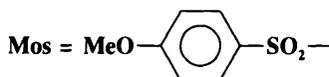
faster than that of the saturated compound **32**.¹⁰⁶ Furthermore, both **31** and its stereoisomer **33** gave the same mixture of solvolysis products, showing that the stereoselectivity in the solvolysis of **26** is not present here. The difference between **31** and **26** is that in the case of **31** the positive charge generated at the 7 position in the transition state is greatly stabilized by the *p*-anisyl group. Apparently the stabilization by the *p*-anisyl group is so great that further stabilization that would come from participation by the C=C bond is not needed.¹⁰⁷ The use of a phenyl instead of a *p*-anisyl group is not sufficient to stop participation by the double bond completely, though it does reduce it.¹⁰⁸ These results permit us to emphasize our previous conclusion that a neighboring group lends anchimeric assistance only when there is sufficient demand for it.¹⁰⁹

The ability of C=C to serve as a neighboring group can depend on its electron density. When the strongly electron-withdrawing CF₃ group was attached to a double bond carbon of **34**, the solvolysis rate was lowered by a factor of about 10⁶.¹¹⁰ A second CF₃ group had



Relative Rates

$\text{R}^1 = \text{R}^2 = \text{H}$	1.4×10^{12}
$\text{R}^1 = \text{H}, \text{R}^2 = \text{CF}_3$	1.5×10^6
$\text{R}^1 = \text{R}^2 = \text{CF}_3$	1



¹⁰³Bly; Bly; Bedenbaugh; Vail *J. Am. Chem. Soc.* **1967**, *89*, 880.

¹⁰⁴See, for example, Closson; Roman *Tetrahedron Lett.* **1966**, 6015; Hanack; Herterich; Vött *Tetrahedron Lett.* **1967**, 3871; Lambert; Papay; Mark *J. Org. Chem.* **1975**, *40*, 633; Peterson; Vidrine *J. Org. Chem.* **1979**, *44*, 891. For a review of participation by triple bonds and allylic groups, see Rappoport *React. Intermed. (Plenum)* **1983**, *3*, 440-453.

¹⁰⁵Jacobs; Macomber *Tetrahedron Lett.* **1967**, 4877; Bly; Kooch *J. Am. Chem. Soc.* **1969**, *91*, 3292, 3299; Von Lehman; Macomber *J. Am. Chem. Soc.* **1975**, *97*, 1531.

¹⁰⁶Gassman; Zeller; Lamb *Chem. Commun.* **1968**, 69.

¹⁰⁷Nevertheless, there is evidence from ¹³C nmr spectra that some π participation is present, even in the cation derived from **31**: Olah; Berrier; Arvanaghi; Prakash *J. Am. Chem. Soc.* **1981**, *103*, 1122.

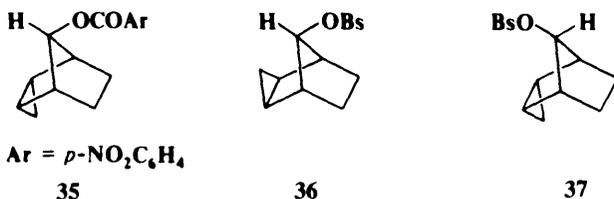
¹⁰⁸Gassman; Fentiman *J. Am. Chem. Soc.* **1969**, *91*, 1545, **1970**, *92*, 2549.

¹⁰⁹For a discussion of the use of the tool of increasing electron demand to probe neighboring-group activity by double bonds, sigma bonds, and aryl rings, see Lambert; Mark; Holcomb; Magyar *Acc. Chem. Res.* **1979**, *12*, 317-324.

¹¹⁰Gassman; Hall *J. Am. Chem. Soc.* **1984**, *106*, 4267.

an equally strong effect. In this case two CF_3 groups decrease the electron density of the $\text{C}=\text{C}$ bond to the point that the solvolysis rate for **34** ($\text{R}^1 = \text{R}^2 = \text{CF}_3$) was about the same as (actually about 17 times slower than) the rate for the saturated substrate **27** ($\text{X} = \text{OMos}$). Thus, the two CF_3 groups completely remove the ability of the $\text{C}=\text{C}$ bond to act as a neighboring group.

2. Cyclopropyl¹¹¹ as a neighboring group.¹¹² On p. 152 we saw that the properties of a cyclopropane ring are in some ways similar to those of a double bond. Therefore it is not surprising that a suitably placed cyclopropyl ring can also be a neighboring group. Thus *endo-anti*-tricyclo-[3.2.1.0^{2,4}]octan-8-yl *p*-nitrobenzoate (**35**) solvolyzed about 10^{14} times



faster than the *p*-nitrobenzoate of **27-OH**.¹¹³ Obviously, a suitably placed cyclopropyl ring can be even more effective¹¹⁴ as a neighboring group than a double bond.¹¹⁵ The need for suitable placement is emphasized by the fact that **37** solvolyzed only about five times faster than **27-OBs**,¹¹⁶ while **36** solvolyzed three times *slower* than **27-OBs**.¹¹⁷ In the case of **35** and of all other cases known where cyclopropyl lends considerable anchimeric assistance, the developing *p* orbital of the carbocation is orthogonal to the participating bond of the cyclopropane ring.¹¹⁸ An experiment designed to test whether a developing *p* orbital that would be parallel to the participating bond would be assisted by that bond showed no rate enhancement.¹¹⁸ This is in contrast to the behavior of cyclopropane rings directly attached to positively charged carbons, where the *p* orbital is parallel to the plane of the ring (pp. 169, 324). Rate enhancements, though considerably smaller, have also been reported for suitably placed cyclobutyl rings.¹¹⁹

3. Aromatic rings as neighboring groups.¹²⁰ There is a great deal of evidence that aromatic rings in the β position can function as neighboring groups. Stereochemical evidence

¹¹¹In this section we consider systems in which at least one carbon separates the cyclopropyl ring from the carbon bearing the leaving group. For a discussion of systems in which the cyclopropyl group is directly attached to the leaving-group carbon, see p. 323.

¹¹²For a review, see Haywood-Farmer *Chem. Rev.* **1974**, *74*, 315-350.

¹¹³Tanida; Tsuji; Irie *J. Am. Chem. Soc.* **1967**, *89*, 1953; Battiste; Deyrup; Pincock; Haywood-Farmer *J. Am. Chem. Soc.* **1967**, *89*, 1954.

¹¹⁴For a competitive study of cyclopropyl vs. double-bond participation, see Lambert; Jovanovich; Hamersma; Koeng; Oliver *J. Am. Chem. Soc.* **1973**, *95*, 1570.

¹¹⁵For other evidence for anchimeric assistance by cyclopropyl, see Sargent; Lowry; Reich *J. Am. Chem. Soc.* **1967**, *89*, 5985; Battiste; Haywood-Farmer; Malkus; Seidl; Winstein *J. Am. Chem. Soc.* **1970**, *92*, 2144; Coates; Yano *Tetrahedron Lett.* **1972**, 2289; Masamune; Vukov; Bennett; Purdham *J. Am. Chem. Soc.* **1972**, *94*, 8239; Gassman; Creary *J. Am. Chem. Soc.* **1973**, *95*, 2729; Costanza; Geneste; Lamaty; Roque *Bull. Soc. Chim. Fr.* **1975**, 2358; Takakis; Rhodes *Tetrahedron Lett.* **1983**, *24*, 4959.

¹¹⁶Battiste; Deyrup; Pincock; Haywood-Farmer, Ref. 113; Haywood-Farmer; Pincock *J. Am. Chem. Soc.* **1969**, *91*, 3020.

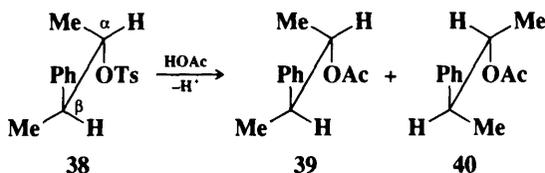
¹¹⁷Haywood-Farmer; Pincock; Wells *Tetrahedron* **1966**, *22*, 2007; Haywood-Farmer; Pincock, Ref. 116. For some other cases where there was little or no rate enhancement by cyclopropyl, see Wiberg; Wenzinger *J. Org. Chem.* **1965**, *30*, 2278; Sargent; Taylor; Demisch *Tetrahedron Lett.* **1968**, 2275; Rhodes; Takino *J. Am. Chem. Soc.* **1970**, *92*, 4469; Hanack; Krause *Liebigs Ann. Chem.* **1972**, 760, 17.

¹¹⁸Gassman; Seter; Williams *J. Am. Chem. Soc.* **1971**, *93*, 1673. For a discussion, see Haywood-Farmer; Pincock, Ref. 116. See also Chenier; Jensen; Wulff *J. Org. Chem.* **1982**, *47*, 770.

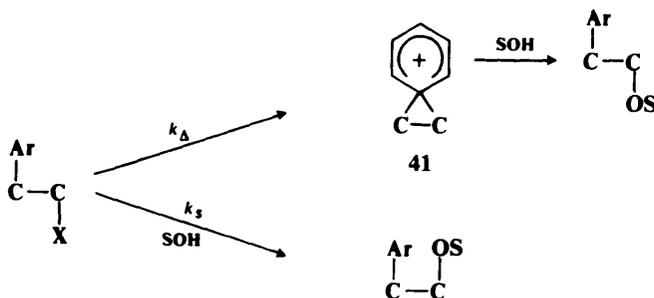
¹¹⁹For example, see Sakai; Diaz; Winstein *J. Am. Chem. Soc.* **1970**, *92*, 4452; Battiste; Nebzydoski *J. Am. Chem. Soc.* **1970**, *92*, 4450; Schipper; Driessen; de Haan; Buck *J. Am. Chem. Soc.* **1974**, *96*, 4706; Ohkata; Doecke; Klein; Paquette *Tetrahedron Lett.* **1980**, *21*, 3253.

¹²⁰For a review, see Lancelot; Cram; Schleyer, in Olah; Schleyer, Ref. 92, vol. 3, 1972, pp. 1347-1483.

was obtained by solvolysis of *L-threo*-3-phenyl-2-butyl tosylate (**38**) in acetic acid.¹²¹ Of the acetate product 96% was the *threo* isomer and only about 4% was *erythro*. Moreover, both



the (+) and (-) *threo* isomers (**39** and **40**) were produced in approximately equal amounts (a racemic mixture). When solvolysis was conducted in formic acid, even less *erythro* isomer was obtained. This result is similar to that found on reaction of 3-bromo-2-butanol with HBr (p. 309) and leads to the conclusion that configuration is retained because phenyl acts as a neighboring group. However, evidence from rate studies is not so simple. If β -aryl groups assist the departure of the leaving group, solvolysis rates should be enhanced. In general they are not. However, solvolysis rate studies in 2-arylethyl systems are complicated by the fact that, for primary and secondary systems, two pathways can exist.¹²² In one of these (designated k_{Δ}), the aryl, behaving as a neighboring group, pushes out the leaving group to give a bridged ion, called a *phenonium ion* (**41**), and is in turn pushed out by the solvent



SOH, so the net result is substitution with retention of configuration (or rearrangement, if **41** is opened from the other side). The other pathway (k_s) is simple S_N2 attack by the solvent at the leaving-group carbon. The net result here is substitution with inversion and no possibility of rearrangement. Whether the leaving group is located at a primary or a secondary carbon, there is no crossover between these pathways; they are completely independent.¹²³ (Both the k_{Δ} and k_s pathways are unimportant when the leaving group is at a tertiary carbon. In these cases the mechanism is S_N1 and open carbocations $ArCH_2CR_2^+$ are intermediates. This pathway is designated k_c .) Which of the two pathways (k_s or k_{Δ}) predominates in any given case depends on the solvent and on the nature of the aryl group. As expected from the results we have seen for Cl as a neighboring group (p. 312), the k_{Δ}/k_s ratio is highest for solvents that are poor nucleophiles and so compete very poorly with the aryl group. For several common solvents the k_{Δ}/k_s ratio increases in the order $EtOH < CH_3COOH <$

¹²¹Cram *J. Am. Chem. Soc.* **1949**, *71*, 3863, **1952**, *74*, 2129.

¹²²Winstein; Heck *J. Am. Chem. Soc.* **1956**, *78*, 4801; Brookhart; Anet; Cram; Winstein *J. Am. Chem. Soc.* **1966**, *88*, 5659; Lee; Unger; Vassie *Can. J. Chem.* **1972**, *50*, 1371.

¹²³Harris; Schadt; Schleyer; Lancelot *J. Am. Chem. Soc.* **1969**, *91*, 7508; Brown; Kim; Lancelot; Schleyer *J. Am. Chem. Soc.* **1970**, *92*, 5244; Brown; Kim *J. Am. Chem. Soc.* **1971**, *93*, 5765.

$\text{HCOOH} < \text{CF}_3\text{COOH}$.¹²⁴ In accord with this, the following percentages of retention were obtained in solvolysis of 1-phenyl-2-propyl tosylate at 50°C: solvolysis in EtOH 7%, CH_3COOH 35%, HCOOH 85%.¹²⁴ This indicates that k_s predominates in EtOH (phenyl participates very little), while k_d predominates in HCOOH . Trifluoroacetic acid is a solvent of particularly low nucleophilic power, and in this solvent the reaction proceeds entirely by k_d ;¹²⁵ deuterium labeling showed 100% retention.¹²⁶ This case provides a clear example of neighboring-group rate enhancement by phenyl: the rate of solvolysis of $\text{PhCH}_2\text{CH}_2\text{OTs}$ at 75°C in CF_3COOH is 3040 times the rate for $\text{CH}_3\text{CH}_2\text{OTs}$.¹²⁵

With respect to the aromatic ring, the k_d pathway is electrophilic aromatic substitution (Chapter 11). We predict that groups on the ring which activate that reaction (p. 507) will increase, and deactivating groups will decrease, the rate of this pathway. This prediction has been borne out by several investigations. The *p*-nitro derivative of **38** solvolyzed in acetic acid 190 times slower than **38**, and there was much less retention of configuration; the acetate produced was only 7% threo and 93% erythro.¹²⁷ At 90°C, acetolysis of *p*- $\text{ZC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OTs}$ gave the rate ratios shown in Table 10.1.¹²⁸ Throughout this series k_s is fairly constant, as it should be since it is affected only by the rather remote field effect of Z. It is k_d that changes substantially as Z is changed from activating to deactivating. The evidence is thus fairly clear that participation by aryl groups depends greatly on the nature of the group. For some groups, e.g., *p*-nitrophenyl, in some solvents, e.g., acetic acid, there is essentially no neighboring-group participation at all,¹²⁹ while for others, e.g., *p*-methoxyphenyl, neighboring-group participation is substantial. The combined effect of solvent and structure is shown in Table 10.2, where the figures shown were derived by three different methods.¹³⁰ The decrease in neighboring-group effectiveness when aromatic rings are substituted by electron-withdrawing groups is reminiscent of the similar case of $\text{C}=\text{C}$ bonds substituted by CF_3 groups (p. 315).

Several phenonium ions have been prepared as stable ions in solution where they can be studied by nmr, among them **42**,¹³¹ **43**,¹³² and the unsubstituted **41**.¹³³ These were

TABLE 10.1 Approximate k_d/k_s ratios for acetolysis of *p*- $\text{ZC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OTs}$ at 90°C¹²⁸

Z	k_d/k_s
MeO	30
Me	11
H	1.3
Cl	0.3

TABLE 10.2 Percent of product formed by the k_d pathway in solvolysis of *p*- $\text{ZC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OMeOTs}$ ¹³⁰

Z	Solvent	Percent by k_d
H	CH_3COOH	35–38
H	HCOOH	72–79
MeO	CH_3COOH	91–93
MeO	HCOOH	99

¹²⁴Diaz; Lazdins; Winstein *J. Am. Chem. Soc.* **1968**, *90*, 6546; Diaz; Winstein *J. Am. Chem. Soc.* **1969**, *91*, 4300. See also Schadt; Lancelot; Schleyer *J. Am. Chem. Soc.* **1978**, *100*, 228.

¹²⁵Nordlander; Deadman *J. Am. Chem. Soc.* **1968**, *90*, 1590; Nordlander; Kelly *J. Am. Chem. Soc.* **1969**, *91*, 996.

¹²⁶Jablonski; Snyder *J. Am. Chem. Soc.* **1969**, *91*, 4445.

¹²⁷Thompson; Cram *J. Am. Chem. Soc.* **1969**, *91*, 1778. See also Tanida; Tsuji; Ishitobi; Irie *J. Org. Chem.* **1969**, *34*, 1086; Kingsbury; Best *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3440.

¹²⁸Coke; McFarlane; Mourning; Jones *J. Am. Chem. Soc.* **1969**, *91*, 1154; Jones; Coke *J. Am. Chem. Soc.* **1969**, *91*, 4284. See also Harris; Schadt; Schleyer; Lancelot, Ref. 123.

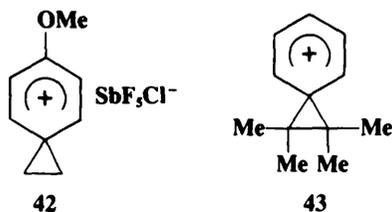
¹²⁹The k_d pathway is important for *p*-nitrophenyl in CF_3COOH : Ando; Shimizu; Kim; Tsuno; Yukawa *Tetrahedron Lett.* **1973**, 117.

¹³⁰Lancelot; Schleyer *J. Am. Chem. Soc.* **1969**, *91*, 4291, 4296; Lancelot; Harper; Schleyer *J. Am. Chem. Soc.* **1969**, *91*, 4294; Schleyer; Lancelot *J. Am. Chem. Soc.* **1969**, *91*, 4297.

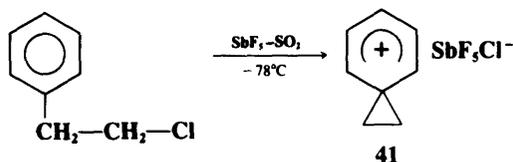
¹³¹Olah; Comisarow; Namanworth; Ramsey *J. Am. Chem. Soc.* **1967**, *89*, 5259; Ramsey; Cook; Manner *J. Org. Chem.* **1972**, *37*, 3310.

¹³²Olah; Comisarow; Kim *J. Am. Chem. Soc.* **1969**, *91*, 1458. See, however, Ramsey; Cook; Manner, Ref. 131.

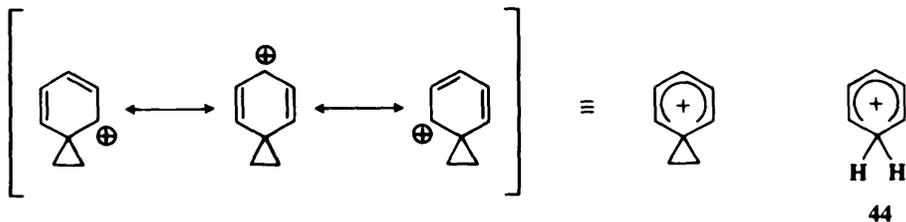
¹³³Olah; Porter *J. Am. Chem. Soc.* **1971**, *93*, 6877; Olah; Spear; Forsyth *J. Am. Chem. Soc.* **1976**, *98*, 6284.



prepared¹³⁴ by the method shown for **41**: treatment of the corresponding β -arylethyl chloride with $\text{SbF}_5\text{-SO}_2$ at low temperatures. These conditions are even more extreme than the



solvolysis in CF_3COOH mentioned earlier. The absence of any nucleophile at all eliminates not only the k_s pathways but also nucleophilic attack on **41**. Although **41** is not in equilibrium with the open-chain ion $\text{PhCH}_2\text{CH}_2^+$ (which is primary and hence unstable), **43** is in equilibrium with the open-chain tertiary ions $\text{PhCMe}_2\text{CMe}_2^+$ and PhCMeCMe_3^+ , though only **43** is present in appreciable concentration. Proton and ^{13}C nmr show that **41**, **42**, and **43** are classical carbocations where the only resonance is in the six-membered ring. The three-



membered ring is a normal cyclopropane ring that is influenced only to a relatively small extent by the positive charge on the adjacent ring. Nmr spectra show that the six-membered rings have no aromatic character but are similar in structure to the arenium ions, e.g., **44**, that are intermediates in electrophilic aromatic substitution (Chapter 11). A number of phenonium ions, including **41**, have also been reported to be present in the gas phase, where their existence has been inferred from reaction products and from ^{13}C labeling.¹³⁵

It is thus clear that β -aryl groups can function as neighboring groups.¹³⁶ Much less work

¹³⁴For some others, see Olah; Singh; Liang *J. Org. Chem.* **1984**, *49*, 2922; Olah; Singh *J. Am. Chem. Soc.* **1984**, *106*, 3265.

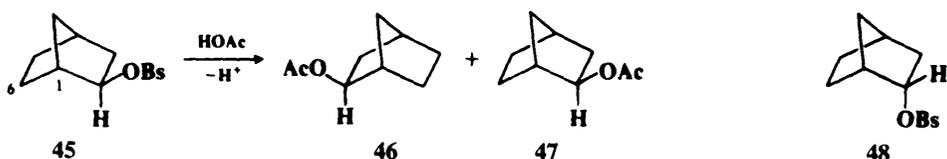
¹³⁵Fornarini; Sparapani; Speranza *J. Am. Chem. Soc.* **1988**, *110*, 34, 42; Fornarini; Muraglia *J. Am. Chem. Soc.* **1989**, *111*, 873; Mishima; Tsuno; Fujio *Chem. Lett.* **1990**, 2277.

¹³⁶For additional evidence, see Tanida *Acc. Chem. Res.* **1968**, *1*, 239-245; Kingsbury; Best *Tetrahedron Lett.* **1967**, 1499; Braddon; Wiley; Dirlam; Winstein *J. Am. Chem. Soc.* **1968**, *90*, 1901; Tanida; Ishitobi; Irie *J. Am. Chem. Soc.* **1968**, *90*, 2688; Brown; Tritle *J. Am. Chem. Soc.* **1968**, *90*, 2689; Bentley; Dewar *J. Am. Chem. Soc.* **1970**, *92*, 3996; Raber; Harris; Schleyer *J. Am. Chem. Soc.* **1971**, *93*, 4829; Shiner; Seib *J. Am. Chem. Soc.* **1976**, *98*, 862; Fain; Dubois *Tetrahedron Lett.* **1978**, 791; Yukawa; Ando; Token; Kawada; Matsuda; Kim; Yamataka *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3536; Ferber; Gream *Aust. J. Chem.* **1981**, *34*, 2217; Fujio; Goto; Seki; Mishima; Tsuno; Sawada; Takai *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1097. For a discussion of evidence obtained from isotope effects, see Scheppele *Chem. Rev.* **1972**, *72*, 511-532, pp. 522-525.

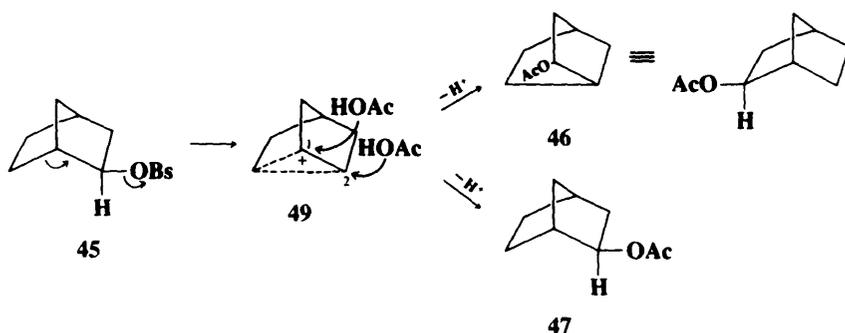
has been done on aryl groups located in positions farther away from the leaving group, but there is evidence that these too can lend anchimeric assistance.¹³⁷

4. The carbon-carbon single bond as a neighboring group.¹³⁸

a. *The 2-norbornyl system.* In the investigations to determine whether a C—C σ bond can act as a neighboring group, by far the greatest attention has been paid to the 2-norbornyl system.¹³⁹ Winstein and Trifan found that solvolysis in acetic acid of optically active *exo*-2-norbornyl brosylate (**45**) gave a racemic mixture of the two *exo* acetates; no *endo* isomers were formed:¹⁴⁰



Furthermore, **45** solvolyzed about 350 times faster than its *endo* isomer **48**. Similar high *exo*/*endo* rate ratios have been found in many other [2.2.1] systems. These two results—(1) that solvolysis of an optically active *exo* isomer gave only racemic *exo* isomers and (2) the high *exo*/*endo* rate ratio—were interpreted by Winstein and Trifan as indicating that the 1,6 bond assists in the departure of the leaving group and that a nonclassical intermediate (**49**)



is involved. They reasoned that solvolysis of the *endo* isomer **48** is not assisted by the 1,6 bond because it is not in a favorable position for backside attack, and that consequently solvolysis of **48** takes place at a “normal” rate. Therefore the much faster rate for the solvolysis of **45** must be caused by anchimeric assistance. The stereochemistry of the product is also explained by the intermediacy of **49**, since in **49** the 1 and 2 positions are equivalent and would be attacked by the nucleophile with equal facility, but only from the *exo* direction in either case. Incidentally, acetolysis of **48** also leads exclusively to the *exo* acetates (**46**

¹³⁷Heck; Winstein *J. Am. Chem. Soc.* **1957**, *79*, 3105; Muneyuki; Tanida *J. Am. Chem. Soc.* **1968**, *90*, 656; Ouellette; Papa; Attea; Levin *J. Am. Chem. Soc.* **1970**, *92*, 4893; Jackman; Haddon *J. Am. Chem. Soc.* **1974**, *96*, 5130; Gates; Frank; von Felten *J. Am. Chem. Soc.* **1974**, *96*, 5138; Ando; Yamawaki; Saito *Bull. Chem. Soc. Jpn.* **1978**, *51*, 219.

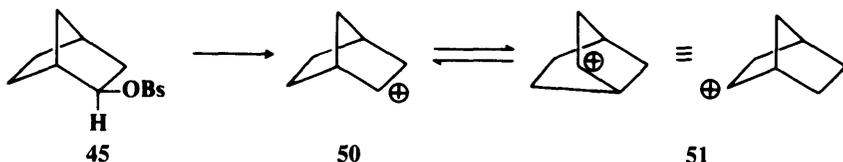
¹³⁸For a review pertaining to studies of this topic at low temperatures, see Olah *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 173-212, pp. 192-198 [*Angew. Chem.* **85**, 183-225].

¹³⁹For reviews, see Olah; Prakash; Williams *Hypercarbon Chemistry*; Wiley: New York, 1987, pp. 157-170; Grob *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 87-96 [*Angew. Chem.* **94**, 87-96]; Sargent, in Olah; Schleyer, Ref. 92, vol. 3, 1972, pp. 1099-1200; Sargent *Q. Rev., Chem. Soc.* **1966**, *20*, 301-371; Gream *Rev. Pure Appl. Chem.* **1966**, *16*, 25-60; Ref. 92. For a closely related review, see Kirmse *Acc. Chem. Res.* **1986**, *19*, 36-41. See also Ref. 143.

¹⁴⁰Winstein; Trifan *J. Am. Chem. Soc.* **1952**, *74*, 1147, 1154; Winstein; Clippinger; Howe; Vogelfanger *J. Am. Chem. Soc.* **1965**, *87*, 376.

and **47**), so that in this case Winstein and Trifan postulated that a classical ion (**50**) is first formed and then converted to the more stable **49**. Evidence for this interpretation is that the product from solvolysis of **48** is not racemic but contains somewhat more **47** than **46** (corresponding to 3 to 13% inversion, depending on the solvent),¹⁴⁰ suggesting that when **50** is formed, some of it goes to give **47** before it can collapse to **49**.

The concepts of σ participation and the nonclassical ion **49** have been challenged by H. C. Brown,⁹⁶ who has suggested that the two results can also be explained by postulating that **45** solvolyzes without participation of the 1,6 bond to give the classical ion **50** which is in rapid equilibrium with **51**. This rapid interconversion has been likened to the action of



a windshield wiper.¹⁴¹ Obviously, in going from **50** to **51** and back again, **49** must be present, but in Brown's view it is a transition state and not an intermediate. Brown's explanation for the stereochemical result is that exclusive exo attack is a property to be expected from any 2-norbornyl system, not only for the cation but even for reactions not involving cations, because of steric hindrance to attack from the endo side. There is a large body of data that shows that exo attack on norbornyl systems is fairly general in many reactions. As for the obtention of a racemic mixture, this will obviously happen if **50** and **51** are present in equal amounts, since they are equivalent and exo attack on **50** and **51** gives, respectively, **47** and **46**. Brown explains the high exo/endo rate ratios by contending that it is not the endo rate that is normal and the exo rate abnormally high, but the exo rate that is normal and the endo rate abnormally low, because of steric hindrance to removal of the leaving group in that direction.¹⁴²

A vast amount of work has been done¹⁴³ on solvolysis of the 2-norbornyl system in an effort to determine whether the 1,6 bond participates and whether **49** is an intermediate. Most,¹⁴⁴ although not all,¹⁴⁵ chemists now accept the intermediacy of **49**.

Besides the work done on solvolysis of 2-norbornyl compounds, the 2-norbornyl cation

¹⁴¹Another view is somewhere in between: There are two interconverting ions, but each is asymmetrically bridged: Bielmann; Fuso; Grob *Helv. Chim. Acta* **1988**, *71*, 312; Flury; Grob; Wang; Lennartz; Roth *Helv. Chim. Acta* **1988**, *71*, 1017.

¹⁴²For evidence against steric hindrance as the only cause of this effect, see Menger; Perinis; Jerkunica; Glass *J. Am. Chem. Soc.* **1978**, *100*, 1503.

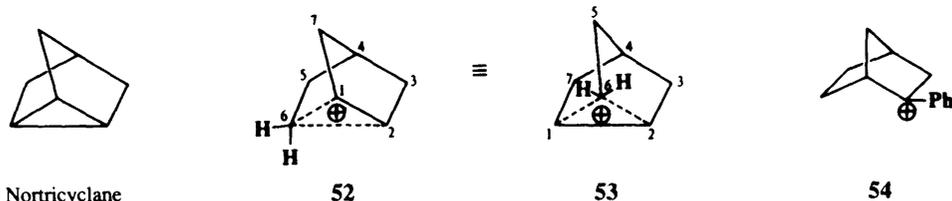
¹⁴³For thorough discussions, see Lenoir; Apeloig; Arad; Schleyer *J. Org. Chem.* **1988**, *53*, 661; Grob *Acc. Chem. Res.* **1983**, *16*, 426-431; Brown *Acc. Chem. Res.* **1983**, *16*, 432-440; Walling *Acc. Chem. Res.* **1983**, *16*, 448-454; Refs. 92, 96, and 139. For commentary on the controversy, see Arnett; Hofelich; Schriver *Repts. Interned. (Wiley)* **1985**, *3*, 189-226, pp. 193-202.

¹⁴⁴For some recent evidence in favor of a nonclassical **49**, see Arnett; Petro; Schleyer *J. Am. Chem. Soc.* **1979**, *101*, 522; Albano; Wold *J. Chem. Soc., Perkin Trans. 2* **1980**, 1447; Wilcox; Tuszyński *Tetrahedron Lett.* **1982**, *23*, 3119; Kirmse; Siegfried *J. Am. Chem. Soc.* **1983**, *105*, 950; Creary; Geiger *J. Am. Chem. Soc.* **1983**, *105*, 7123; Chang; le Noble *J. Am. Chem. Soc.* **1984**, *106*, 810; Kirmse; Brandt *Chem. Ber.* **1984**, *117*, 2510; Wilcox; Brungardt *Tetrahedron Lett.* **1984**, *25*, 3403; Lajunen *Acc. Chem. Res.* **1985**, *18*, 254-258; Sharma; Sen Sharma; Hiraoka; Kebarle *J. Am. Chem. Soc.* **1985**, *107*, 3747; Servis; Domenick; Forsyth; Pan *J. Am. Chem. Soc.* **1987**, *109*, 7263; Lenoir et al., Ref. 143.

¹⁴⁵For some recent evidence against a nonclassical **49**, see Dewar; Haddon; Komornicki; Rzepa *J. Am. Chem. Soc.* **1977**, *99*, 377; Lambert; Mark *J. Am. Chem. Soc.* **1978**, *100*, 2501; Christol; Coste; Pietrasanta; Plénat; Renard *J. Chem. Soc., (S)* **1978**, 62; Brown; Ravindranathan; Rao; Chloupek; Rei *J. Org. Chem.* **1978**, *43*, 3667; Brown; Rao *J. Org. Chem.* **1979**, *44*, 133, 3536, **1980**, *45*, 2113; Liu; Yen; Hwang *J. Chem. Res.(S)* **1980**, 152; Werstiuk; Dhanoa; Timmins *Can. J. Chem.* **1983**, *61*, 2403; Brown; Chloupek; Takeuchi *J. Org. Chem.* **1985**, *50*, 826; Brown; Ikegami; Vander Jagt *J. Org. Chem.* **1985**, *50*, 1165; Nickon; Swartz; Sainsbury; Toth *J. Org. Chem.* **1986**, *51*, 3736. See also Brown *Top. Curr. Chem.* **1979**, *80*, 1-18.

has also been extensively studied at low temperatures; there is much evidence that under these conditions the ion is definitely nonclassical. Olah and co-workers have prepared the 2-norbornyl cation in stable solutions at temperatures below -150°C in $\text{SbF}_5\text{-SO}_2$ and $\text{FSO}_3\text{H-SbF}_5\text{-SO}_2$, where the structure is static and hydride shifts are absent.¹⁴⁶ Studies by proton and ^{13}C nmr, as well as by laser Raman spectra and x-ray electron spectroscopy, led to the conclusion¹⁴⁷ that under these conditions the ion is nonclassical.¹⁴⁸ A similar result has been reported for the 2-norbornyl cation in the solid state where at 77 K and even 5 K, ^{13}C nmr spectra gave no evidence of the freezing out of a single classical ion.¹⁴⁹

Olah and co-workers represented the nonclassical structure as a corner-protonated nortricyclane (**52**); the symmetry is better seen when the ion is drawn as in **53**. Almost all the



positive charge resides on C-1 and C-2 and very little on the bridging carbon C-6. Other evidence for the nonclassical nature of the 2-norbornyl cation in stable solutions comes from heat of reaction measurements that show that the 2-norbornyl cation is more stable (by about 6-10 kcal/mol or 25-40 kJ/mol) than would be expected without the bridging.¹⁵⁰ Studies of ir spectra of the 2-norbornyl cation in the gas phase also show the nonclassical structure.¹⁵¹ Ab initio calculations show that the nonclassical structure corresponds to an energy minimum.¹⁵²

The spectra of other norbornyl cations have also been investigated at low temperatures. Spectra of the tertiary 2-methyl- and 2-ethylnorbornyl cations show less delocalization,¹⁵³ and the 2-phenylnorbornyl cation (**54**) is essentially classical,¹⁵⁴ as are the 2-methoxy¹⁵⁵ and 2-chloronorbornyl cations.¹⁵⁶ We may recall (p. 170) that methoxy and halo groups also

¹⁴⁶The presence of hydride shifts (p. 1069) under solvolysis conditions has complicated the interpretation of the data.

¹⁴⁷Olah; White; DeMember; Commcyras; Lui *J. Am. Chem. Soc.* **1970**, *92*, 4627; Olah *J. Am. Chem. Soc.* **1972**, *94*, 808; *Acc. Chem. Res.* **1976**, *9*, 41-52; Olah; Liang; Mateescu; Riemenschneider *J. Am. Chem. Soc.* **1973**, *95*, 8698; Saunders; Kates *J. Am. Chem. Soc.* **1980**, *102*, 6867, **1983**, *105*, 3571; Olah; Prakash; Arvanaghi; Anet *J. Am. Chem. Soc.* **1982**, *104*, 7105; Olah; Prakash; Saunders *Acc. Chem. Res.* **1983**, *16*, 440-448. See also Schleyer; Lenoir; Mison; Liang; Prakash; Olah *J. Am. Chem. Soc.* **1980**, *102*, 683; Johnson; Clark *J. Am. Chem. Soc.* **1988**, *110*, 4112.

¹⁴⁸This conclusion has been challenged: Fong *J. Am. Chem. Soc.* **1974**, *96*, 7638; Kramer *Adv. Phys. Org. Chem.* **1975**, *11*, 177-224; Brown; Periasamy; Kelly; Giansiracusa *J. Org. Chem.* **1982**, *47*, 2089; Kramer; Scouten *Adv. Carbocation Chem.* **1989**, *1*, 93-120. See, however, Olah; Prakash; Farnum; Clausen *J. Org. Chem.* **1983**, *48*, 2146.

¹⁴⁹Yannoni; Macho; Myhre *J. Am. Chem. Soc.* **1982**, *104*, 907, 7380, *Bull. Soc. Chim. Belg.* **1982**, *91*, 422; Myhre; Webb; Yannoni *J. Am. Chem. Soc.* **1990**, *112*, 8991.

¹⁵⁰For some examples, see Hogeveen; Gaasbeek *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 719; Hogeveen *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 74; Solomon; Field *J. Am. Chem. Soc.* **1976**, *98*, 1567; Staley; Wieting; Beauchamp *J. Am. Chem. Soc.* **1977**, *99*, 5964; Arnett; Petro *J. Am. Chem. Soc.* **1978**, *100*, 2563; Arnett; Pienta; Petro *J. Am. Chem. Soc.* **1980**, *102*, 398; Saluja; Kebarle *J. Am. Chem. Soc.* **1979**, *101*, 1084; Schleyer; Chandrasekhar *J. Org. Chem.* **1981**, *46*, 225; Lossing; Holmes *J. Am. Chem. Soc.* **1984**, *106*, 6917.

¹⁵¹Koch; Liu; DeFrees; Sunko; Vančik *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 183 [*Angew. Chem.* **102**, 198].

¹⁵²See, for example Koch; Liu; DeFrees *J. Am. Chem. Soc.* **1989**, *111*, 1527.

¹⁵³Olah; DeMember; Lui; White *J. Am. Chem. Soc.* **1969**, *91*, 3958. See also Laube *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 560 [*Angew. Chem.* **99**, 578]; Forsyth; Panyachotipun *J. Chem. Soc., Chem. Commun.* **1988**, 1564.

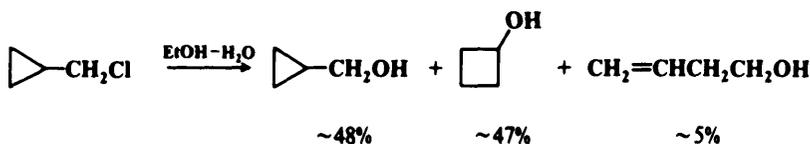
¹⁵⁴Olah; Liang *J. Am. Chem. Soc.* **1974**, *96*, 195; Olah; White; DeMember; Commcyras; Lui. Ref. 147; Farnum; Mehta *J. Am. Chem. Soc.* **1969**, *91*, 3256; Ref. 153. See also Schleyer; Kleinfelter; Richey *J. Am. Chem. Soc.* **1963**, *85*, 479; Farnum; Wolf *J. Am. Chem. Soc.* **1974**, *96*, 5166.

¹⁵⁵Nickon; Lin *J. Am. Chem. Soc.* **1969**, *91*, 6861. See also Montgomery; Grendze; Huffman *J. Am. Chem. Soc.* **1987**, *109*, 4749.

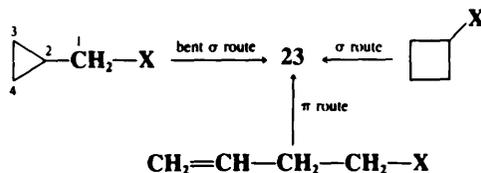
¹⁵⁶Fry; Farnham *J. Org. Chem.* **1969**, *34*, 2314.

stabilize a positive charge. ^{13}C nmr data show that electron-withdrawing groups on the benzene ring of **54** cause the ion to become less classical, while electron-donating groups enhance the classical nature of the ion.¹⁵⁷

b. The cyclopropylmethyl system. Apart from the 2-norbornyl system, the greatest amount of effort in the search for C—C participation has been devoted to the cyclopropylmethyl system.¹⁵⁸ It has long been known that cyclopropylmethyl substrates solvolyze with abnormally high rates and that the products often include not only unrearranged cyclopropylmethyl but also cyclobutyl and homoallylic compounds. An example is¹⁵⁹

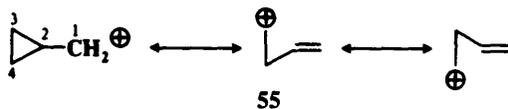


Cyclobutyl substrates also solvolyze abnormally rapidly and give similar products. Furthermore, when the reactions are carried out with labeled substrates, considerable, though not complete, scrambling is observed. For these reasons it has been suggested that a common intermediate (some kind of nonclassical intermediate, e.g., **23**, p. 313) is present in these cases. This common intermediate could then be obtained by three routes:



In recent years much work has been devoted to the study of these systems, and it is apparent that matters are not so simple. Though there is much that is still not completely understood, some conclusions can be drawn.

i. In solvolysis of simple primary cyclopropylmethyl systems the rate is enhanced because of participation by the σ bonds of the ring.¹⁶⁰ The ion that forms initially is an unrearranged cyclopropylmethyl cation¹⁶¹ that is *symmetrically* stabilized, that is, both the 2,3 and 2,4 σ bonds help stabilize the positive charge. We have already seen (p. 169) that a cyclopropyl group stabilizes an adjacent positive charge even better than a phenyl group. One way of representing the structure of this cation is as shown in **55. Among the evidence that **55** is a**



symmetrical ion is that substitution of one or more methyl groups in the 3 and 4 positions increases the rate of solvolysis of cyclopropylcarbonyl 3,5-dinitrobenzoates by approximately

¹⁵⁷Olah; Prakash; Liang *J. Am. Chem. Soc.* **1977**, *99*, 5683; Farnum; Botto; Chambers; Lam *J. Am. Chem. Soc.* **1978**, *100*, 3847. See also Olah; Berrier; Prakash *J. Org. Chem.* **1982**, *47*, 3903.

¹⁵⁸For reviews, see in Olah; Schleyer, Ref. 92, vol. 3, 1972, the articles by Richey, pp. 1201-1294, and by Wiberg; Hess; Ashe, pp. 1295-1345; Hanack; Schneider *Fortschr. Chem. Forsch.* **1967**, *8*, 554-607, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 666-677 [*Angew. Chem.* **79**, 709-720]; Sarel; Yovell; Sarel-Imber *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 577-588 [*Angew. Chem.* **90**, 592-603].

¹⁵⁹Roberts; Mazur *J. Am. Chem. Soc.* **1951**, *73*, 2509.

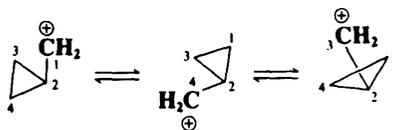
¹⁶⁰See, for example, Roberts; Snyder *J. Org. Chem.* **1979**, *44*, 2860, and references cited therein.

¹⁶¹Wiberg; Ashe *J. Am. Chem. Soc.* **1968**, *90*, 63.

a factor of 10 for *each* methyl group.¹⁶² If only one of the σ bonds (say, the 2,3 bond) stabilizes the cation, then methyl substitution at the 3 position should increase the rate, and a second methyl group at the 3 position should increase it still more, but a second methyl group at the 4 position should have little effect.¹⁶³

ii. The most stable geometry of simple cyclopropylmethyl cations is the bisected one shown on p. 169. There is much evidence that in systems where this geometry cannot be obtained, solvolysis is greatly slowed.¹⁶⁴

iii. Once a cyclopropylmethyl cation is formed, it can rearrange to two other cyclopropylmethyl cations:



This rearrangement, which accounts for the scrambling, is completely stereospecific.¹⁶⁵ The rearrangements probably take place through a nonplanar cyclobutyl cation intermediate or transition state. The formation of cyclobutyl and homoallylic products from a cyclopropylmethyl cation is also completely stereospecific. These products may arise by direct attack of the nucleophile on **55** or on the cyclobutyl cation intermediate.¹⁶⁵ A planar cyclobutyl cation is ruled out in both cases because it would be symmetrical and the stereospecificity would be lost.

iv. The rate enhancement in the solvolysis of secondary cyclobutyl substrates is probably caused by participation by a bond leading directly to **55**, which accounts for the fact that solvolysis of cyclobutyl and of cyclopropylmethyl substrates often gives similar product



mixtures. There is no evidence that requires the cyclobutyl cations to be intermediates in most secondary cyclobutyl systems, though tertiary cyclobutyl cations can be solvolysis intermediates.

v. The unsubstituted cyclopropylmethyl cation has been generated in super-acid solutions at low temperatures, where ¹³C nmr spectra have led to the conclusion that it consists of a mixture of the bicyclobutonium ion **23** and the bisected cyclopropylmethyl cation **55**, in equilibrium with **23**.¹⁶⁶ Molecular orbital calculations show that these two species are energy minima, and that both have nearly the same energy.¹⁶⁷

¹⁶²Schleyer; Van Dine *J. Am. Chem. Soc.* **1966**, *88*, 2321.

¹⁶³For a summary of additional evidence for the symmetrical nature of cyclopropylmethyl cations, see Wiberg; Hess; Ashe, Ref. 158, pp. 1300-1303.

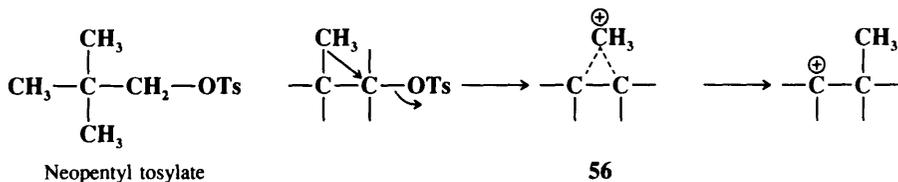
¹⁶⁴For example, see Ree; Martin *J. Am. Chem. Soc.* **1970**, *92*, 1660; Rhodes; DiFate *J. Am. Chem. Soc.* **1972**, *94*, 7582. See, however, Brown; Peters *J. Am. Chem. Soc.* **1975**, *97*, 1927.

¹⁶⁵Wiberg; Szeimies *J. Am. Chem. Soc.* **1968**, *90*, 4195, **1970**, *92*, 571; Majerski; Schleyer *J. Am. Chem. Soc.* **1971**, *93*, 665.

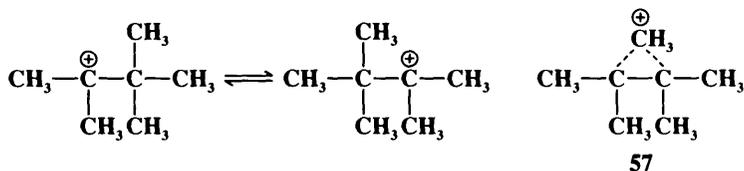
¹⁶⁶Staral; Yavari; Roberts; Prakash; Donovan; Olah *J. Am. Chem. Soc.* **1978**, *100*, 8016. See also Olah; Jeuell; Kelly; Porter *J. Am. Chem. Soc.* **1972**, *94*, 146; Olah; Spear; Hiberty; Hehre *J. Am. Chem. Soc.* **1976**, *98*, 7470; Saunders; Siehl *J. Am. Chem. Soc.* **1980**, *102*, 6868; Brittain; Squillacote; Roberts *J. Am. Chem. Soc.* **1984**, *106*, 7280; Siehl; Koch *J. Chem. Soc., Chem. Commun.* **1985**, 496; Prakash; Arvanaghi; Olah *J. Am. Chem. Soc.* **1985**, *107*, 6017; Myhre; Webb; Yannoni *J. Am. Chem. Soc.* **1990**, *112*, 8992.

¹⁶⁷Koch; Liu; DeFrees *J. Am. Chem. Soc.* **1988**, *110*, 7325; Saunders; Laidig; Wiberg; Schleyer *J. Am. Chem. Soc.* **1988**, *110*, 7652.

c. *Methyl as a neighboring group.* Both the 2-norbornyl and cyclopropylmethyl system contain a σ bond that is geometrically constrained to be in a particularly favorable position for participation as a neighboring group. However, there have been a number of investigations to determine whether a C—C bond can lend anchimeric assistance even in a simple open-chain compound such as neopentyl tosylate. On solvolysis, neopentyl systems undergo almost exclusive rearrangement and **56** must lie on the reaction path, but the two questions



that have been asked are: (1) Is the departure of the leaving group concerted with the formation of the $\text{CH}_3\text{---C}$ bond (that is, does the methyl participate)? (2) Is **56** an intermediate or only a transition state? With respect to the first question, there is evidence, chiefly from isotope effect studies, that indicates that the methyl group in the neopentyl system does indeed participate,¹⁶⁸ though it may not greatly enhance the rate. As to the second question, evidence that **56** is an intermediate is that small amounts of cyclopropanes (10 to 15%) can be isolated in these reactions.¹⁶⁹ **56** is a protonated cyclopropane and would give cyclopropane on loss of a proton.¹⁷⁰ In an effort to isolate a species that has structure **56**, the 2,3,3-trimethyl-2-butyl cation was prepared in super-acid solutions at low temperatures.¹⁷¹ However, proton and ¹³C nmr, as well as Raman spectra, showed this to be a pair of rapidly equilibrating open ions.



Of course, **57** must lie on the reaction path connecting the two open ions, but it is evidently a transition state and not an intermediate. However, evidence from x-ray photoelectron spectroscopy (ESCA) has shown that the 2-butyl cation is substantially methyl bridged.¹⁷²

5. *Hydrogen as a neighboring group.* The questions relating to hydrogen are similar to those relating to methyl. There is no question that hydride can migrate, but the two questions are: (1) Does the hydrogen participate in the departure of the leaving group? (2) Is **58** an intermediate or only a transition state? There is some evidence that a β hydrogen can

¹⁶⁸For example, see Dauben; Chitwood *J. Am. Chem. Soc.* **1968**, *90*, 6876; Ando; Morisaki *Tetrahedron Lett.* **1979**, 121; Shiner; Seib *Tetrahedron Lett.* **1979**, 123; Shiner; Tai *J. Am. Chem. Soc.* **1981**, *103*, 436; Yamataka; Ando *J. Am. Chem. Soc.* **1982**, *104*, 1808; Yamataka; Ando; Nagase; Hanamura; Morokuma *J. Org. Chem.* **1984**, *49*, 631. For an opposing view, see Zamashchikov; Rudakov; Bezbozhnaya; Matveev *J. Org. Chem. USSR* **1984**, *20*, 11.

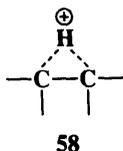
¹⁶⁹Skell; Starer *J. Am. Chem. Soc.* **1960**, *82*, 2971; Silver *J. Am. Chem. Soc.* **1960**, *82*, 2971; Friedman; Bayless *J. Am. Chem. Soc.* **1969**, *91*, 1790; Friedman; Jurewicz *J. Am. Chem. Soc.* **1969**, *91*, 1800, 1803; Dupuy; Hudson; Karam *Tetrahedron Lett.* **1971**, 3193; Silver; Meek *Tetrahedron Lett.* **1971**, 3579; Dupuy; Hudson *J. Chem. Soc., Perkin Trans. 2* **1972**, 1715.

¹⁷⁰For further discussions of protonated cyclopropanes, see pp. 757, 1056.

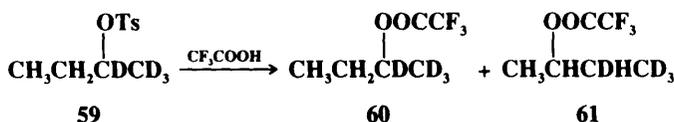
¹⁷¹Olah; White *J. Am. Chem. Soc.* **1969**, *91*, 5801; Olah; Comisarow; Kim *J. Am. Chem. Soc.* **1969**, *91*, 1458; Olah; DeMember; Commeyras; Bribes *J. Am. Chem. Soc.* **1971**, *93*, 459.

¹⁷²Johnson; Clark. Ref. 147. See also Carneiro; Schleyer; Koch; Raghavachari *J. Am. Chem. Soc.* **1990**, *112*, 4064.

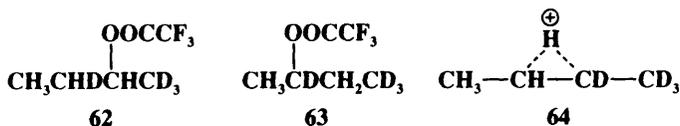
participate.¹⁷³ Evidence that **58** can be an intermediate in solvolysis reactions comes from a study of the solvolysis in trifluoroacetic acid of deuterated *sec*-butyl tosylate **59**. In this



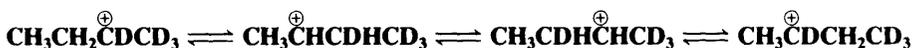
solvent of very low nucleophilic power, the products were an equimolar mixture of **60** and **61**,¹⁷⁴ but *no* **62** or **63** was found. If this reaction did not involve neighboring hydrogen at



all (pure S_N2 or S_N1), the product would be only **60**. On the other hand, if hydrogen does migrate, but only open cations are involved, then there should be an equilibrium among



these four cations:



leading not only to **60** and **61**, but also to **62** and **63**. The results are most easily compatible with the intermediacy of the bridged ion **64** which can then be attacked by the solvent equally at the 2 and 3 positions. Attempts to prepare **58** as a stable ion in super-acid solutions at low temperatures have not been successful.¹⁷²

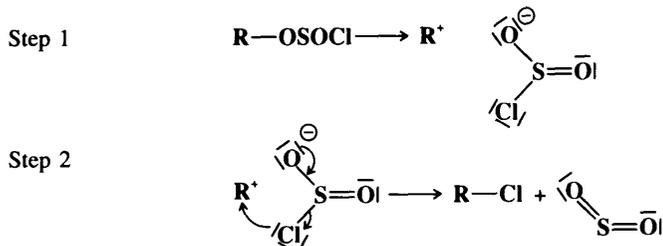
The S_Ni Mechanism

In a few reactions, nucleophilic substitution proceeds with retention of configuration, even where there is no possibility of a neighboring-group effect. In the S_Ni mechanism (*substitution nucleophilic internal*) part of the leaving group must be able to attack the substrate, detaching

¹⁷³See, for example, Shiner; Jewett *J. Am. Chem. Soc.* **1965**, *87*, 1382; Pánková; Sicher; Tichý; Whiting *J. Chem. Soc. B* **1968**, 365; Tichý; Hapala; Sicher *Tetrahedron Lett.* **1969**, 3739; Myhre; Evans *J. Am. Chem. Soc.* **1969**, *91*, 5641; Inomoto; Robertson; Sarkis *Can. J. Chem.* **1969**, *47*, 4599; Shiner; Stoffer *J. Am. Chem. Soc.* **1970**, *92*, 3191; Krapcho; Johanson *J. Org. Chem.* **1971**, *36*, 146; Chuit; Felkin; Le Ny; Lion; Prunier *Tetrahedron* **1972**, *28*, 4787; Stéhelin; Lhomme; Ourisson *J. Am. Chem. Soc.* **1971**, *93*, 1650; Stéhelin; Kanellias; Ourisson *J. Org. Chem.* **1973**, *38*, 847, 851; Hirsš-Starčević; Majerski; Sunko *J. Org. Chem.* **1980**, *45*, 3388; Buzek; Schleyer; Sieber; Koch; Carneiro; Vančík; Sunko *J. Chem. Soc., Chem. Commun.* **1991**, 671; Imhoff; Ragain; Moore; Shiner *J. Org. Chem.* **1991**, *56*, 3542.

¹⁷⁴Dannenberg; Goldberg; Barton; Dill; Weinwurz; Longas *J. Am. Chem. Soc.* **1981**, *103*, 7764. See also Dannenberg; Barton; Bunch; Goldberg; Kowalski *J. Org. Chem.* **1983**, *48*, 4524; Allen; Ambidge; Tidwell *J. Org. Chem.* **1983**, *48*, 4527.

itself from the rest of the leaving group in the process. The IUPAC designation is $D_N + A_N D_c$. The first step is the same as the very first step of the S_N1 mechanism—dissociation into an intimate ion pair.¹⁷⁵ But in the second step part of the leaving group attacks, necessarily from the front since it is unable to get to the rear. This results in retention of configuration:



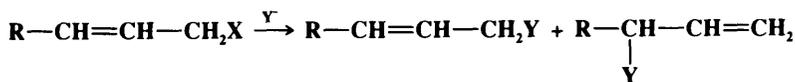
The example shown is the most important case of this mechanism yet discovered, since the reaction of alcohols with thionyl chloride to give alkyl halides usually proceeds in this way, with the first step in this case being $ROH + SOCl_2 \rightarrow ROSOCl$ (these alkyl chlorosulfites can be isolated).

Evidence for this mechanism is as follows: the addition of pyridine to the mixture of alcohol and thionyl chloride results in the formation of alkyl halide with *inverted* configuration. Inversion results because the pyridine reacts with $ROSOCl$ to give $ROSON^+C_5H_5$ before anything further can take place. The Cl^- freed in this process now attacks from the rear. The reaction between alcohols and thionyl chloride is second order, which is predicted by this mechanism, but the decomposition by simple heating of $ROSOCl$ is first order.¹⁷⁶

The S_Ni mechanism is relatively rare. Another example is the decomposition of $ROCOCl$ (alkyl chloroformates) into RCl and CO_2 .¹⁷⁷

Nucleophilic Substitution at an Allylic Carbon. Allylic Rearrangements

Allylic substrates undergo nucleophilic substitution reactions especially rapidly (see p. 341), but we discuss them in a separate section because they are usually accompanied by a certain kind of rearrangement known as an *allylic rearrangement*.¹⁷⁸ When allylic substrates are treated with nucleophiles under S_N1 conditions, two products are usually obtained: the normal one and a rearranged one.



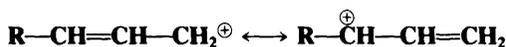
¹⁷⁵Lee; Finlayson *Can. J. Chem.* **1961**, *39*, 260; Lee; Clayton; Lee; Finlayson *Tetrahedron* **1962**, *18*, 1395.

¹⁷⁶Lewis; Boozer *J. Am. Chem. Soc.* **1952**, *74*, 308.

¹⁷⁷Lewis; Herndon; Duffey *J. Am. Chem. Soc.* **1961**, *83*, 1959; Lewis; Witte *J. Chem. Soc. B* **1968**, 1198. For other examples, see Hart; Elia *J. Am. Chem. Soc.* **1961**, *83*, 985; Stevens; Dittmer; Kovacs *J. Am. Chem. Soc.* **1963**, *85*, 3394; Kice; Hanson *J. Org. Chem.* **1973**, *38*, 1410; Cohen; Solash *Tetrahedron Lett.* **1973**, 2513; Verrinder; Hourigan; Prokipcak *Can. J. Chem.* **1978**, *56*, 2582.

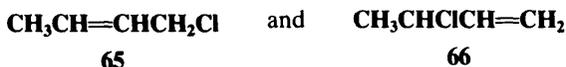
¹⁷⁸For a review, see DeWolfe, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 9; Elsevier: New York, 1973, pp. 417-437. For comprehensive older reviews, see DeWolfe; Young *Chem. Rev.* **1956**, *56*, 753-901; in Patai *The Chemistry of Alkenes*; Wiley: New York, 1964, the sections by Mackenzie, pp. 436-453 and DeWolfe; Young, pp. 681-738.

Two products are formed because an allylic type of carbocation is a resonance hybrid



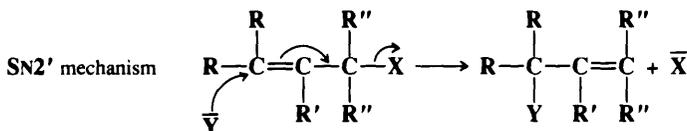
so that C-1 and C-3 each carry a partial positive charge and both are attacked by Y. Of course, an allylic rearrangement is undetectable in the case of symmetrical allylic cations, as in the case where R = H, unless isotopic labeling is used. This mechanism has been called the S_N1' mechanism. The IUPAC designation is 1/D_N + 3/A_N, the numbers 1 and 3 signifying the *relative* positions where the nucleophile attacks and from which the nucleofuge leaves.

As with other S_N1 reactions, there is clear evidence that S_N1' reactions can involve ion pairs. If the intermediate attacked by the nucleophile is a completely free carbocation, then, say,



should give the same mixture of alcohols when reacting with hydroxide ion, since the carbocation from each should be the same. When treated with 0.8 N aqueous NaOH at 25°C, **65** gave 60% CH₃CH=CHCH₂OH and 40% CH₃CHOHCH=CH₂, while **66** gave the products in yields of 38 and 62%, respectively.¹⁷⁹ This phenomenon is called the *product spread*. In this case, and in most others, the product spread is in the direction of the starting compound. With increasing polarity of solvent, the product spread decreases and in some cases is entirely absent. It is evident that in such cases the high polarity of the solvent stabilizes completely free carbocations. There is other evidence for the intervention of ion pairs in many of these reactions. When H₂C=CHCMe₂Cl was treated with acetic acid, both acetates were obtained, but also some ClCH₂CH=CMe₂,¹⁸⁰ and the isomerization was faster than the acetate formation. This could not have arisen from a completely free Cl⁻ returning to the carbon, since the rate of formation of the rearranged chloride was unaffected by the addition of external Cl⁻. All these facts indicate that the first step in these reactions is the formation of an unsymmetrical intimate ion pair that undergoes a considerable amount of internal return and in which the counterion remains close to the carbon from which it departed. Thus, **65** and **66**, for example, give rise to two *different* intimate ion pairs. The field of the anion polarizes the allylic cation, making the nearby carbon atom more electrophilic, so that it has a greater chance of attracting the nucleophile.¹⁸¹

Nucleophilic substitution at an allylic carbon can also take place by an S_N2 mechanism, in which case no allylic rearrangement usually takes place. However, allylic rearrangements can also take place under S_N2 conditions, by the following mechanism, in which the nucleophile attacks at the γ carbon rather than the usual position:¹⁸²



¹⁷⁹DeWolfe; Young, *Chem. Rev.*, Ref. 178, give several dozen such examples.

¹⁸⁰Young; Winstein; Goering *J. Am. Chem. Soc.* **1951**, *73*, 1958.

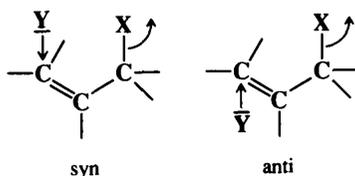
¹⁸¹For additional evidence for the involvement of ion pairs in S_N1' reactions, see Goering; Lindsay *J. Am. Chem. Soc.* **1969**, *91*, 7435; d'Incan; Viout *Bull. Soc. Chim. Fr.* **1971**, 3312; Astin; Whiting *J. Chem. Soc., Perkin Trans. 2* **1976**, 1157; Kantner; Humski; Goering *J. Am. Chem. Soc.* **1982**, *104*, 1693; Thibblin *J. Chem. Soc., Perkin Trans. 2* **1986**, 313; Ref. 56.

¹⁸²For a review of the S_N2' mechanism, see Magid *Tetrahedron* **1980**, *36*, 1901-1930, pp. 1901-1910.

The IUPAC designation is $3/1/A_ND_N$. This mechanism is a second-order allylic rearrangement; it usually comes about where S_N2 conditions hold but where α substitution sterically retards the normal S_N2 mechanism. There are thus few well-established cases of the S_N2' mechanism on substrates of the type $C=C-CH_2X$, while compounds of the form $C=C-CR_2X$ give the S_N2' rearrangement almost exclusively when they give bimolecular reactions at all. Increasing the size of the nucleophile can also increase the extent of the S_N2' reaction at the expense of the S_N2 .¹⁸³ In certain cases the leaving group can also have an effect on whether the rearrangement occurs. Thus $PhCH=CHCH_2X$, treated with $LiAlH_4$, gave 100% S_N2 reaction (no rearrangement) when $X = Br$ or Cl , but 100% S_N2' when $X = PPh_3^+ Br^-$.¹⁸⁴

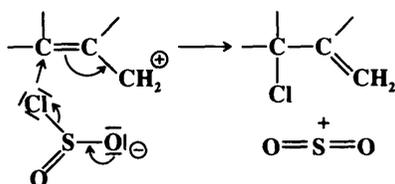
The S_N2' mechanism as shown above involves the simultaneous movement of three pairs of electrons. However, Bordwell has contended that there is no evidence that requires that this bond making and bond breaking be in fact concerted,¹⁸⁵ and that a true S_N2' mechanism is a myth. There is evidence both for¹⁸⁶ and against¹⁸⁷ this proposal.

The stereochemistry of S_N2' reactions has been investigated. It has been found that both syn¹⁸⁸ (the nucleophile enters on the side from which the leaving group departs) and anti¹⁸⁹



reactions can take place, depending on the nature of X and Y,¹⁹⁰ though the syn pathway predominates in most cases.

When a molecule has in an allylic position a nucleofuge capable of giving the S_Ni reaction, it is possible for the nucleophile to attack at the γ position instead of the α position. This is called the S_Ni' mechanism and has been demonstrated on 2-buten-1-ol and 3-buten-2-ol,



¹⁸³Bordwell; Clemens; Cheng *J. Am. Chem. Soc.* **1987**, *109*, 1773.

¹⁸⁴Hirabe; Nojima; Kusabayashi *J. Org. Chem.* **1984**, *49*, 4084.

¹⁸⁵Bordwell; Schexnayder *J. Org. Chem.* **1968**, *33*, 3240; Bordwell; Mecca *J. Am. Chem. Soc.* **1972**, *94*, 5829; Bordwell *Acc. Chem. Res.* **1970**, *3*, 281-290, pp. 282-285. See also de la Mare; Vernon *J. Chem. Soc. B* **1971**, 1699; Dewar *J. Am. Chem. Soc.* **1984**, *106*, 209.

¹⁸⁶See Uebel; Milaszewski; Arlt *J. Org. Chem.* **1977**, *42*, 585.

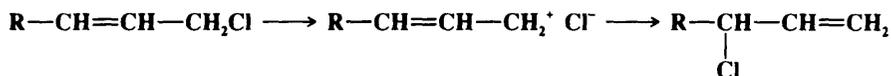
¹⁸⁷See Fry *Pure Appl. Chem.* **1964**, *8*, 409; Georgoulis; Ville *J. Chem. Res. (S)* **1978**, 248, *Bull. Soc. Chim. Fr.* **1985**, 485; Weislich; Jasne *J. Org. Chem.* **1982**, *47*, 2517.

¹⁸⁸See, for example, Stork; White *J. Am. Chem. Soc.* **1956**, *78*, 4609; Jefford; Sweeney; Delay *Helv. Chim. Acta* **1972**, *55*, 2214; Kirmse; Scheidt; Vater *J. Am. Chem. Soc.* **1978**, *100*, 3945; Gallina; Ciattini *J. Am. Chem. Soc.* **1979**, *101*, 1035; Magid; Fruchey *J. Am. Chem. Soc.* **1979**, *101*, 2107; Bäckvall; Vågberg; Genêt *J. Chem. Soc., Chem. Commun.* **1987**, 159.

¹⁸⁹See, for example, Borden; Corey *Tetrahedron Lett.* **1969**, 313; Takahashi; Satoh *Bull. Chem. Soc. Jpn.* **1975**, *48*, 69; Staroscik; Rickborn *J. Am. Chem. Soc.* **1971**, *93*, 3046; See also Liotta *Tetrahedron Lett.* **1975**, 523; Stork; Schoofs *J. Am. Chem. Soc.* **1979**, *101*, 5081.

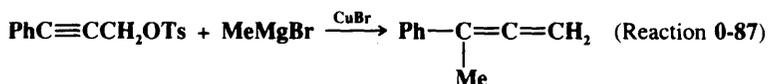
¹⁹⁰Stork; Krefit *J. Am. Chem. Soc.* **1977**, *99*, 3850, 3851; Oritani; Overton *J. Chem. Soc., Chem. Commun.* **1978**, 454; Bach; Wolber *J. Am. Chem. Soc.* **1985**, *107*, 1352. See also Chapleo; Finch; Roberts; Woolley; Newton; Selby *J. Chem. Soc., Perkin Trans. 1* **1980**, 1847; Stohrer *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 613 [*Angew. Chem.* **95**, 642].

both of which gave 100% allylic rearrangement when treated with thionyl chloride in ether.¹⁹¹ Ordinary allylic rearrangements (S_N1') or S_N2' mechanisms could not be expected to give 100% rearrangement in *both* cases. In the case shown, the nucleophile is only part of the leaving group, not the whole. But it is also possible to have reactions in which a simple leaving group, such as Cl, comes off to form an ion pair and then returns not to the position whence it came but to the allylic position:

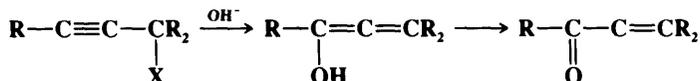


Most S_Ni' reactions are of this type.

Allylic rearrangements have also been demonstrated in propargyl systems, e.g.,¹⁹²



The product in this case is an allene,¹⁹³ but such shifts can also give triple-bond compounds or, if Y = OH, an enol will be obtained that tautomerizes to an α,β-unsaturated aldehyde or ketone.



When X = OH, this conversion of acetylenic alcohols to unsaturated aldehydes or ketones is called the *Meyer-Schuster rearrangement*.¹⁹⁴ The propargyl rearrangement can also go the other way; that is, 1-haloalkenes, treated with organocopper compounds, give alkynes.¹⁹⁵

Nucleophilic Substitution at an Aliphatic Trigonal Carbon. The Tetrahedral Mechanism

All the mechanisms so far discussed take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double-bonded to an oxygen, a sulfur, or a nitrogen. Nucleophilic substitution at vinylic carbons is considered in the next section; at aromatic carbons in Chapter 13.

Substitution at a carbonyl group (or the corresponding nitrogen and sulfur analogs) most often proceeds by a second-order mechanism, which in this book is called the *tetrahedral*¹⁹⁶

¹⁹¹Young, *J. Chem. Educ.* **1962**, 39, 456. For other examples, see Pegolotti; Young *J. Am. Chem. Soc.* **1961**, 83, 3251; Mark *Tetrahedron Lett.* **1962**, 281; Czernecki; Georgoulis; Labertrande; Prévost *Bull. Soc. Chim. Fr.* **1969**, 3568; Lewis; Witte, Ref. 177; Corey; Boaz *Tetrahedron Lett.* **1984**, 25, 3055.

¹⁹²Vermeer; Meijer; Brandsma *Recl. Trav. Chim. Pays-Bas* **1975**, 94, 112.

¹⁹³For reviews of such rearrangements, see Schuster; Coppola *Allenes in Organic Synthesis*; Wiley: New York, 1984, pp. 12-19, 26-30; Taylor *Chem. Rev.* **1967**, 67, 317-359, pp. 324-328.

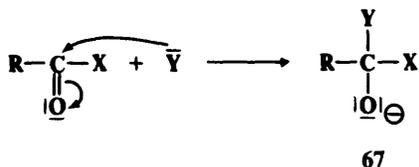
¹⁹⁴For a review, see Swaminathan; Narayanan *Chem. Rev.* **1971**, 71, 429-438. For discussions of the mechanism, see Edens; Boerner; Chase; Nass; Schiavelli *J. Org. Chem.* **1977**, 42, 3403; Andres; Cardenas, Silla; Tapia *J. Am. Chem. Soc.* **1988**, 110, 666.

¹⁹⁵Corey; Boaz *Tetrahedron Lett.* **1984**, 25, 3059, 3063.

¹⁹⁶This mechanism has also been called the "addition-elimination mechanism," but in this book we limit this term to the type of mechanism shown on p. 335.

*mechanism.*¹⁹⁷ The IUPAC designation is $A_N + D_N$. S_N1 mechanisms, involving carbocations, are sometimes found with these substrates, especially with essentially ionic substrates such as $RCO^+ BF_4^-$; there is evidence that in certain cases simple S_N2 mechanisms can take place, especially with a very good leaving group such as Cl^- ;¹⁹⁸ and an SET mechanism has also been reported.¹⁹⁹ However, the tetrahedral mechanism is by far the most prevalent. Although this mechanism displays second-order kinetics, it is not the same as the S_N2 mechanism previously discussed. In the tetrahedral mechanism, first Y attacks to give an intermediate containing both X and Y, and then X leaves. This sequence, impossible at a saturated carbon, is possible at an unsaturated one because the central carbon can release a pair of electrons to the oxygen and so preserve its octet:

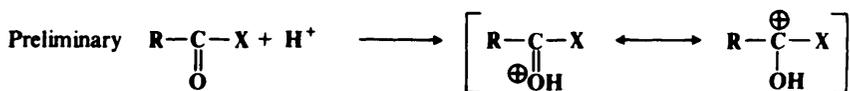
Step 1



Step 2



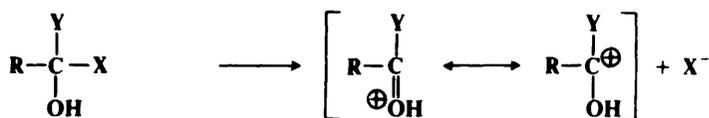
When reactions are carried out in acid solution, there may also be a preliminary and a final step:



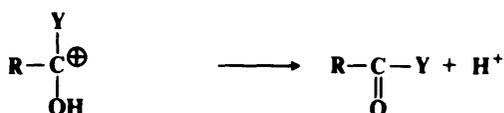
Step 1



Step 2



Final

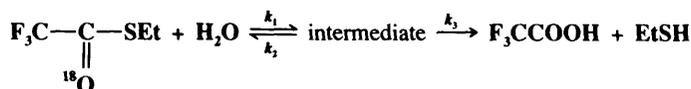


¹⁹⁷For reviews of this mechanism, see Talbot, in Bamford; Tipper, Ref. 178, vol. 10, 1972, pp. 209-223; Jencks *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969, pp. 463-554; Satchell; Satchell, in Patai *The Chemistry of Carboxylic Acids and Esters*; Wiley: New York, 1969, pp. 375-452; Johnson *Adv. Phys. Org. Chem.* **1967**, 5, 237-330.

¹⁹⁸For a review, see Williams *Acc. Chem. Res.* **1989**, 22, 387-392. For examples, see Kevill; Foss *J. Am. Chem. Soc.* **1969**, 91, 5054; Haberfield; Trattner *Chem. Commun.* **1971**, 1481; Shpan'ko; Goncharov; Litvinenko *J. Org. Chem. USSR* **1979**, 15, 1472, 1478; De Tar *J. Am. Chem. Soc.* **1982**, 104, 7205; Bentley; Carter; Harris *J. Chem. Soc., Perkin Trans. 2* **1985**, 983; Shpan'ko; Goncharov *J. Org. Chem. USSR* **1987**, 23, 2287; Guthrie; Pike *Can. J. Chem.* **1987**, 65, 1951; Kevill; Kim *Bull. Soc. Chim. Fr.* **1988**, 383; *J. Chem. Soc., Perkin Trans. 2* **1988**, 1353; Bentley; Koo *J. Chem. Soc., Perkin Trans. 2* **1989**, 1385. See however, Buncl; Um; Hoz *J. Am. Chem. Soc.* **1989**, 111, 971.

¹⁹⁹Bacaloglu; Blaskó; Bunton; Ortega *J. Am. Chem. Soc.* **1990**, 112, 9336.

The intermediates **68** and **70** can now lose OR' to give the acid (not shown in the equations given), or they can lose OH to regenerate the carboxylic ester. If **68** goes back to ester, the ester will still be labeled, but if **70** reverts to ester, the ^{18}O will be lost. A test of the two possible mechanisms is to stop the reaction before completion and to analyze the recovered ester for ^{18}O . This is just what was done by Bender, who found that in alkaline hydrolysis of methyl, ethyl, and isopropyl benzoates, the esters had lost ^{18}O . A similar experiment carried out for acid-catalyzed hydrolysis of ethyl benzoate showed that here too the ester lost ^{18}O . However, alkaline hydrolysis of substituted benzyl benzoates showed *no* ^{18}O loss.²⁰⁵ This result does not necessarily mean that no tetrahedral intermediate is involved in this case. If **68** and **70** do not revert to ester, but go entirely to acid, no ^{18}O loss will be found even with a tetrahedral intermediate. In the case of benzyl benzoates this may very well be happening, because formation of the acid relieves steric strain. Another possibility is that **68** loses OR' before it can become protonated to **69**.²⁰⁶ Even the experiments that *do* show ^{18}O loss do not *prove* the existence of the tetrahedral intermediate, since it is possible that ^{18}O is lost by some independent process not leading to ester hydrolysis. To deal with this possibility, Bender and Heck²⁰⁷ measured the rate of ^{18}O loss in the hydrolysis of ethyl trifluorothioacetate- ^{18}O :



This reaction had previously been shown²⁰⁸ to involve an intermediate by the kinetic methods mentioned on p. 332. Bender and Heck showed that the rate of ^{18}O loss and the value of the partitioning ratio k_2/k_3 as determined by the oxygen exchange technique were exactly in accord with these values as previously determined by kinetic methods. Thus the original ^{18}O -exchange measurements showed that there is a tetrahedral species present, though not necessarily on the reaction path, while the kinetic experiments showed that there is some intermediate present, though not necessarily tetrahedral. Bender and Heck's results demonstrate that there is a tetrahedral intermediate and that it lies on the reaction pathway.

4. In some cases, tetrahedral intermediates have been isolated²⁰⁹ or detected spectrally.²¹⁰

Several studies have been made of the directionality of approach by the nucleophile.²¹¹ Menger has proposed for reactions in general, and specifically for those that proceed by the tetrahedral mechanism, that there is no single definable preferred transition state, but rather a "cone" of trajectories. All approaches within this cone lead to reaction at comparable rates; it is only when the approach comes outside of the cone that the rate falls.

Directionality has also been studied for the second step. Once the tetrahedral intermediate (**67**) is formed, it loses Y (giving the product) or X (reverting to the starting compound). Deslongchamps has proposed that one of the factors affecting this choice is the conformation of the intermediate; more specifically, the positions of the lone pairs. In this view, a leaving

²⁰⁵Bender; Matsui; Thomas; Tobey *J. Am. Chem. Soc.* **1961**, *83*, 4193. See also Shain; Kirsch *J. Am. Chem. Soc.* **1968**, *90*, 5848.

²⁰⁶For evidence for this possibility, see McClelland *J. Am. Chem. Soc.* **1984**, *106*, 7579.

²⁰⁷Bender; Heck *J. Am. Chem. Soc.* **1967**, *89*, 1211.

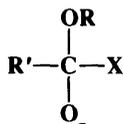
²⁰⁸Fedor; Bruice *J. Am. Chem. Soc.* **1965**, *87*, 4138.

²⁰⁹Rogers; Bruice *J. Am. Chem. Soc.* **1974**, *96*, 2481; Khouri; Kaloustian *J. Am. Chem. Soc.* **1986**, *108*, 6683.

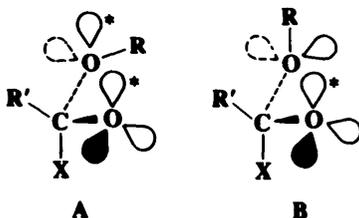
²¹⁰For reviews, see Capon; Dosunmu; Sanchez *Adv. Phys. Org. Chem.* **1985**, *21*, 37-98; McClelland; Santry *Acc. Chem. Res.* **1983**, *16*, 394-399; Capon; Ghosh; Grieve *Acc. Chem. Res.* **1981**, *14*, 306-312. See also Lobo; Marques; Prabhakar; Rzepa *J. Chem. Soc., Chem. Commun.* **1985**, 1113; van der Wel; Nibbering *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 479, 491.

²¹¹For discussions, see Menger *Tetrahedron* **1983**, *39*, 1013-1040; Liotta; Burgess; Eberhardt *J. Am. Chem. Soc.* **1984**, *106*, 4849.

group X or Y can depart only if the other two atoms on the carbon both have an orbital antiperiplanar to the C—X or C—Y bond. For example, consider an intermediate

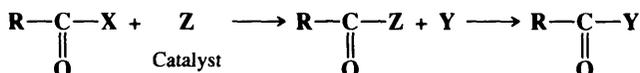


formed by attack of OR^- on a substrate $\text{R}'\text{COX}$. Cleavage of the C—X bond with loss of X can take place from conformation **A**, because the two lone-pair orbitals marked * are



antiperiplanar to the C—X bond, but not from **B** because only the O^- has such an orbital. If the intermediate is in conformation **B**, the OR may leave (if X has a lone-pair orbital in the proper position) rather than X. This factor is called *stereoelectronic control*.²¹² Of course, there is free rotation in acyclic intermediates, and many conformations are possible, but some are preferred, and cleavage reactions may take place faster than rotation, so stereoelectronic control can be a factor in some situations. Much evidence has been presented for this concept.²¹³ More generally, the term *stereoelectronic effects* refers to any case in which orbital position requirements affect the course of a reaction. The backside attack in the $\text{S}_{\text{N}}2$ mechanism is an example of a stereoelectronic effect.

Some nucleophilic substitutions at a carbonyl carbon are *catalyzed* by nucleophiles.²¹⁴ There occur, in effect, two tetrahedral mechanisms:



(For an example, see 0-9.) When this happens internally, we have an example of a neighboring-group mechanism at a carbonyl carbon.²¹⁵ For example, the hydrolysis of phthalamic

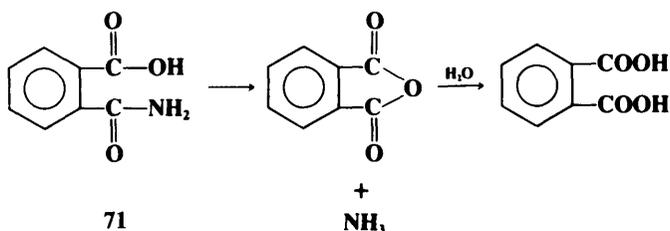
²¹²It has also been called the "antiperiplanar lone pair hypothesis (ALPH)." For a reinterpretation of this factor in terms of the principle of least nuclear motion (see 5-10), see Hosie; Marshall; Sinnott *J. Chem. Soc., Perkin Trans. 2* **1984**, 1121; Sinnott *Adv. Phys. Org. Chem.* **1988**, *24*, 113-204.

²¹³For monographs, see Kirby *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: New York, 1983; Deslongchamps *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983. For lengthy treatments, see Sinnott, Ref. 212; Gorenstein *Chem. Rev.* **1987**, *87*, 1047-1077; Deslongchamps *Heterocycles* **1977**, *7*, 1271-1317; *Tetrahedron* **1975**, *31*, 2463-2490. For additional evidence, see Deslongchamps; Barlet; Taillefer *Can. J. Chem.* **1980**, *58*, 2167; Perrin; Arrhenius *J. Am. Chem. Soc.* **1982**, *104*, 2839; Briggs; Evans; Glenn; Kirby *J. Chem. Soc., Perkin Trans. 2* **1983**, 1637; Deslongchamps; Guay; Chênevert *Can. J. Chem.* *63*, **1985**, 2493; Ndiwami; Deslongchamps *Can. J. Chem.* **1986**, *64*, 1788; Hegarty; Mullane *J. Chem. Soc., Perkin Trans. 2* **1986**, 995. For evidence against the theory, see Perrin; Nuñez *J. Am. Chem. Soc.* **1986**, *108*, 5997, **1987**, *109*, 522.

²¹⁴For reviews of nucleophilic catalysis, see Bender *Mechanisms of Homogeneous Catalysis from Protons to Proteins*; Wiley: New York, 1971, pp. 147-179; Jencks, Ref. 197, pp. 67-77; Johnson, Ref. 197, pp. 271-318. For a review where Z = a tertiary amine (the most common case), see Cherkasova; Bogatkov; Golovina *Russ. Chem. Rev.* **1977**, *46*, 246-263.

²¹⁵For reviews, see Kirby; Fersht *Prog. Bioorg. Chem.* **1971**, *1*, 1-82; Capon *Essays Chem.* **1972**, *3*, 127-156.

acid (**71**) takes place as follows:



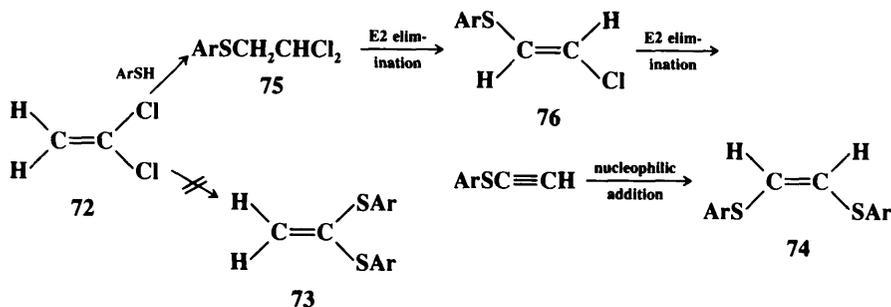
Evidence comes from comparative rate studies.²¹⁶ Thus **71** was hydrolyzed about 10^5 times faster than benzamide (PhCONH_2) at about the same concentration of hydrogen ions. That this enhancement of rate was not caused by the resonance or field effects of COOH (an electron-withdrawing group) was shown by the fact both *o*-nitrobenzamide and terephthalamic acid (the para isomer of **71**) were hydrolyzed more slowly than benzamide. Many other examples of neighboring-group participation at a carbonyl carbon have been reported.²¹⁷ It is likely that nucleophilic catalysis is involved in enzyme catalysis of ester hydrolysis.

The attack of a nucleophile on a carbonyl group can result in substitution or addition (Chapter 16), though the first step of each mechanism is the same. The main factor that determines the product is the identity of the group X in RCOX . When X is alkyl or hydrogen, addition usually takes place. When X is halogen, OH, OCOR , NH_2 , etc., the usual reaction is substitution.

For a list of some of the more important reactions that operate by the tetrahedral mechanism, see Table 10.8.

Nucleophilic Substitution at a Vinylic Carbon

Nucleophilic substitution at a vinylic carbon²¹⁸ is difficult (see p. 341), but many examples are known. The most common mechanisms are the tetrahedral mechanism and the closely related *addition-elimination mechanism*. Both of these mechanisms are impossible at a saturated substrate. The addition-elimination mechanism has been demonstrated for the reaction between 1,1-dichloroethene (**72**) and ArS^- , catalyzed by EtO^- .²¹⁹ The product was



²¹⁶Bender; Chow; Chloupek *J. Am. Chem. Soc.* **1958**, *80*, 5380.

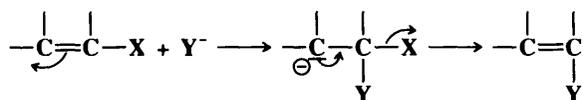
²¹⁷For examples, see Bruice; Pandit *J. Am. Chem. Soc.* **1960**, *82*, 5858; Zimmering; Westhead; Morawetz *Biochim. Biophys. Acta* **1957**, *25*, 376; Kirby; McDonald; Smith *J. Chem. Soc., Perkin Trans. 2* **1974**, 1495; Martin; Tan *J. Chem. Soc., Perkin Trans. 2* **1974**, 129; Kluger; Lam *J. Am. Chem. Soc.* **1978**, *100*, 2191; Page; Render; Bernáth *J. Chem. Soc., Perkin Trans. 2* **1986**, 867.

²¹⁸For reviews, see Rappoport *Recl. Trav. Chim. Pays-Bas* **1986**, *104*, 309-349, *React. Intermed. (Plenum)* **1983**, *3*, 427-615, *Adv. Phys. Org. Chem.* **1969**, *7*, 1-114; Shainyan *Russ. Chem. Rev.* **1986**, *55*, 511-530; Modena *Acc. Chem. Res.* **1971**, *4*, 73-80.

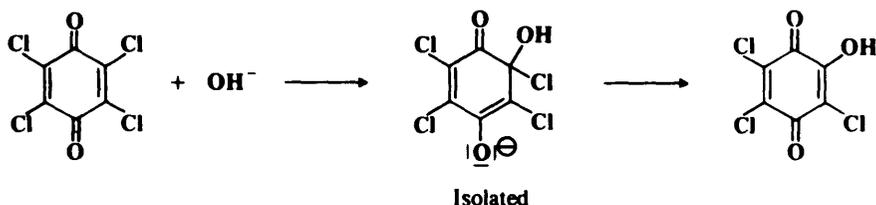
²¹⁹Truce; Boudakian *J. Am. Chem. Soc.* **1956**, *78*, 2748.

not the 1,1-dithiophenoxy compound **73** but the "rearranged" compound **74**. Isolation of **75** and **76** showed that an addition–elimination mechanism had taken place. In the first step ArSH adds to the double bond (nucleophilic addition, p. 741) to give the saturated **75**. The second step is an E2 elimination reaction (p. 983) to give the alkene **76**. A second elimination and addition give **74**.

The tetrahedral mechanism, often also called addition–elimination (*Ad_N-E*), takes place with much less facility than with carbonyl groups, since the negative charge of the intermediate must be borne by a carbon, which is less electronegative than oxygen, sulfur, or nitrogen:



Such an intermediate can also stabilize itself by combining with a positive species. When it does, the reaction is nucleophilic addition to a C=C double bond (see Chapter 15). It is not surprising that with vinylic substrates addition and substitution often compete. For chloroquinones, where the charge is spread by resonance, tetrahedral intermediates have been isolated.²²⁰



In the case of $\text{Ph}(\text{MeO})\text{C}=\text{C}(\text{NO}_2)\text{Ph} + \text{RS}^-$, the intermediate lived long enough to be detected by uv spectroscopy.²²¹

Since both the tetrahedral and addition–elimination mechanisms begin the same way, it is usually difficult to tell them apart, and often no attempt is made to do so. The strongest kind of evidence for the addition–elimination sequence is the occurrence of a "rearrangement" (as in the conversion of **72** to **74**), but of course the mechanism could still take place even if no rearrangement is found. Evidence²²² that a tetrahedral or an addition–elimination mechanism takes place in certain cases (as opposed, for example, to an $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanism) is that the reaction rate increases when the leaving group is changed from Br to Cl to F (this is called the *element effect*).²²³ This clearly demonstrates that the carbon–halogen bond does not break in the rate-determining step (as it would in both the $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms), because fluorine is by far the poorest leaving group among the halogens in both the $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ reactions (p. 352). The rate is faster with fluorides in the cases cited, because the superior electron-withdrawing character of the fluorine makes the carbon of the C–F bond more positive and hence more susceptible to nucleophilic attack.

Ordinary vinylic substrates react very poorly if at all by these mechanisms, but substitution is greatly enhanced in substrates of the type $\text{ZCH}=\text{CHX}$, where Z is an electron-withdrawing

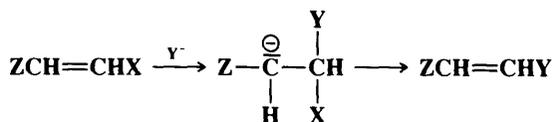
²²⁰Hancock; Morrell; Rhom *Tetrahedron Lett.* **1962**, 987.

²²¹Bernasconi; Fassberg; Killion; Rappoport *J. Am. Chem. Soc.* **1989**, *112*, 3169; *J. Org. Chem.* **1990**, *55*, 4568.

²²²Additional evidence comes from the pattern of catalysis by amines, similar to that discussed for aromatic substrates on p. 643. See Rappoport; Peled *J. Am. Chem. Soc.* **1979**, *101*, 2682, and references cited therein.

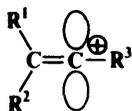
²²³Beltrame; Favini; Cattania; Guella *Gazz. Chim. Ital.* **1968**, *98*, 380. See also Rappoport; Rav-Acha *Tetrahedron Lett.* **1984**, *25*, 117; Solov'yanov; Shtern; Beletskaya; Reutov *J. Org. Chem. USSR* **1983**, *19*, 1945; Avramovitch; Weyerstahl; Rappoport *J. Am. Chem. Soc.* **1987**, *109*, 6687.

group such as HCO, RCO,²²⁴ EtOOC, ArSO₂, NC, F, etc., since these β groups stabilize the carbanion:



Many such examples are known. In most cases where the stereochemistry has been investigated, retention of configuration is observed,²²⁵ but stereoconvergence (the same product mixture from an *E* or *Z* substrate) has also been observed,²²⁶ especially where the carbanionic carbon bears two electron-withdrawing groups. It is not immediately apparent why the tetrahedral mechanism should lead to retention, but this behavior has been ascribed, on the basis of molecular orbital calculations, to hyperconjugation involving the carbanionic electron pair and the substituents on the adjacent carbon.²²⁷

Vinylc substrates are in general very reluctant to undergo S_N1 reactions, but they can be made to do so in two ways:²²⁸ (1) By the use of an α group that stabilizes the vinylic cation. For example, α-aryl vinylic halides ArCBr=CR'₂ have often been shown to give S_N1 reactions.²²⁹ S_N1 reactions have also been demonstrated with other stabilizing groups: cyclopropyl,²³⁰ vinylic,²³¹ alkynyl,²³² and an adjacent double bond (R₂C=C=CR'X).²³³ (2) Even without α stabilization, by the use of a very good leaving group, e.g., OSO₂CF₃ (triflate).²³⁴ The stereochemical outcome of S_N1 reactions at a vinylic substrate is often randomization,²³⁵ that is, either a *cis* or a *trans* substrate gives a 1:1 mixture of *cis* and *trans* products, indicating that vinylic cations are linear. Another indication that vinylic cations prefer to be linear is the fact that reactivity in cycloalkenyl systems decreases with decreasing ring size.²³⁶ However, a linear vinylic cation need not give random products.²³⁷ The empty *p* orbital lies in the plane of the double bond, so entry of the nucleophile can be and often



²²⁴For a review, see Rybinskaya; Nesmeyanov; Kochetkov *Russ. Chem. Rev.* **1969**, *38*, 433-456.

²²⁵Rappoport *Adv. Phys. Org. Chem.*, Ref. 218, pp. 31-62; Shainyan, Ref. 218, pp. 516-520. See also Rappoport; Gazit *J. Am. Chem. Soc.* **1987**, *109*, 6698.

²²⁶See Rappoport; Gazit *J. Org. Chem.* **1985**, *50*, 3184; *J. Am. Chem. Soc.* **1986**, *51*, 4112; Park; Ha *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3006.

²²⁷Apeloig; Rappoport *J. Am. Chem. Soc.* **1979**, *101*, 5095.

²²⁸For reviews of the S_N1 mechanism at a vinylic substrate, see Stang; Rappoport; Hanack; Subramanian *Vinyl Cations*, Chapter 5; Academic Press: New York, 1979; Stang *Acc. Chem. Res.* **1978**, *11*, 107-114; *Prog. Phys. Org. Chem.* **1973**, *10*, 205-325; Rappoport *Acc. Chem. Res.* **1976**, *9*, 265-273; Subramanian; Hanack *J. Chem. Educ.* **1975**, *52*, 80-86; Hanack *Acc. Chem. Res.* **1970**, *3*, 209-216; Modena; Tonellato *Adv. Phys. Org. Chem.* **1971**, *9*, 185-280, pp. 231-253; Grob *Chimia* **1971**, *25*, 87-91; Rappoport; Bässler; Hanack *J. Am. Chem. Soc.* **1970**, *92*, 4985-4987.

²²⁹For a review, see Stang; Rappoport; Hanack; Subramanian, Ref. 228, Chapter 6.

²³⁰Sherrod; Bergman *J. Am. Chem. Soc.* **1969**, *91*, 2115, **1971**, *93*, 1925; Kelsey; Bergman *J. Am. Chem. Soc.* **1970**, *92*, 238, **1971**, *93*, 1941; Hanack; Bässler *J. Am. Chem. Soc.* **1969**, *91*, 2117; Hanack; Bässler; Eymann; Heyd; Kopp *J. Am. Chem. Soc.* **1974**, *96*, 6686.

²³¹Grob; Spaar *Tetrahedron Lett.* **1969**, 1439; *Helv. Chim. Acta* **1970**, *53*, 2119.

²³²Hassdenteufel; Hanack *Tetrahedron Lett.* **1980**, 503. See also Kobayashi; Nishi; Koyama; Taniguchi *J. Chem. Soc., Chem. Commun.* **1980**, 103.

²³³Schiavelli; Gilbert; Boynton; Boswell *J. Am. Chem. Soc.* **1972**, *94*, 5061.

²³⁴See, for example, Stang; Summerville *J. Am. Chem. Soc.* **1969**, *91*, 4600; Clarke; Bergman *J. Am. Chem. Soc.* **1972**, *94*, 3627, **1974**, *96*, 7934; Summerville; Schleyer *J. Am. Chem. Soc.* **1972**, *94*, 3629, **1974**, *96*, 1110; Eckes; Subramanian; Hanack *Tetrahedron Lett.* **1973**, 1967; Hanack; Märkl; Martinez *Chem. Ber.* **1982**, *115*, 772.

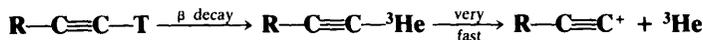
²³⁵Rappoport; Apeloig *J. Am. Chem. Soc.* **1969**, *91*, 6734; Kelsey; Bergman, Ref. 230.

²³⁶Pfeifer; Bahn; Schleyer; Bocher; Harding; Hummel; Hanack; Stang *J. Am. Chem. Soc.* **1971**, *93*, 1513.

²³⁷For examples of inversion, see Clarke; Bergman, Ref. 234; Summerville; Schleyer, Ref. 234.

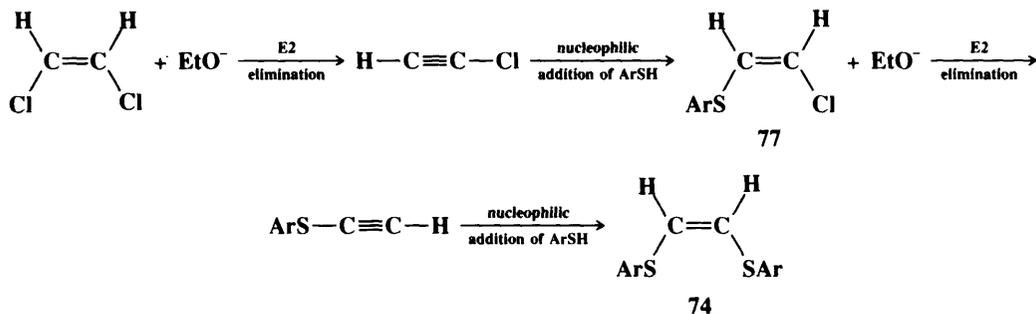
is influenced by the relative size of R^1 and R^2 .²³⁸ It must be emphasized that even where vinylic substrates do give S_N1 reactions, the rates are generally lower than those of the corresponding saturated compounds.

Alkynyl cations are so unstable that they cannot be generated even with very good leaving groups. However, one way in which they have been generated was by formation of a tritiated substrate.



When the tritium (half-life 12.26 y) decays it is converted to the helium-3 isotope, which, of course, does not form covalent bonds, and so immediately departs, leaving behind the alkynyl cation. When this was done in the presence of benzene, $RC\equiv CC_6H_5$ was isolated.²³⁹ The tritium-decay technique has also been used to generate vinylic and aryl cations.²⁴⁰

Besides the mechanisms already discussed, another mechanism, involving an *elimination-addition* sequence, has been observed in vinylic systems (a similar mechanism is known for aromatic substrates, p. 646). An example of a reaction involving this mechanism is the reaction of 1,2-dichloroethane with ArS^- and OEt^- to produce **74**. The mechanism may be formulated as:



The steps are the same as in the addition-elimination mechanism, but in reverse order. Evidence for this sequence²⁴¹ is as follows: (1) The reaction does not proceed without ethoxide ion, and the rate is dependent on the concentration of this ion and not on that of ArS^- . (2) Under the same reaction conditions, chloroacetylene gave **77** and **74**. (3) **77**, treated with ArS^- , gave no reaction but, when EtO^- was added, **74** was obtained. It is interesting that the elimination-addition mechanism has even been shown to occur in five- and six-membered cyclic systems, where triple bonds are greatly strained.²⁴² Note that both the addition-elimination and elimination-addition sequences, as shown above, lead to overall retention of configuration, since in each case both addition and elimination are anti.

²³⁸Maroni; Melloni; Modena *J. Chem. Soc., Chem. Commun.* **1972**, 857.

²³⁹Angelini; Hanack; Vermehren; Speranza *J. Am. Chem. Soc.* **1988**, *110*, 1298.

²⁴⁰For a review, see Cacace *Adv. Phys. Org. Chem.* **1970**, *8*, 79-149. See also Angelini; Fornarini; Speranza *J. Am. Chem. Soc.* **1982**, *104*, 4773; Fornarini; Speranza *Tetrahedron Lett.* **1984**, *25*, 869; *J. Am. Chem. Soc.* **1985**, *107*, 5358.

²⁴¹Truce; Boudakian; Heine; McManimie *J. Am. Chem. Soc.* **1956**, *78*, 2743; Flynn; Badiger; Truce *J. Org. Chem.* **1963**, *28*, 2298. See also Shainyan; Mirskova *J. Org. Chem. USSR* **1984**, *20*, 885, 1989; **1985**, *21*, 283.

²⁴²Montgomery; Scardiglia; Roberts *J. Am. Chem. Soc.* **1965**, *87*, 1917; Montgomery; Clouse; Crelrier; Applegate *J. Am. Chem. Soc.* **1967**, *89*, 3453; Caubere; Brunet *Tetrahedron* **1971**, *27*, 3515; Bottini; Corson; Fitzgerald; Frost *Tetrahedron* **1972**, *28*, 4883.

The elimination–addition sequence has also been demonstrated for certain reactions of saturated substrates, e.g., $\text{ArSO}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Ar}$.²⁴³ Treatment of this with ethoxide proceeds as follows:



Mannich bases (see 6-16) of the type $\text{RCOCH}_2\text{CH}_2\text{NR}_2$ similarly undergo nucleophilic substitution by the elimination–addition mechanism.²⁴⁴ The nucleophile replaces the NR_2 group.

The simple $\text{S}_{\text{N}}2$ mechanism has never been convincingly demonstrated for vinylic substrates.²⁴⁵

REACTIVITY

A large amount of work has been done on this subject. Though a great deal is known, much is still poorly understood, and many results are anomalous and hard to explain. In this section only approximate generalizations are attempted. The work discussed here, and the conclusions reached, pertain to reactions taking place in solution. Some investigations have also been carried out in the gas phase.²⁴⁶

The Effect of Substrate Structure

The effect on the reactivity of a change in substrate structure depends on the mechanism.

1. *Branching at the α and β carbons.* For the $\text{S}_{\text{N}}2$ mechanism, branching at either the α or the β carbon decreases the rate. Tertiary systems seldom²⁴⁷ react by the $\text{S}_{\text{N}}2$ mechanism and neopentyl systems react so slowly as to make such reactions, in general, synthetically useless.²⁴⁸ Table 10.3 shows average relative rates for some alkyl substrates.²⁴⁹ The reason for these low rates is almost certainly steric.²⁵⁰ The transition state **1** is more crowded when larger groups are close to the central carbon.

TABLE 10.3 Average relative $\text{S}_{\text{N}}2$ rates for some alkyl substrates²⁴⁹

R	Relative rate	R	Relative rate
Methyl	30	Isobutyl	0.03
Ethyl	1	Neopentyl	10^{-5}
Propyl	0.4	Allyl	40
Butyl	0.4	Benzyl	120
Isopropyl	0.025		

²⁴³Kader; Stirling *J. Chem. Soc.* **1962**, 3686. For another example, see Popov; Piskunova; Matvienko *J. Org. Chem. USSR* **1986**, 22, 1299.

²⁴⁴For an example, see Andrisano; Angeloni; De Maria; Tramontini *J. Chem. Soc. C* **1967**, 2307.

²⁴⁵For discussions, see Miller *Tetrahedron* **1977**, 33, 1211; Texier; Henri-Rousseau; Bourgois *Bull. Soc. Chim. Fr.* **1979**, II-11.86; Rappoport *Acc. Chem. Res.* **1981**, 14, 7-15; Rappoport; Avramovitch *J. Org. Chem.* **1982**, 47, 1397.

²⁴⁶See, for example DePuy; Gronert; Mullin; Bierbaum *J. Am. Chem. Soc.* **1990**, 112, 8650.

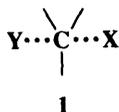
²⁴⁷For a reported example, see Edwards; Grieco *Can. J. Chem.* **1974**, 52, 3561.

²⁴⁸ $\text{S}_{\text{N}}2$ reactions on neopentyl tosylates have been conveniently carried out in the solvents HMPA and Me_2SO : Lewis; Gustafson; Erman *Tetrahedron Lett.* **1967**, 401; Paquette; Philips *Tetrahedron Lett.* **1967**, 4645; Stephenson; Solladié; Mosher *J. Am. Chem. Soc.* **1972**, 94, 4184; Anderson; Stephenson; Mosher *J. Am. Chem. Soc.* **1974**, 96, 3171.

²⁴⁹This table is from Streitwieser, Ref. 1, p. 13. Also see Table 9.2.

²⁵⁰For evidence, see Caldwell; Magnera; Kebarle *J. Am. Chem. Soc.* **1984**, 106, 959.

The tetrahedral mechanism for substitution at a carbonyl carbon is also slowed or blocked completely by α or β branching for similar reasons. For example, esters of the formula



$\text{R}_3\text{CCOOR}'$ cannot generally be hydrolyzed by the tetrahedral mechanism (see 0-10), nor can acids R_3CCOOH be easily esterified.²⁵¹ Synthetic advantage can be taken of this fact, for example, when in a molecule containing two ester groups only the less hindered one is hydrolyzed.

For the $\text{S}_{\text{N}}1$ mechanism, α branching increases the rate, as shown in Table 10.4.²⁵² We can explain this by the stability order of alkyl cations (tertiary > secondary > primary). Of course, the rates are not actually dependent on the stability of the ions, but on the difference in free energy between the starting compounds and the transition states. We use the Hammond postulate (p. 215) to make the assumption that the transition states resemble the cations and that anything (such as α branching) that lowers the free energy of the ions also lowers it for the transition states. For simple alkyl groups, the $\text{S}_{\text{N}}1$ mechanism is important under all conditions only for tertiary substrates.²⁵³ As previously indicated (p. 306), secondary substrates generally react by the $\text{S}_{\text{N}}2$ mechanism,²⁵⁴ except that the $\text{S}_{\text{N}}1$ mechanism may become important at high solvent polarities. Table 10.4 shows that isopropyl bromide reacts less than twice as fast as ethyl bromide in the relatively nonpolar 60% ethanol (compare this with the 10^4 ratio for *t*-butyl bromide, where the mechanism is certainly $\text{S}_{\text{N}}1$), but in the more polar water the rate ratio is 11.6. The 2-adamantyl system is an exception; it is a secondary system that reacts by the $\text{S}_{\text{N}}1$ mechanism because backside attack is hindered for steric reasons.²⁵⁵ Because there is no $\text{S}_{\text{N}}2$ component, this system provides an opportunity for comparing the pure $\text{S}_{\text{N}}1$ reactivity of secondary and tertiary substrates. It has been found that substitution of a methyl group for the α hydrogen of 2-adamantyl substrates (thus changing a secondary to a tertiary system) increases solvolysis rates by a factor of about 10^8 .²⁵⁶ Simple primary substrates react by the $\text{S}_{\text{N}}2$ mechanism (or with participation by neighboring alkyl or hydrogen) but not by the $\text{S}_{\text{N}}1$ mechanism, even when solvolyzed in

TABLE 10.4 Relative rates of solvolysis of RBr in two solvents²⁵²

RBr substrate	In 60% ethanol at 55°C	In water at 50°C
MeBr	2.08	1.05
EtBr	1.00	1.00
iso-PrBr	1.78	11.6
<i>t</i> -BuBr	2.41×10^4	1.2×10^6

²⁵¹For a molecular mechanics study of this phenomenon, see DeTar; Binzet; Darba *J. Org. Chem.* **1987**, 52, 2074.

²⁵²These values are from Streitwieser, Ref. 1, p. 43, where values are also given for other conditions. Methyl bromide reacts faster than ethyl bromide (and in the case of 60% ethanol, isopropyl bromide) because most of it (probably all) reacts by the $\text{S}_{\text{N}}2$ mechanism.

²⁵³For a report of an $\text{S}_{\text{N}}1$ mechanism at a primary carbon, see Zamashchikov; Bezbozhnaya; Chanyшева *J. Org. Chem. USSR* **1986**, 22, 1029.

²⁵⁴See Raber; Harris *J. Chem. Educ.* **1972**, 49, 60; Lambert; Putz; Mixan *J. Am. Chem. Soc.* **1972**, 94, 5132; Nordlander; McCrary *J. Am. Chem. Soc.* **1972**, 94, 5133; Ref. 38; Dietze; Jencks, Ref. 62; Dietze; Hariri; Khattak, Ref. 62.

²⁵⁵Fry; Harris; Bingham; Schleyer *J. Am. Chem. Soc.* **1970**, 92, 2540; Schleyer; Fry; Lam; Lancelot *J. Am. Chem. Soc.* **1970**, 92, 2542. See also Pritt; Whiting *J. Chem. Soc., Perkin Trans. 2* **1975**, 1458. For an ab initio molecular orbital study of the 2-adamantyl cation, see Dutler; Rauk; Sorensen; Whitworth *J. Am. Chem. Soc.* **1989**, 111, 9024.

²⁵⁶Fry; Engler; Schleyer *J. Am. Chem. Soc.* **1972**, 94, 4628. See also Gassman; Pascone *J. Am. Chem. Soc.* **1973**, 95, 7801.

solvents of very low nucleophilicity (e.g., trifluoroacetic acid or trifluoroethanol²⁵⁷), and even when very good leaving groups (e.g., OSO₂F) are present²⁵⁸ (see, however, p. 359).

For some tertiary substrates, the rate of S_N1 reactions is greatly increased by the relief of B strain in the formation of the carbocation (see p. 276). Except where B strain is involved, β branching has little effect on the S_N1 mechanism, except that carbocations with β branching undergo rearrangements readily. Of course, isobutyl and neopentyl are primary substrates, and for this reason react very slowly by the S_N1 mechanism, but not more slowly than the corresponding ethyl or propyl compounds.

To sum up, primary and secondary substrates generally react by the S_N2 mechanism and tertiary by the S_N1 mechanism. However, tertiary substrates seldom undergo nucleophilic substitution at all. Elimination is always a possible side reaction of nucleophilic substitutions (wherever a β hydrogen is present), and with tertiary substrates it usually predominates. With a few exceptions, nucleophilic substitutions at a tertiary carbon have little or no preparative value. However, tertiary substrates that can react by the SET mechanism (e.g., *p*-NO₂C₆H₄CMe₂Cl) give very good yields of substitution products when treated with a variety of nucleophiles.²⁵⁹

2. Unsaturation at the α carbon. Vinylic, acetylenic,²⁶⁰ and aryl substrates are very unreactive toward nucleophilic substitutions. For these systems both the S_N1 and S_N2 mechanisms are greatly slowed or stopped altogether. One reason that has been suggested for this is that *sp*² (and even more, *sp*) carbons have a higher electronegativity than *sp*³ carbons and thus a greater attraction for the electrons of the bond. As we have seen (p. 269), an *sp*—H bond has a higher acidity than an *sp*³—H bond, with that of an *sp*²—H bond in between. This is reasonable; the carbon retains the electrons when the proton is lost and an *sp* carbon, which has the greatest hold on the electrons, loses the proton most easily. But in nucleophilic substitution, the leaving group carries off the electron pair, so the situation is reversed and it is the *sp*³ carbon that loses the leaving group and the electron pair most easily. It may be recalled (p. 20) that bond distances decrease with increasing *s* character. Thus the bond length for a vinylic or aryl C—Cl bond is 1.73 Å compared with 1.78 Å for a saturated C—Cl bond. Other things being equal, a shorter bond is a stronger bond.

Of course we have seen (p. 337) that S_N1 reactions at vinylic substrates can be accelerated by α substituents that stabilize that cation, and that reactions by the tetrahedral mechanism can be accelerated by β substituents that stabilize the carbanion. Also, reactions at vinylic substrates can in certain cases proceed by addition–elimination or elimination–addition sequences (pp. 335, 338).

In contrast to such systems, substrates of the type RCOX are usually much *more* reactive than the corresponding RCH₂X. Of course, the mechanism here is almost always the tetrahedral one. Three reasons can be given for the enhanced reactivity of RCOX: (1) The carbonyl carbon has a sizable partial positive charge that makes it very attractive to nucleophiles. (2) In an S_N2 reaction a σ bond must break in the rate-determining step, which requires more energy than the shift of a pair of π electrons, which is what happens in a tetrahedral mechanism. (3) A trigonal carbon offers less steric hindrance to a nucleophile than a tetrahedral carbon.

For reactivity in aryl systems, see Chapter 13.

3. Unsaturation at the β carbon. S_N1 rates are increased when there is a double bond in the β position, so that allylic and benzylic substrates react rapidly (Table 10.5).²⁶¹ The

²⁵⁷Dafforn; Streitwieser *Tetrahedron Lett.* **1970**, 3159.

²⁵⁸Cafferata; Desvard; Sicre *J. Chem. Soc., Perkin Trans. 2* **1981**, 940.

²⁵⁹Kornblum et al. *J. Org. Chem.* **1987**, 52, 196.

²⁶⁰For a discussion of S_N reactions at acetylenic substrates, see Miller; Dickstein *Acc. Chem. Res.* **1976**, 9, 358-363.

²⁶¹Streitwieser, Ref. 1, p. 75. Actually, the figures for Ph₂CHOTs and Ph₃COTs are estimated from the general reactivity of these substrates.

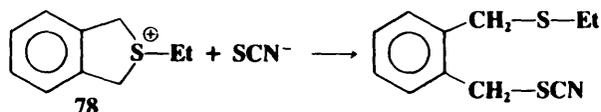
TABLE 10.5 Relative rates for the S_N1 reaction between ROTs and ethanol at 25°C²⁶¹

Group	Relative rate
Et	0.26
iso-Pr	0.69
CH ₂ =CHCH ₂	8.6
PhCH ₂	100
Ph ₂ CH	~10 ⁵
Ph ₃ C	~10 ¹⁰

reason is that allylic (p. 168) and benzylic (p. 169) cations are stabilized by resonance. As shown in Table 10.5, a second and a third phenyl group increase the rate still more, because these carbocations are more stable yet. It should be remembered that allylic rearrangements are possible with allylic systems.

In general, S_N1 rates at an allylic substrate are increased by any substituent in the 1 or 3 position that can stabilize the carbocation by resonance or hyperconjugation.²⁶² Among these are alkyl, aryl, and halo groups.

S_N2 rates for allylic and benzylic systems are also increased (see Table 10.3), probably owing to resonance possibilities in the transition state. Evidence for this in benzylic systems is that the rate of the reaction



was 8000 times slower than the rate with (PhCH₂)₂SEt⁺.²⁶³ The cyclic **78** does not have the proper geometry for conjugation in the transition state.

Triple bonds in the β position (in propargyl systems) have about the same effect as double bonds.²⁶⁴ Alkyl, aryl, halo, and cyano groups, among others, in the 3 position of allylic substrates increase S_N2 rates, owing to increased resonance in the transition state, but alkyl and halo groups in the 1 position decrease the rates because of steric hindrance.

4. α substitution. Compounds of the formula ZCH₂X, where Z = RO, RS, or R₂N undergo S_N1 reactions very rapidly,²⁶⁵ because of the increased resonance in the carbocation. These groups have an unshared pair on an atom directly attached to the positive carbon, which stabilizes the carbocation (p. 170). The field effects of these groups would be expected to decrease S_N1 rates (see Section 6, p. 344), so the resonance effect is far more important.

When Z in ZCH₂X is RCO,²⁶⁶ HCO, ROCO, NH₂CO, NC, or F₃C,²⁶⁷ S_N1 rates are decreased compared to CH₃X, owing to the electron-withdrawing field effects of these

²⁶²For a discussion of the relative reactivities of different allylic substrates, see DeWolfe; Young, in Patai, Ref. 178, pp. 683-688, 695-697.

²⁶³King; Tsang; Abdel-Malik; Payne *J. Am. Chem. Soc.* **1985**, *107*, 3224.

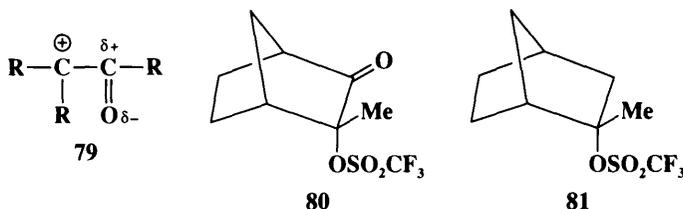
²⁶⁴Hatch; Chiola *J. Am. Chem. Soc.* **1951**, *73*, 360; Jacobs; Brill *J. Am. Chem. Soc.* **1953**, *75*, 1314.

²⁶⁵For a review of the reactions of α-haloamines, sulfides, and ethers, see Gross; Höft *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 335-355 [*Angew. Chem.* **79**, 358-378].

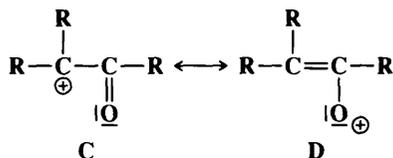
²⁶⁶For a review of α-halo ketones, including reactivity, see Verhé; De Kimpe, in Patai; Rappoport, Ref. 88, pt. 1, pp. 813-931. This review has been reprinted, and new material added, in De Kimpe; Verhé *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*; Wiley: New York, 1988, pp. 225-368.

²⁶⁷Allen; Jansen; Koshy; Mangru; Tidwell *J. Am. Chem. Soc.* **1982**, *104*, 207; Liu; Kuo; Shu *J. Am. Chem. Soc.* **1982**, *104*, 211; Gassman; Harrington *J. Org. Chem.* **1984**, *49*, 2258; Allen; Girdhar; Jansen; Mayo; Tidwell *J. Org. Chem.* **1986**, *51*, 1324; Allen; Kanagasabapathy; Tidwell *J. Am. Chem. Soc.* **1986**, *108*, 3470; Richard *J. Am. Chem. Soc.* **1989**, *111*, 1455.

groups. Furthermore, carbocations²⁶⁸ with an α CO or CN group are greatly destabilized because of the partial positive charge on the adjacent carbon (**79**). S_N1 reactions have been carried out on such compounds,²⁶⁹ but the rates are very low. For example, from a comparison of the solvolysis rates of **80** and **81**, a rate-retarding effect of $10^{7.3}$ was estimated for the



$C=O$ group.²⁷⁰ However, when a different kind of comparison is made: $RCO-CR_2X$ vs. HCR_2X (where $X =$ a leaving group), the RCO had only a small or negligible rate-retarding effect, indicating that resonance stabilization²⁷¹



may be offsetting the inductive destabilization for this group.²⁷² For a CN group also, the rate-retarding effect is reduced by this kind of resonance.²⁷³ A carbocation with an α COR group has been isolated.²⁷⁴

When S_N2 reactions are carried out on these substrates, rates are greatly increased for certain nucleophiles (e.g., halide or halide-like ions), but decreased or essentially unaffected by others.²⁷⁵ For example, α -chloroacetophenone ($PhCOCH_2Cl$) reacts with KI in acetone at 75° about 32,000 times faster than 1-chlorobutane,²⁷⁶ but α -bromoacetophenone reacts with the nucleophile triethylamine 0.14 times as fast as iodomethane.²⁷⁵ The reasons for this varying behavior are not clear, but those nucleophiles that form a "tight" transition state (one in which bond making and bond breaking have proceeded to about the same extent) are more likely to accelerate the reaction.²⁷⁷

²⁶⁸For reviews of such carbocations, see Bégué; Charpentier-Morize *Acc. Chem. Res.* **1980**, *13*, 207-212; Charpentier-Morize *Bull. Soc. Chim. Fr.* **1974**, 343-351.

²⁶⁹For reviews, see Creary *Acc. Chem. Res.* **1985**, *18*, 3-8; Creary; Hopkinson; Lee-Ruff *Adv. Carbocation Chem.* **1989**, *1*, 45-92; Charpentier-Morize; Bonnet-Delpon *Adv. Carbocation Chem.* **1989**, *1*, 219-253.

²⁷⁰Creary *J. Org. Chem.* **1979**, *44*, 3938.

²⁷¹**D**, which has the positive charge on the more electronegative atom, is less stable than **C**, according to rule c on p. 36, but it nevertheless seems to be contributing in this case.

²⁷²Creary; Geiger *J. Am. Chem. Soc.* **1982**, *104*, 4151; Creary *J. Am. Chem. Soc.* **1984**, *106*, 5568. See however Takeuchi; Yoshida; Ohga; Tsugen; Kitagawa *J. Org. Chem.* **1990**, *55*, 6063.

²⁷³Gassman; Saito; Talley *J. Am. Chem. Soc.* **1980**, *102*, 7613.

²⁷⁴Takeuchi; Kitagawa; Okamoto *J. Chem. Soc., Chem. Commun.* **1983**, *7*. See also Dao; Maleki; Hopkinson; Lee-Ruff *J. Am. Chem. Soc.* **1986**, *108*, 5237.

²⁷⁵Halvorsen; Songstad *J. Chem. Soc., Chem. Commun.* **1978**, 327.

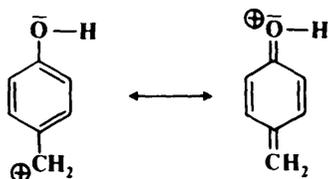
²⁷⁶Bordwell; Brannen *J. Am. Chem. Soc.* **1964**, *86*, 4645. For some other examples, see Conant; Kirner; Hussey *J. Am. Chem. Soc.* **1925**, *47*, 488; Sisti; Lowell *Can. J. Chem.* **1964**, *42*, 1896.

²⁷⁷For discussions of possible reasons, see McLennan; Pross *J. Chem. Soc., Perkin Trans. 2* **1984**, 981; Yousaf; Lewis *J. Am. Chem. Soc.* **1987**, *109*, 6137; Lee; Shim; Chung; Lee *J. Chem. Soc., Perkin Trans. 2* **1988**, 975; Yoh; Lee *Tetrahedron Lett.* **1988**, *29*, 4431.

When Z is SOR or SO₂R (e.g., α-halo sulfoxides and sulfones), nucleophilic substitution is retarded.²⁷⁸ The S_N1 mechanism is slowed by the electron-withdrawing effect of the SOR or SO₂R group,²⁷⁹ and the S_N2 mechanism presumably by the steric effect.

5. β substitution. For compounds of the type ZCH₂CH₂X, where Z is any of the groups listed in the previous section as well as halogen or phenyl, S_N1 rates are lower than for unsubstituted systems, because the resonance effects mentioned in Section 4 are absent, but the field effects are still there, though smaller. These groups in the β position do not have much effect on S_N2 rates unless they behave as neighboring groups and enhance the rate through anchimeric assistance,²⁸⁰ or unless their size causes the rates to decrease for steric reasons.²⁸¹

6. The effect of electron-donating and electron-withdrawing groups. If substitution rates of series of compounds *p*-ZC₆H₄CH₂X are measured, it is possible to study the electronic effects of groups Z on the reaction. Steric effects of Z are minimized or eliminated, because Z is so far from the reaction site. For S_N1 reactions electron-withdrawing Z decrease the rate and electron-donating Z increase it,²⁸² because the latter decrease the energy of the transition state (and of the carbocation) by spreading the positive charge, e.g.,

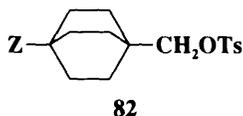


while electron-withdrawing groups concentrate the charge. The Hammett σ_p relationship (p. 278) correlates fairly successfully the rates of many of these reactions (with σ^+ instead of σ). ρ values are generally about -4 , which is expected for a reaction where a positive charge is created in the transition state.

For S_N2 reactions no such simple correlations are found.²⁸³ In this mechanism bond breaking is about as important as bond making in the rate-determining step, and substituents have an effect on both processes, often in opposite directions. The unsubstituted benzyl chloride and bromide solvolyze by the S_N2 mechanism.²⁸²

For Z = alkyl, the Baker-Nathan order (p. 68) is usually observed both for S_N1 and S_N2 reactions.

In para-substituted benzyl systems, steric effects have been removed, but resonance and field effects are still present. However, Holtz and Stock studied a system that removes not only steric effects but also resonance effects. This is the 4-substituted bicyclo[2.2.2]octylmethyl tosylate system (**82**).²⁸⁴ In this system steric effects are completely



²⁷⁸Bordwell; Jarvis *J. Org. Chem.* **1968**, *33*, 1182; Loepky; Chang *Tetrahedron Lett.* **1968**, 5414; Cinquini; Colonna; Landini; Maia *J. Chem. Soc., Perkin Trans. 2* **1976**, 996.

²⁷⁹See, for example Creary; Mehrsheikh-Mohammadi; Eggers *J. Am. Chem. Soc.* **1987**, *109*, 2435.

²⁸⁰For example, substrates of the type RSCH₂CH₂X are so prone to the neighboring-group mechanism that ordinary S_N2 reactions have only recently been observed: Sedaghat-Herati; McManus; Harris *J. Org. Chem.* **1988**, *53*, 2539.

²⁸¹See, for example, Okamoto; Kita; Araki; Shingu *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1913.

²⁸²Jorge; Kiyari; Miyata; Miller *J. Chem. Soc., Perkin Trans. 2* **1981**, *100*; Vitullo; Grabowski; Sridharan *J. Chem. Soc., Chem. Commun.* **1981**, 737.

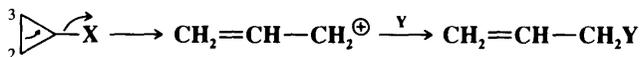
²⁸³See Sugden; Willis *J. Chem. Soc.* **1951**, 1360; Baker; Nathan *J. Chem. Soc.* **1935**, 1840; Hayami; Tanaka; Kurabayashi; Kotani; Kaji *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3091; Westaway; Waszczylo *Can. J. Chem.* **1982**, *60*, 2500; Lee; Sohn; Oh; Lee *Tetrahedron* **1986**, *42*, 4713.

²⁸⁴Holtz; Stock *J. Am. Chem. Soc.* **1965**, *87*, 2404.

absent, owing to the rigidity of the molecules, and only field effects operate. By this means Holtz and Stock showed that electron-withdrawing groups increase the rate of S_N2 reactions. This can be ascribed to stabilization of the transition state by withdrawal of some of the electron density.

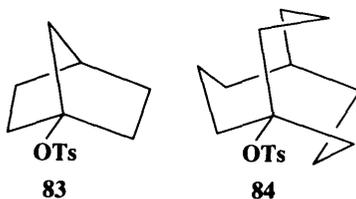
For substrates that react by the tetrahedral mechanism, electron-withdrawing groups increase the rate and electron-donating groups decrease it.

7. Cyclic substrates. Cyclopropyl substrates are extremely resistant to nucleophilic attack.²⁸⁵ For example, cyclopropyl tosylate solvolyzes about 10^6 times more slowly than cyclobutyl tosylate in acetic acid at 60°C .²⁸⁶ When such attack does take place, the result is generally not normal substitution (though exceptions are known,²⁸⁷ especially when an α stabilizing group such as aryl or alkoxy is present) but ring opening:²⁸⁶



There is much evidence that the ring opening is usually concerted with the departure of the leaving group²⁸⁸ (as in the similar case of cyclobutyl substrates, p. 324), from which we can conclude that if the 2,3 bond of the cyclopropane ring did not assist, the rates would be lower still. It has been estimated²⁸⁹ that without this assistance the rates of these already slow reactions would be further reduced by a factor of perhaps 10^{12} . For a discussion of the stereochemistry of the ring opening, see p. 1119. For larger rings, we have seen (p. 276) that, because of I strain, cyclohexyl substrates solvolyze slower than analogous compounds in which the leaving group is attached to a ring of 5 or of from 7 to 11 members.

8. Bridgeheads.¹⁰ The S_N2 mechanism is impossible at bridgeheads (p. 296). S_N1 reactions can take place if the rings are large enough (p. 301).²⁹⁰ Solvolytic reactivity at bridgehead positions spans a wide range; e.g., from $k = 4 \times 10^{-17} \text{ s}^{-1}$ for **83** (very slow)



to $3 \times 10^6 \text{ s}^{-1}$ for the [3.3.3] compound **84** (very fast);²⁹¹ a range of 22 orders of magnitude. Molecular mechanics calculations show that S_N1 bridgehead reactivity is determined by strain changes between the substrate and the carbocation intermediate.²⁹²

²⁸⁵For reviews, see Friedrich, in *Rapport The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley: New York, 1987, pp. 633-700; Aksenov; Terent'eva; Savinykh *Russ. Chem. Rev.* **1980**, *49*, 549-557.

²⁸⁶Roberts; Chambers *J. Am. Chem. Soc.* **1951**, *73*, 5034.

²⁸⁷For example, see Kirmse; Schütte *J. Am. Chem. Soc.* **1967**, *89*, 1284; Landgrebe; Becker *J. Am. Chem. Soc.* **1967**, *89*, 2505; Howell; Jewett *J. Am. Chem. Soc.* **1971**, *93*, 798; van der Vecht; Steinberg; de Boer *Recl. Trav. Chim. Pays-Bas* **1978**, *96*, 313; Engbert; Kirmse *Liebigs Ann. Chem.* **1980**, 1689; Turkenburg; de Wolf; Bickelhaupt; Stam; Konijn *J. Am. Chem. Soc.* **1982**, *104*, 3471; Banert *Chem. Ber.* **1985**, *118*, 1564; Vilmaier; Weber; Weidner *J. Org. Chem.* **1987**, *52*, 4921.

²⁸⁸For example, see Schleyer; Van Dine; Schöllkopf; Paust *J. Am. Chem. Soc.* **1966**, *88*, 2868; DePuy; Schnack; Hausser *J. Am. Chem. Soc.* **1966**, *88*, 3343; Jefford; Medary *Tetrahedron* **1967**, *23*, 4123; Jefford; Wojnarowski *Tetrahedron* **1969**, *25*, 2089; Hausser; Uchic *J. Org. Chem.* **1972**, *37*, 4087.

²⁸⁹Sliwinski; Su; Schleyer *J. Am. Chem. Soc.* **1972**, *94*, 133; Brown; Rao; Ravindranathan *J. Am. Chem. Soc.* **1978**, *100*, 7946.

²⁹⁰For a review of organic synthesis using bridgehead carbocations, see Kraus; Hon; Thomas; Laramay; Liras; Hanson *Chem. Rev.* **1989**, *89*, 1591-1598.

²⁹¹Bentley; Roberts *J. Org. Chem.* **1988**, *50*, 5852.

²⁹²Gleicher; Schleyer *J. Am. Chem. Soc.* **1967**, *89*, 582; Bingham; Schleyer *J. Am. Chem. Soc.* **1971**, *93*, 3189; Müller; Blanc; Mareda *Chimia* **1987**, *41*, 399; Müller; Mareda *Helv. Chim. Acta* **1987**, *70*, 1017; Ref. 291.

TABLE 10.6 List of groups in approximately descending order of reactivity toward S_N1 and S_N2 reactions*Z is RCO, HCO, ROCO, NH₂CO, NC, or a similar group*

S _N 1 reactivity	S _N 2 reactivity
Ar ₃ CX	Ar ₃ CX
Ar ₂ CHX	Ar ₂ CHX
ROCH ₂ X, RSCH ₂ X, R ₂ NCH ₂ X	ArCH ₂ X
R ₃ CX	ZCH ₂ X
ArCH ₂ X	—C=CCH ₂ X
—C=CCH ₂ X	RCH ₂ X ≈ RCHDX ≈ RCHDCH ₂ X
R ₂ CHX	R ₂ CHX
RCH ₂ X ≈ R ₃ CCH ₂ X	R ₃ CX
RCHDX	ZCH ₂ CH ₂ X
RCHDCH ₂ X	R ₃ CCH ₂ X
—C=CX	—C=CX
ZCH ₂ X	
ZCH ₂ CH ₂ X	ArX
ArX	Bridgehead-X
[2.2.1] Bridgehead-X	

TABLE 10.7 The more important synthetic reactions of Chapter 10 that take place by the S_N2 mechanism (R = primary, often secondary, alkyl). Catalysts are not shown^a

0-1	RX + OH ⁻ → ROH
0-12	RX + OR' ⁻ → ROR'
0-13	$\begin{array}{c} \quad \\ -C - C- \\ \quad \\ Cl \quad OH \end{array} \longrightarrow \begin{array}{c} \quad \\ -C - C- \\ \diagdown \quad / \\ O \end{array}$
0-14	R-OSO ₂ OR' + OR' ⁻ → ROR'
0-16	2ROH → ROR
0-18	$\begin{array}{c} \quad \\ -C - C- \\ \diagdown \quad / \\ O \end{array} \longrightarrow \begin{array}{c} \quad \\ -C - C- \\ \quad \\ OH \quad OR \end{array}$
0-19	R ₃ O ⁺ + R'OH → ROR'
0-24	RX + R'COO ⁻ → R'COOR
0-31	RX + OOH ⁻ → ROOH
0-35	RX + SH ⁻ → RSH
0-36	RX + R'S ⁻ → RSR'
0-38	RX + S ₂ ²⁻ → RSSR
0-41	RX + SO ₃ ²⁻ → RSO ₂ O ⁻
0-42	RX + SCN ⁻ → RSCN
0-43	RX + R' ₂ NH → RR' ₂ N
0-43	RX + R' ₃ N → RR' ₃ N ⁺ X ⁻
0-44	RX + (CH ₂) ₆ N ₄ → N ₂ (CH ₂) ₆ NR ⁺ X ⁻ $\xrightarrow{H^+}$ RNH ₂
0-49	$\begin{array}{c} \quad \\ -C - C- \\ \diagdown \quad / \\ O \end{array} + RNH_2 \longrightarrow \begin{array}{c} \quad \\ -C - C- \\ \quad \\ OH \quad NHR \end{array}$
0-58	RX + R'CONH ⁻ → RNHCOR'

TABLE 10.7 (Continued)

0-60	$RX + NO_2^- \rightarrow RNO_2 + RONO$
0-61	$RX + N_3^- \rightarrow RN_3$
0-62	$RX + NCO^- \rightarrow RNCO$
0-62	$RX + NCS^- \rightarrow RNCS$
0-65	$RX + X'^- \rightarrow RX'$
0-66	$R-OSO_2OR' + X^- \rightarrow RX$
0-67	$ROH + PCl_5 \rightarrow RCl$
0-68	$ROR' + 2HI \rightarrow RI + R'I$
0-69	$\begin{array}{c} \quad \\ -C \quad C- \\ \quad \\ \quad O \end{array} + HX \longrightarrow \begin{array}{c} \quad \\ -C \quad C- \\ \quad \\ OH \quad X \end{array}$
0-70	$R-O-COR' + LiI \rightarrow RI + R'COO^-$
0-76	$RX + LiAlH_4 \rightarrow RH$
0-77	$R-OSO_2R' + LiAlH_4 \rightarrow RH$
0-80	$\begin{array}{c} \quad \\ -C \quad C- \\ \quad \\ \quad O \end{array} + LiAlH_4 \longrightarrow \begin{array}{c} \quad \\ -C \quad C- \\ \quad \\ OH \quad H \end{array}$
0-87	$RX + R'_2CuLi \rightarrow RR'$
0-93	$\begin{array}{c} \quad \\ -C \quad C- \\ \quad \\ \quad O \end{array} + RMgX \longrightarrow \begin{array}{c} \quad \\ -C \quad C- \\ \quad \\ OH \quad R \end{array}$
0-94	$RX + \overset{\ominus}{C}(CO_2R')_2 \rightarrow RCH(CO_2R')_2$
0-95	$RX + R'\overset{\ominus}{C}H-COR' \rightarrow RCR''-COR'$
0-96	$RX + R'\overset{\ominus}{C}HCOO^- \rightarrow RR'CHCOO^-$
0-97	$RX + \begin{array}{c} \ominus \\ \\ S \\ \\ H \end{array} \begin{array}{c} \diagup \\ \diagdown \end{array} \longrightarrow \begin{array}{c} R \\ \\ S \\ \\ H \end{array} \begin{array}{c} \diagup \\ \diagdown \end{array}$
0-100	$RX + R'C \equiv C^\ominus \rightarrow RC \equiv CR'$
0-101	$RX + CN^- \rightarrow RCN$

^aThis is schematic list only. Some of these reactions may also take place by other mechanisms and the scope may vary greatly. See the discussion of each reaction for details.

9. Deuterium substitution. α and β secondary isotope effects affect the rate in various ways (p. 228). The measurement of α secondary isotope effects provides a means of distinguishing between S_N1 and S_N2 mechanisms, since for S_N2 reactions the values range from 0.95 to 1.06 per α D, while for S_N1 reactions the values are higher.²⁹³ This method is especially good because it provides the minimum of perturbation of the system under study; changing from α H to α D hardly affects the reaction, while other probes, such as changing a substituent or the polarity of the solvent, may have a much more complex effect.

Table 10.6 is an approximate listing of groups in order of S_N1 and S_N2 reactivity. Table 10.7 shows the main reactions that proceed by the S_N2 mechanism (if R = primary or, often, secondary alkyl); Table 10.8 shows the main reactions that proceed by the tetrahedral mechanism.

²⁹³Ref. 39. For a review of secondary isotope effects in S_N2 reactions, see Westaway *Isot. Org. Chem.* **1987**, *7*, 275-392.

TABLE 10.8 The more important synthetic reactions of Chapter 10 that take place by the tetrahedral mechanism. Catalysts are not shown

0-8	$\text{RCOX} + \text{H}_2\text{O} \rightarrow \text{RCOOH}$
0-9	$\text{RCOOCOR}' + \text{H}_2\text{O} \rightarrow \text{RCOOH} + \text{R}'\text{COOH}$
0-10	$\text{RCO}_2\text{R}' + \text{H}_2\text{O} \rightarrow \text{RCOOH} + \text{R}'\text{OH}$
0-11	$\text{RCONR}'_2 + \text{H}_2\text{O} \rightarrow \text{RCOOH} + \text{R}'_2\text{NH} \quad (\text{R}' = \text{H, alkyl, aryl})$
0-20	$\text{RCOX} + \text{R}'\text{OH} \rightarrow \text{RCO}_2\text{R}'$
0-21	$\text{RCOOCOR} + \text{R}'\text{OH} \rightarrow \text{RCO}_2\text{R}'$
0-22	$\text{RCOOH} + \text{R}'\text{OH} \rightarrow \text{RCO}_2\text{R}'$
0-23	$\text{RCO}_2\text{R}' + \text{R}''\text{OH} \rightarrow \text{RCO}_2\text{R}'' + \text{R}'\text{OH}$
0-27	$\text{RCOX} + \text{R}'\text{COO}^- \rightarrow \text{RCOOCOR}'$
0-31	$\text{RCOX} + \text{H}_2\text{O}_2 \rightarrow \text{RCO}_3\text{H}$
<hr/>	
0-37	$\text{RCOX} + \text{R}'\text{SH} \rightarrow \text{RCOSR}'$
0-52	$\text{RCOX} + \text{NHR}'_2 \rightarrow \text{RCONR}'_2 \quad (\text{R}' = \text{H, alkyl, aryl})$
0-53	$\text{RCOOCOR} + \text{NHR}'_2 \rightarrow \text{RCONR}'_2 \quad (\text{R}' = \text{H, alkyl, aryl})$
0-54	$\text{RCOOH} + \text{NHR}'_2 \xrightarrow[\text{agent}]{\text{coupling}} \text{RCONR}'_2 \quad (\text{R}' = \text{H, alkyl, aryl})$
0-55	$\text{RCO}_2\text{R}' + \text{NHR}''_2 \quad (\text{R}'' = \text{H, alkyl, aryl})$
0-74	$\text{RCOOH} + \text{SOCl}_2 \rightarrow \text{RCOCl}$
0-83	$\text{RCOX} + \text{LiAlH}(\text{O}-t\text{-Bu})_3 \rightarrow \text{RCHO}$
0-85	$\text{RCONR}'_2 + \text{LiAlH}_4 \rightarrow \text{RCHO}$
0-104	$\text{RCOX} + \text{R}_2\text{CuLi} \rightarrow \text{RCOR}'$
0-108	$2\text{RCH}_2\text{CO}_2\text{R}' \rightarrow \text{RCH}_2\text{COCHR}'\text{CO}_2\text{R}'$

The Effect of the Attacking Nucleophile²⁹⁴

Any species that has an unshared pair (i.e., any Lewis base) can be a nucleophile, whether it is neutral or has a negative charge. The rates of $\text{S}_{\text{N}}1$ reactions are independent of the identity of the nucleophile, since it does not appear in the rate-determining step.²⁹⁵ This may be illustrated by the effect of changing the nucleophile from H_2O to OH^- for a primary and a tertiary substrate. For methyl bromide, which reacts by an $\text{S}_{\text{N}}2$ mechanism, the rate is multiplied more than 5000 by the change to the more powerful nucleophile OH^- , but for *t*-butyl bromide, which reacts by an $\text{S}_{\text{N}}1$ mechanism, the rate is unaffected.²⁹⁶ A change in nucleophile can, however, change the *product* of an $\text{S}_{\text{N}}1$ reaction. Thus solvolysis of benzyl tosylate in methanol gives benzyl methyl ether (the nucleophile is the solvent methanol). If the more powerful nucleophile Br^- is added, the rate is unchanged, but the product is now benzyl bromide.

For $\text{S}_{\text{N}}2$ reactions in solution there are four main principles that govern the effect of the nucleophile on the rate, though the nucleophilicity order is not invariant but depends on substrate, solvent, leaving group, etc.

1. A nucleophile with a negative charge is always a more powerful nucleophile than its conjugate acid (assuming the latter is also a nucleophile). Thus OH^- is more powerful than H_2O , NH_2^- more powerful than NH_3 , etc.

²⁹⁴For a monograph, see Harris; McManus *Nucleophilicity*; American Chemical Society: Washington, 1987. For reviews, see Klumpp *Reactivity in Organic Chemistry*; Wiley: New York, 1982, pp. 145-167, 181-186; Hudson, in Klopman *Chemical Reactivity and Reaction Paths*; Wiley: New York, 1974, pp. 167-252.

²⁹⁵It is, however, possible to measure the rates of reaction of nucleophiles with fairly stable carbocations: see Ritchie *Acc. Chem. Res.* **1972**, *5*, 348-354; Ritchie; Minasz; Kamego; Sawada *J. Am. Chem. Soc.* **1977**, *99*, 3747; McClelland; Banait; Steenken *J. Am. Chem. Soc.* **1986**, *108*, 7023.

²⁹⁶Bateman; Cooper; Hughes; Ingold *J. Chem. Soc.* **1940**, 925.

2. In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is approximately in order of basicity, though basicity is thermodynamically controlled and nucleophilicity is kinetically controlled. So an approximate order of nucleophilicity is $\text{NH}_2^- > \text{RO}^- > \text{OH}^- > \text{R}_2\text{NH} > \text{ArO}^- > \text{NH}_3 > \text{pyridine} > \text{F}^- > \text{H}_2\text{O} > \text{ClO}_4^-$, and another is $\text{R}_3\text{C}^- > \text{R}_2\text{N}^- > \text{RO}^- > \text{F}^-$ (see Table 8.1). This type of correlation works best when the structures of the nucleophiles being compared are similar, as with a set of substituted phenoxides. Within such a series, linear relationships can often be established between nucleophilic rates and $\text{p}K$ values.²⁹⁷

3. Going down the periodic table, nucleophilicity increases, though basicity decreases. Thus the usual order of halide nucleophilicity is $\text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$ (though as we shall see below, this order is solvent-dependent). Similarly, any sulfur nucleophile is more powerful than its oxygen analog, and the same is true for phosphorus vs. nitrogen. The main reason for this distinction between basicity and nucleophilic power is that the smaller negatively charged nucleophiles are more solvated by the usual polar protic solvents; that is, because the negative charge of Cl^- is more concentrated than the charge of I^- , the former is more tightly surrounded by a shell of solvent molecules that constitute a barrier between it and the substrate. This is most important for protic polar solvents in which the solvent may be hydrogen-bonded to small nucleophiles. Evidence for this is that many nucleophilic substitutions with small negatively charged nucleophiles are much more rapid in aprotic polar solvents than in protic ones²⁹⁸ and that, in DMF, an aprotic solvent, the order of nucleophilicity was $\text{Cl}^- > \text{Br}^- > \text{I}^-$.²⁹⁹ Another experiment was the use of $\text{Bu}_4\text{N}^+ \text{X}^-$ and LiX as nucleophiles in acetone, where X^- was a halide ion. The halide ion in the former salt is much less associated than in LiX . The relative rates with LiX were Cl^- , 1; Br^- , 5.7; I^- , 6.2, which is in the normal order, while with $\text{Bu}_4\text{N}^+ \text{X}^-$, where X^- is much freer, the relative rates were Cl^- , 68; Br^- , 18; I^- , 3.7.³⁰⁰ In a further experiment halide ions were allowed to react with the molten salt $(n\text{-C}_5\text{H}_{11})_4\text{N}^+ \text{X}^-$ at 180°C in the absence of a solvent.³⁰¹ Under these conditions, where the ions are unsolvated and unassociated, the relative rates were Cl^- , 620; Br^- , 7.7; I^- , 1. In the gas phase, where no solvent is present, an approximate order of nucleophilicity was found to be $\text{OH}^- > \text{F}^- \sim \text{MeO}^- > \text{MeS}^- \gg \text{Cl}^- > \text{CN}^- > \text{Br}^-$,³⁰² providing further evidence that solvation is responsible for the effect in solution.

However, solvation is not the entire answer since, even for *uncharged* nucleophiles, nucleophilicity increases going down a column in the periodic table. These nucleophiles are not so greatly solvated and changes in solvent do not greatly affect their nucleophilicity.³⁰³ To explain these cases we may use the principle of hard and soft acids and bases (p. 261).³⁰⁴ The proton is a hard acid, but an alkyl substrate (which may be considered to act as a Lewis acid toward the nucleophile considered as a base) is a good deal softer. According to the principle given on p. 263, we may then expect the alkyl group to prefer softer nucleophiles than the proton does. Thus the larger, more polarizable (softer) nucleophiles have a greater (relative) attraction toward an alkyl carbon than toward a proton.

²⁹⁷See, for example, Jokinen; Luukkonen; Ruostesuo; Virtanen; Koskikallio *Acta Chem. Scand.* **1971**, 25, 3367; Bordwell; Hughes *J. Org. Chem.* **1983**, 48, 2206. *J. Am. Chem. Soc.* **1984**, 106, 3234.

²⁹⁸Parker *J. Chem. Soc.* **1961**, 1328 has a list of about 20 such reactions.

²⁹⁹Weaver; Hutchison *J. Am. Chem. Soc.* **1964**, 86, 261; See also Rodewald; Mahendran; Bear; Fuchs *J. Am. Chem. Soc.* **1968**, 90, 6698; Fuchs; Mahendran *J. Org. Chem.* **1971**, 36, 730; Müller; Siegfried *Helv. Chim. Acta* **1971**, 54, 2675; Liotta; Grisdale; Hopkins *Tetrahedron Lett.* **1975**, 4205; Bordwell; Hughes *J. Org. Chem.* **1981**, 46, 3570. For a contrary result in liquid SO_2 , see Lichtin; Puar; Wasserman *J. Am. Chem. Soc.* **1967**, 89, 6677.

³⁰⁰Winstein; Savedoff; Smith; Stevens; Gall *Tetrahedron Lett.* **1960**, no. 9, 24.

³⁰¹Gordon; Varughese *Chem. Commun.* **1971**, 1160. See also Ford; Hauri; Smith *J. Am. Chem. Soc.* **1974**, 96, 4316.

³⁰²Olmstead; Brauman *J. Am. Chem. Soc.* **1977**, 99, 4219. See also Tanaka; Mackay; Payzant; Bohme *Can. J. Chem.* **1976**, 54, 1643.

³⁰³Parker *J. Chem. Soc.* **1961**, 4398.

³⁰⁴Pearson *Surv. Prog. Chem.* **1969**, 5, 1-52, pp. 21-38.

4. The freer the nucleophile, the greater the rate.³⁰⁵ We have already seen one instance of this.³⁰⁰ Another is that the rate of attack by $(\text{EtOOC})_2\text{CBu}^- \text{Na}^+$ in benzene was increased by the addition of substances (for example, 1,2-dimethoxyethane, adipamide) that specifically solvated the Na^+ and thus left the anion freer.³⁰⁶ In a nonpolar solvent such as benzene, salts such as $(\text{EtOOC})_2\text{CBu}^- \text{Na}^+$ usually exist as ion-pair aggregations of large molecular weights.³⁰⁷ Similarly, it was shown that the half-life of the reaction between $\text{C}_6\text{H}_5\text{COCH}_2\text{Et}^-$ and ethyl bromide depended on the positive ion: K^+ , 4.5×10^{-3} ; Na^+ , 3.9×10^{-5} ; Li^+ , 3.1×10^{-7} .³⁰⁸ Presumably, the potassium ion leaves the negative ion most free to attack most rapidly. Further evidence is that in the gas phase,³⁰⁹ where nucleophilic ions are completely free, without solvent or counterion, reactions take place orders of magnitude faster than the same reactions in solution.³⁰² It has proven possible to measure the rates of reaction of OH^- with methyl bromide in the gas phase, with OH^- either unsolvated or solvated with one, two, or three molecules of water.³¹⁰ The rates were, with the number of water molecules in parentheses: (0) 1.0×10^{-9} ; (1) 6.3×10^{-10} ; (2) 2×10^{-12} ; (3) $2 \times 10^{-13} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. This provides graphic evidence that solvation of the nucleophile decreases the rate. The rate of this reaction in aqueous solution is $2.3 \times 10^{-25} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. Similar results were found for other nucleophiles and other solvents.³¹¹ In solution too, studies have been made of the effect of solvation of the nucleophile by a specific number of water molecules. When the salt $(n\text{-C}_6\text{H}_{13})_4\text{N}^+ \text{F}^-$ was allowed to react with *n*-octyl methanesulfonate, the relative rate fell from 822 for no water molecules to 96 for 1.5 water molecules to 1 for 6 water molecules.³¹²

In Chapter 3 we saw that cryptands specifically solvate the alkali metal portion of salts like KF, KOAc, etc. Synthetic advantage can be taken of this fact to allow anions to be freer, thus increasing the rates of nucleophilic substitutions and other reactions (see p. 364).

However, the four rules given above do not always hold. One reason is that steric influences often play a part. For example, the *t*-butoxide ion Me_3CO^- is a stronger base than OH^- or OEt^- , but a much poorer nucleophile because its large bulk hinders it from closely approaching a substrate.

The following overall nucleophilicity order for $\text{S}_\text{N}2$ mechanisms (in protic solvents) was given by Edwards and Pearson:³¹³ $\text{RS}^- > \text{ArS}^- > \text{I}^- > \text{CN}^- > \text{OH}^- > \text{N}_3^- > \text{Br}^- > \text{ArO}^- > \text{Cl}^- > \text{pyridine} > \text{AcO}^- > \text{H}_2\text{O}$. A quantitative relationship³¹⁴ (the *Swain-Scott equation*) has been worked out similar to the linear free-energy equations considered in Chapter 9:³¹⁵

$$\log \frac{k}{k_0} = sn$$

³⁰⁵For a review of the effect of nucleophile association on nucleophilicity, see Guibe; *Bull. Soc. Chim. Fr.* **1975**, 933-948.

³⁰⁶Zaugg; Horrom; Borgwardt *J. Am. Chem. Soc.* **1960**, *82*, 2895; Zaugg; Leonard *J. Org. Chem.* **1972**, *37*, 2253. See also Solov'yanov; Dem'yanov; Beletskaya; Reutov *J. Org. Chem. USSR* **1976**, *12*, 714, 2215; Solov'yanov; Ahmed; Beletskaya; Reutov *J. Org. Chem. USSR* **1987**, *23*, 1243; Jackman; Lange *J. Am. Chem. Soc.* **1981**, *103*, 4494.

³⁰⁷See, for example Williard; Carpenter *J. Am. Chem. Soc.* **1986**, *108*, 462.

³⁰⁸Zook; Gumby *J. Am. Chem. Soc.* **1960**, *82*, 1386. See also Cacciapaglia; Mandolini *J. Org. Chem.* **1988**, *53*, 2579.

³⁰⁹For some other measurements of rates of $\text{S}_\text{N}2$ reactions in the gas phase, see Barlow; Van Doren; Bierbaum *J. Am. Chem. Soc.* **1988**, *110*, 7240; Merkel; Havlas; Zahradna'ak *J. Am. Chem. Soc.* **1988**, *110*, 8355.

³¹⁰Bohme; Mackay *J. Am. Chem. Soc.* **1981**, *103*, 978; Bohme; Raksit *J. Am. Chem. Soc.* **1984**, *106*, 3447. See also Hierl; Ahrens; Henchman; Viggiano; Paulson; Clary *J. Am. Chem. Soc.* **1986**, *108*, 3142.

³¹¹Bohme; Raksit *Can. J. Chem.* **1985**, *63*, 3007.

³¹²Landini; Maia; Rampoldi *J. Org. Chem.* **1989**, *54*, 328.

³¹³Edwards; Pearson *J. Am. Chem. Soc.* **1962**, *84*, 16.

³¹⁴Swain; Scott *J. Am. Chem. Soc.* **1953**, *75*, 141.

³¹⁵This is not the only equation that has been devised in an attempt to correlate nucleophilic reactivity. For reviews of attempts to express nucleophilic power quantitatively, see Ritchie *Pure Appl. Chem.* **1978**, *50*, 1281-1290; Duboc, in Chapman; *Shorter Correlation Analysis in Chemistry: Recent Advances*; Plenum: New York, 1978, pp. 313-355; Ibne-Rasa *J. Chem. Educ.* **1967**, *44*, 89-94. See also Hoz; Speizman *J. Org. Chem.* **1983**, *48*, 2904; Kawazoc; Ninomiya; Kohda; Kimoto *Tetrahedron Lett.* **1986**, *27*, 2897; Kevill; Fujimoto *J. Chem. Res. (S)* **1988**, 408.

where n is the nucleophilicity of a given group, s is the sensitivity of a substrate to nucleophilic attack, and k_0 is the rate for H_2O , which is taken as the standard and for which n is assigned a value of zero. s is defined as 1.0 for methyl bromide. Table 10.9 contains values of n for some common nucleophiles.³¹⁶ The order is similar to that of Edwards and Pearson. The Swain–Scott equation can be derived from Marcus theory.³¹⁷

It is now evident that an absolute order of either nucleophilicity³¹⁸ or leaving-group ability, even in the gas phase where solvation is not a factor, does not exist, because they have an effect on each other. When the nucleophile and leaving group are both hard or both soft, the reaction rates are relatively high, but when one is hard and the other soft, rates are reduced.³¹⁹ Although this effect is smaller than the effects in paragraphs 1 and 4 above, it still prevents an absolute scale of either nucleophilicity or leaving-group ability. There has been controversy as to whether the selectivity of a reaction should increase with decreasing reactivity of a series of nucleophiles, or whether the opposite holds. There is evidence for both views.³²⁰

For substitution at a carbonyl carbon, the nucleophilicity order is not the same as it is at a saturated carbon, but follows the basicity order more closely. The reason is presumably that the carbonyl carbon, with its partial positive charge, resembles a proton more than does the carbon at a saturated center. That is, a carbonyl carbon is a much harder acid than a saturated carbon. The following nucleophilicity order for these substrates has been determined:³²¹ $\text{Me}_2\text{C}=\text{NO}^- > \text{EtO}^- > \text{MeO}^- > \text{OH}^- > \text{OAr}^- > \text{N}_3^- > \text{F}^- > \text{H}_2\text{O} > \text{Br}^- \sim \text{I}^-$. Soft bases are ineffective at a carbonyl carbon.³²² In a reaction carried out in the gas phase with alkoxide nucleophiles OR^- solvated by only one molecule of an alcohol $\text{R}'\text{OH}$, it was found that both RO^- and $\text{R}'\text{O}^-$ attacked the formate substrate (HCOOR'') about equally, though in the unsolvated case, the more basic alkoxide is the better nucleophile.³²³ In this study, the product ion $\text{R}''\text{O}^-$ was also solvated by one molecule of ROH or $\text{R}'\text{OH}$.

If, adjacent to the attacking atom on the nucleophile, there is an atom containing one or more unshared pairs, the nucleophilicity is enhanced. Examples of such nucleophiles are HO_2^- , $\text{Me}_2\text{C}=\text{NO}^-$, NH_2NH_2 , etc. This is called the *alpha effect*,³²⁴ and the reasons for it

TABLE 10.9 Nucleophilicities of some common reagents³¹⁶

Nucleophile	n	Nucleophile	n
SH^-	5.1	Br^-	3.5
CN^-	5.1	PhO^-	3.5
I^-	5.0	AcO^-	2.7
PhNH_2	4.5	Cl^-	2.7
OH^-	4.2	F^-	2.0
N_3^-	4.0	NO_3^-	1.0
Pyridine	3.6	H_2O	0.0

³¹⁶From Wells *Chem. Rev.* **1963**, 63, 171-219, p. 212. See also Koskikallio *Acta Chem. Scand.* **1969**, 23, 1477, 1490.

³¹⁷Albery; Kreevoy *Adv. Phys. Org. Chem.* **1978**, 16, 87-157, pp. 113-115.

³¹⁸However, for a general model of intrinsic nucleophilicity in the gas phase, see Pellerite; Brauman *J. Am. Chem. Soc.* **1983**, 105, 2672.

³¹⁹Olmstead; Brauman, Ref. 302.

³²⁰For discussions, see Dietze; Jencks *J. Am. Chem. Soc.* **1989**, 111, 5880.

³²¹Hudson; Green *J. Chem. Soc.* **1962**, 1055; Bender; Glasson *J. Am. Chem. Soc.* **1959**, 81, 1590; Jencks; Gilchrist *J. Am. Chem. Soc.* **1968**, 90, 2622.

³²²For theoretical treatments of nucleophilicity at a carbonyl carbon, see Buncl; Shaik; Um; Wolfe *J. Am. Chem. Soc.* **1988**, 110, 1275, and references cited therein.

³²³Baer; Stoutland; Brauman *J. Am. Chem. Soc.* **1989**, 111, 4097.

³²⁴For reviews, see Grekov; Veselov *Russ. Chem. Rev.* **1978**, 47, 631-648; Fina; Edwards *Int. J. Chem. Kinet.* **1973**, 5, 1-26.

are not completely understood. Several possible explanations have been offered.³²⁵ One is that the ground state of the nucleophile is destabilized by repulsion between the adjacent pairs of electrons;³²⁶ another is that the transition state is stabilized by the extra pair of electrons;³²⁷ a third is that the adjacent electron pair reduces solvation of the nucleophile.³²⁸ Evidence supporting the third explanation is that there was no alpha effect in the reaction of HO_2^- with methyl formate in the gas phase,³²⁹ though HO_2^- shows a strong alpha effect in solution. The alpha effect is substantial for substitution at a carbonyl or other unsaturated carbon, at some inorganic atoms,³³⁰ and for reactions of a nucleophile with a carbocation,³³¹ but is generally smaller or absent entirely for substitution at a saturated carbon.³³²

The Effect of the Leaving Group

1. *At a saturated carbon.* The leaving group comes off more easily the more stable it is as a free entity. This is usually inverse to its basicity, and the best leaving groups are the weakest bases. Thus iodide is the best leaving group among the halides and fluoride the poorest. Since XH is always a weaker base than X^- , nucleophilic substitution is always easier at a substrate RXH^+ than at RX . An example of this effect is that OH and OR are not leaving groups from ordinary alcohols and ethers but can come off when the groups are protonated, that is, converted to ROH_2^+ or RORH^+ .³³³ Reactions in which the leaving group does not come off until it has been protonated have been called SN1cA or SN2cA , depending on whether after protonation the reaction is an SN1 or SN2 process (these designations are often shortened to A1 and A2). The cA stands for conjugate acid, since the substitution takes place on the conjugate acid of the substrate. The IUPAC designations for these mechanisms are, respectively, $\text{A}_h + \text{D}_N + \text{A}_N$ and $\text{A}_h + \text{A}_N\text{D}_N$; that is, the same designations as SN1 and SN2 , with A_h to show the preliminary step. When another electrophile assumes the role of the proton, the symbol A_e is used instead. The ions ROH_2^+ and RORH^+ can be observed as stable entities at low temperatures in super-acid solutions.³³⁴ At higher temperatures they cleave to give carbocations.

It is obvious that the best nucleophiles (e.g., NH_2^- , OH^-) cannot take part in SN1cA or SN2cA processes, because they would be converted to their conjugate acids under the acidic conditions necessary to protonate the leaving groups.³³⁵ Because SN1 reactions do not require powerful nucleophiles but do require good leaving groups, most of them take place under

³²⁵For discussions, see Wolfe; Mitchell; Schlegel; Minot; Eisenstein *Tetrahedron Lett.* **1982**, 23, 615; Hoz; Buncel *Isr. J. Chem.* **1985**, 26, 313.

³²⁶Buncel; Hoz *Tetrahedron Lett.* **1983**, 24, 4777. For evidence that this is not the sole cause, see Oac; Kadoma *Can. J. Chem.* **1986**, 64, 1184.

³²⁷See Hoz *J. Org. Chem.* **1982**, 47, 3545; Laloi-Diard; Verchere; Gosselin; Terrier *Tetrahedron Lett.* **1984**, 25, 1267.

³²⁸For other explanations, see Hudson; Hansell; Wolfe; Mitchell *J. Chem. Soc., Chem. Commun.* **1985**, 1406; Shustov *Doklad. Chem.* **1985**, 280, 80. For a discussion, see Herschlag; Jencks *J. Am. Chem. Soc.* **1990**, 112, 1951.

³²⁹DePuy; Della; Filley; Grabowski; Bierbaum *J. Am. Chem. Soc.* **1983**, 105, 2481; Buncel; Um *J. Chem. Soc., Chem. Commun.* **1986**, 595; Terrier; Degorre; Kiffer; Laloi *Bull. Soc. Chim. Fr.* **1988**, 415. For some evidence against this explanation, see Moss; Swarup; Ganguli *J. Chem. Soc., Chem. Commun.* **1987**, 860.

³³⁰For example, see Kice; Legan *J. Am. Chem. Soc.* **1973**, 95, 3912.

³³¹Dixon; Bruce *J. Am. Chem. Soc.* **1971**, 93, 3248, 6592.

³³²Gregory; Bruce *J. Am. Chem. Soc.* **1967**, 89, 4400; Oac; Kadoma; Yano *Bull. Chem. Soc. Jpn.* **1969**, 42, 1110; McIsaac; Subbaraman; Subbaraman; Mulhausen; Behrman *J. Org. Chem.* **1972**, 37, 1037. See, however, Beale *J. Org. Chem.* **1972**, 37, 3871; Buncel; Wilson; Chuaqui *J. Am. Chem. Soc.* **1982**, 104, 4896, *Int. J. Chem. Kinet.* **1982**, 14, 823.

³³³For a review of ORH^+ as a leaving group, see Staude; Patat, in Patai *The Chemistry of the Ether Linkage*; Wiley: New York, 1967, pp. 22-46.

³³⁴Olah; O'Brien *J. Am. Chem. Soc.* **1967**, 89, 1725; Olah; Sommer; Namanworth *J. Am. Chem. Soc.* **1967**, 89, 3576; Olah; Olah, in Olah; Schleyer, Ref. 92, vol. 2, 1970, pp. 743-747.

³³⁵Even in the gas phase, NH_3 takes a proton from CH_3OH_2^+ rather than acting as a nucleophile: Okada; Abe; Taniguchi; Yamabe *J. Chem. Soc., Chem. Commun.* **1989**, 610.

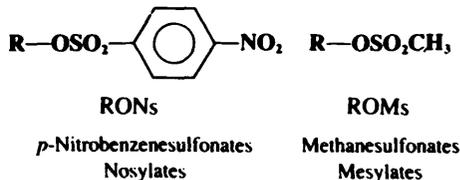
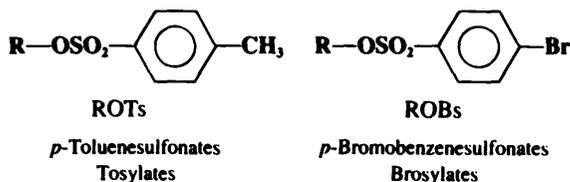
acidic conditions. In contrast, S_N2 reactions, which do require powerful nucleophiles (which are generally strong bases), most often take place under basic or neutral conditions.

Another circumstance that increases leaving-group power is ring strain. Ordinary ethers do not cleave at all and protonated ethers only under strenuous conditions, but epoxides³³⁶ are cleaved quite easily and protonated epoxides even more easily. Aziridines³³⁷ and epi-



sulfides, three-membered rings containing, respectively, nitrogen and sulfur, are also easily cleaved (see p. 368).³³⁸

Although halides are common leaving groups in nucleophilic substitution for synthetic purposes, it is often more convenient to use alcohols. Since OH does not leave from ordinary alcohols, it must be converted to a group that does leave. One way is protonation, mentioned above. Another is conversion to a reactive ester, most commonly a sulfonic ester. The sulfonic ester groups *tosylate*, *brosylate*, *nosylate*, and *mesylate* are better leaving groups



than halides and are frequently used. Other leaving groups are still better, and compounds containing these groups make powerful alkylating agents. Among them are oxonium ions (ROR_2^+),³³⁹ alkyl perchlorates ($ROClO_3$),³⁴⁰ ammonioalkanesulfonate esters (*betylates*) ($ROSO_2(CH_2)_nNMe_3^+$),³⁴¹ alkyl fluorosulfonates ($ROSO_2F$),³⁴² and the fluorinated com-

³³⁶For a review of the reactions of epoxides, see Smith *Synthesis* **1984**, 629-656. For a review of their synthesis and reactions, see Bartók; Láng, in Patai *The Chemistry of Functional Groups, Supplement E*; Wiley: New York, 1980, pp. 609-681.

³³⁷For a review of aziridine cleavages in the synthesis of natural products, see Kametani; Honda *Adv. Heterocycl. Chem.* **1986**, *39*, 181-236.

³³⁸There is evidence that relief of ring strain is not the only factor responsible for the high rates of ring-opening of 3-membered rings: Di Vona; Illuminati; Lillocci *J. Chem. Soc., Perkin Trans. 2* **1985**, 1943; Bury; Earl; Stirling *J. Chem. Soc., Chem. Commun.* **1985**, 393.

³³⁹For a monograph, see Perst, Ref. 84. For reviews, see Perst, in Olah; Schleyer, Ref. 92, vol. 5, 1976, pp. 1961-2047; Granik; Pyatin; Glushkov *Russ. Chem. Rev.* **1971**, *40*, 747-759. For a discussion of their use, see Curphey *Org. Synth.* **VI**, 1021.

³⁴⁰Baum; Beard *J. Am. Chem. Soc.* **1974**, *96*, 3233. See also Kevill; Lin *Tetrahedron Lett.* **1978**, 949.

³⁴¹King; Loosmore; Aslam; Lock; McGarrity *J. Am. Chem. Soc.* **1982**, *104*, 7108; King; Lee *Can. J. Chem.* **1981**, *59*, 356, 362; King; Skonieczny; Poole *Can. J. Chem.* **1983**, *61*, 235.

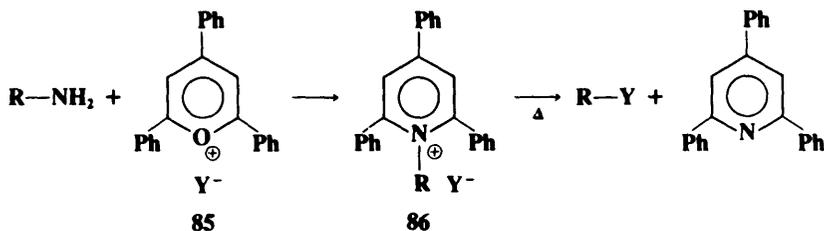
³⁴²Ahmed; Alder; James; Sinnott; Whiting *Chem. Commun.* **1968**, 1533; Ahmed; Alder *Chem. Commun.* **1969**, 1389; Alder *Chem. Ind. (London)* **1973**, 983. For a discussion of the hazards involved in the use of these and other alkylating agents, see Alder; Sinnott; Whiting; Evans *Chem. Br.* **1978**, 324.

pounds triflates³⁴³ and nonaflates.³⁴³ Tresylates are about 400 times less reactive than triflates, but still about 100 times more reactive than tosylates.³⁴⁴ Halonium ions (RCIR^+ , RBrR^+ ,

$\text{R—OSO}_2\text{CF}_3$	$\text{R—OSO}_2\text{C}_4\text{F}_9$	$\text{R—OSO}_2\text{CH}_2\text{CF}_3$
ROTf	Nonafluorobutanesulfonates	2,2,2-Trifluoroethanesulfonates
Trifluoromethanesulfonates	Nonaflates	Tresylates
Triflates		

RIR^+), which can be prepared in super-acid solutions (p. 312) and isolated as solid SbF_6^- salts, are also extremely reactive in nucleophilic substitution.³⁴⁵ Of the above types of compound, the most important in organic synthesis are tosylates, mesylates, oxonium ions, and triflates. The others have been used mostly for mechanistic purposes.

NH_2 , NHR , and NR_2 are extremely poor leaving groups,³⁴⁶ but the leaving-group ability of NH_2 can be greatly improved by converting a primary amine RNH_2 to the ditosylate RNTs_2 . The NTs_2 group has been successfully replaced by a number of nucleophiles.³⁴⁷ Another way of converting NH_2 into a good leaving group has been extensively developed by Katritzky and co-workers.³⁴⁸ In this method the amine is converted to a pyridinium compound (**86**) by treatment with a pyrylium salt (frequently a 2,4,6-triphenylpyrylium salt, **85**).³⁴⁹ When the salt is heated, the counterion acts as a nucleophile. In some cases a



nonnucleophilic ion such as BF_4^- is used as the counterion for the conversion $\text{85} \rightarrow \text{86}$, and then Y^- is added to **86**. Among the nucleophiles that have been used successfully in this reaction are I^- , Br^- , Cl^- , F^- , OAc^- , N_3^- , NHR_2 , and H^- . Ordinary NR_2 groups are good leaving groups when the substrate is a Mannich base (these are compounds of the form $\text{RCOCH}_2\text{CH}_2\text{NR}_2$; see reaction 6-16).³⁵⁰ The elimination-addition mechanism applies in this case.

³⁴³For reviews of triflates, nonaflates, and other fluorinated ester leaving groups, see Stang; Hanack; Subramanian *Synthesis* **1982**, 85-126; Howells; Mc Cown *Chem. Rev.* **1977**, 77, 69-92, pp. 85-87.

³⁴⁴Crossland; Wells; Shiner *J. Am. Chem. Soc.* **1971**, 93, 4217.

³⁴⁵Peterson; Clifford; Slama, Ref. 89; Olah; DeMember; Schlosberg; Halpern *J. Am. Chem. Soc.* **1972**, 94, 156; Peterson; Waller *J. Am. Chem. Soc.* **1972**, 94, 5024; Olah; Svoboda *Synthesis* **1973**, 203; Olah; Mo *J. Am. Chem. Soc.* **1974**, 96, 3560.

³⁴⁶For a review of the deamination of amines, see Baumgarten; Curtis, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 2; Wiley: New York, 1982, pp. 929-997.

³⁴⁷For references, see Müller; Thi *Helv. Chim. Acta* **1980**, 63, 2168; Curtis; Knutson; Baumgarten *Tetrahedron Lett.* **1981**, 22, 199.

³⁴⁸For reviews, see Katritzky; Marson *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 420-429 [*Angew. Chem.* 96, 403-413]; Katritzky *Tetrahedron* **1980**, 36, 679-699. For reviews of the use of such leaving groups to study mechanistic questions, see Katritzky; Sakizadeh; Musumarra *Heterocycles* **1985**, 23, 1765-1813; Katritzky; Musumarra *Chem. Soc. Rev.* **1984**, 13, 47-68.

³⁴⁹For discussions of the mechanism, see Katritzky; Brycki *J. Am. Chem. Soc.* **1986**, 108, 7295, and other papers in this series.

³⁵⁰For a review of Mannich bases, see Tramontini *Synthesis* **1973**, 703-775.

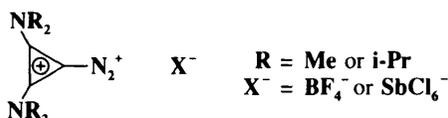
Probably the best leaving group is N_2 from the species RN_2^+ , which can be generated in several ways,³⁵¹ of which the two most important are the treatment of primary amines with nitrous acid (see p. 635 for this reaction)



and the protonation of diazo compounds³⁵²



No matter how produced, RN_2^+ are usually too unstable to be isolable,³⁵³ reacting presumably by the $SN1$ or $SN2$ mechanism.³⁵⁴ Actually, the exact mechanisms are in doubt because the rate laws, stereochemistry, and products have proved difficult to interpret.³⁵⁵ If there are free carbocations they should give the same ratio of substitution to elimination to rearrangements, etc. as carbocations generated in other $SN1$ reactions, but they often do not. "Hot" carbocations (unsolvated and/or chemically activated) that can hold their configuration have been postulated,³⁵⁶ as have ion pairs, in which OH^- (or OAc^- , etc., depending on how the diazonium ion is generated) is the counterion.³⁵⁷ One class of aliphatic diazonium salts of which several members have been isolated as stable salts are the cyclopropeniumdiazonium salts:³⁵⁸



Diazonium ions generated from ordinary aliphatic primary amines are usually useless for preparative purposes, since they lead to a mixture of products giving not only substitution by any nucleophile present, but also elimination and rearrangements if the substrate permits. For example, diazotization of *n*-butylamine gave 25% 1-butanol, 5.2% 1-chlorobutane, 13.2% 2-butanol, 36.5% butenes (consisting of 71% 1-butene, 20% *trans*-2-butene, and 9% *cis*-2-butene), and traces of butyl nitrites.³⁵⁹

³⁵¹For reviews, see Kirmse *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 251-261 [*Angew. Chem.* **88**, 273-283]; Collins *Acc. Chem. Res.* **1971**, *4*, 315-322; Moss *Chem. Eng. News* **1971**, *49*, 28-36 (No. 48, Nov. 22).

³⁵²For a treatise, see Regitz; Maas *Diazo Compounds*; Academic Press: New York, 1986. For reviews of the reactions of aliphatic diazo compounds with acids, see Hegarty, in Patai *The Chemistry of Diazonium and Diazo Groups*, pt. 2; Wiley: New York, 1978, pp. 511-591, pp. 571-575; More O'Ferrall *Adv. Phys. Org. Chem.* **1967**, *5*, 331-399. For review of the structures of these compounds, see Studzinski; Korobitsyna *Russ. Chem. Rev.* **1970**, *39*, 834-843.

³⁵³*Aromatic* diazonium salts can, of course, be isolated (see Chapter 13), but only a few aliphatic diazonium salts have been prepared (see also Ref. 358). For reviews see Laali; Olah *Rev. Chem. Intermed.* **1985**, *6*, 237-253; Bott, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 1; Wiley: New York, 1983, pp. 671-697; Bott *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 259-265 [*Angew. Chem.* **91**, 279-285]. The simplest aliphatic diazonium ion $CH_3N_2^+$ has been prepared at -120° in super-acid solution, where it lived long enough for an nmr spectrum to be taken; Berner; McGarrity *J. Am. Chem. Soc.* **1979**, *101*, 3135.

³⁵⁴For an example of a diazonium ion reacting by an $SN2$ mechanism, see Mohrig; Keegstra; Maverick; Roberts; Wells *J. Chem. Soc., Chem. Commun.* **1974**, 780.

³⁵⁵For reviews of the mechanism, see Manuilov; Barkhash *Russ. Chem. Rev.* **1990**, *59*, 179-192; Saunders; Cockerill *Mechanisms of Elimination Reactions*; Wiley: New York, 1973, pp. 280-317; in Olah; Schleyer, Ref. 92, vol. 2, **1970**, the articles by Keating; Skell, pp. 573-653; and by Friedman, pp. 655-713; White; Woodcock, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 440-483; Ref. 351.

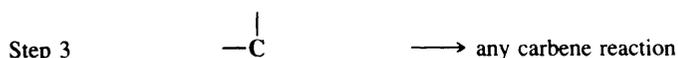
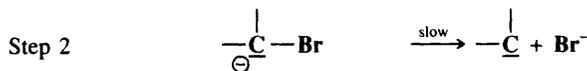
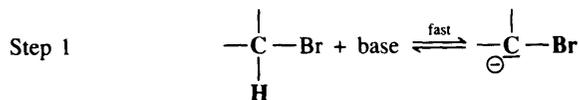
³⁵⁶Semenow; Shih; Young *J. Am. Chem. Soc.* **1958**, *80*, 5472. For a review of "hot" or "free" carbocations, see Keating; Skell, Ref. 355.

³⁵⁷Collins, Ref. 351; Collins; Benjamin *J. Org. Chem.* **1972**, *37*, 4358; White; Field *J. Am. Chem. Soc.* **1975**, *97*, 2148; Cohen; Daniewski; Solash *J. Org. Chem.* **1980**, *45*, 2847; Maskill; Thompson; Wilson *J. Chem. Soc., Perkin Trans. 2* **1984**, 1693; Connor; Maskill *Bull. Soc. Chim. Fr.* **1988**, 342.

³⁵⁸Weiss; Wagner; Priesner; Macheleid *J. Am. Chem. Soc.* **1985**, *107*, 4491.

³⁵⁹Whitmore; Langlois *J. Am. Chem. Soc.* **1932**, *54*, 3441; Streitwieser; Schaeffer *J. Am. Chem. Soc.* **1957**, *79*, 2888.

In the S_N1cA and S_N2cA mechanisms (p. 352) there is a preliminary step, the addition of a proton, before the normal S_N1 or S_N2 process occurs. There are also reactions in which the substrate *loses* a proton in a preliminary step. In these reactions there is a carbene intermediate.



Once formed by this process, the carbene may undergo any of the normal carbene reactions (see p. 199). When the net result is substitution, this mechanism has been called the S_N1cB (for conjugate base) mechanism.³⁶⁰ Though the slow step is an S_N1 step, the reaction is second order; first order in substrate and first order in base.

Table 10.10 lists some leaving groups in approximate order of ability to leave. The order of leaving-group ability is about the same for S_N1 and S_N2 reactions.

2. At a carbonyl carbon. In both the S_N1 and S_N2 mechanisms the leaving group departs during the rate-determining step and so directly affects the rate. In the tetrahedral mechanism at a carbonyl carbon, the bond between the substrate and leaving group is still intact during the slow step. Nevertheless, the nature of the leaving group still affects the reactivity in two ways: (1) By altering the electron density at the carbonyl carbon, the rate of the reaction is affected. The greater the electron-withdrawing character of X, the greater the partial positive charge on C and the more rapid the attack by a nucleophile. (2) The nature of the leaving group affects the *position of equilibrium*. In the intermediate **67** (p. 331) there is competition between X and Y as to which group leaves. If X is a poorer leaving group than Y, then Y will preferentially leave and **67** will revert to the starting compounds. Thus there is a partitioning factor between **67** going on to product (loss of X) or back to starting compound (loss of Y). The sum of these two factors causes the sequence of reactivity to be $\text{RCOCl} > \text{RCOOCOR}' > \text{RCOOAr} > \text{RCOOR}' > \text{RCONH}_2 > \text{RCONR}'_2 > \text{RCOO}^-$.³⁶¹ Note that this order is approximately the order of decreasing stability of the leaving-group anion. If the leaving group is bulky, it may exert a steric effect and retard the rate for this reason.

³⁶⁰Pearson; Edgington *J. Am. Chem. Soc.* **1962**, *84*, 4607.

³⁶¹ RCOOH would belong in this sequence just after RCOOAr , but it fails to undergo many reactions for a special reason. Many nucleophiles, instead of attacking the $\text{C}=\text{O}$ group, are basic enough to take a proton from the acid, converting it to the unreactive RCOO^- .

TABLE 10.10 Leaving groups listed in approximate order of decreasing ability to leave. Groups that are common leaving groups at saturated and carbonyl carbons are indicated

Substrate RX	Common leaving groups	
	At saturated carbon	At carbonyl carbon
RN₂⁺	×	
ROR'₂⁺	×	
ROSO₂C₄F₉		
ROSO₂CF₃	×	
ROSO₂F		
ROTs, etc.^a	×	
RI	×	
RBr	×	
ROH₂⁺	×	
RCI	×	×
RORH⁺	×	
RONO₂, etc.^a		×
RSR'₂⁺³⁶³		
RNR'₃⁺	×	
RF		
ROCOR'³⁶⁴	×	×
RNH₃⁺		
ROAr³⁶⁵		×
ROH		×
ROR		×
RH		
RNH₂		×
RAr		
RR		

^aROTs, etc., includes esters of sulfuric and sulfonic acids in general, for example, ROSO₂OH, ROSO₂OR, ROSO₂R, etc. RONO₂, etc., includes inorganic ester leaving groups, such as ROPO(OH)₂, ROB(OH)₂, etc.

The Effect of the Reaction Medium³⁶²

The effect of solvent polarity on the rate of S_N1 reactions depends on whether the substrate is neutral or positively charged. For neutral substrates, which constitute the majority of cases, the more polar the solvent, the faster the reaction, since there is a greater charge in the transition state than in the starting compound (Table 10.11³⁶⁶) and the energy of an ionic transition state is reduced by polar solvents. However, when the substrate is positively charged, the charge is more spread out in the transition state than in the starting ion, and

³⁶²For a monograph, see Reichardt *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1988. For reviews, see Klumpp, Ref. 294, pp. 186-203; Bentley; Schleyer *Adv. Phys. Org. Chem.* **1977**, *14*, 1-67.

³⁶³For a review of the reactions of sulfonium salts, see Knipe, in *Stirling The Chemistry of the Sulphonium Group*, pt. 1; Wiley: New York, 1981, pp. 313-385. See also Badet; Julia; Lefebvre *Bull. Soc. Chim. Fr.* **1984**, 11-431.

³⁶⁴For a review of S_N2 reactions of carboxylic esters, where the leaving group is OCOR', see McMurry *Org. React.* **1976**, *24*, 187-224.

³⁶⁵Nitro substitution increases the leaving-group ability of ArO groups, and alkyl picrates [2,4,6-ROC₆H₂(NO₂)₃] react at rates comparable to tosylates; Sinnott; Whiting *J. Chem. Soc. B* **1971**, 965. See also Page; Pritt; Whiting *J. Chem. Soc., Perkin Trans. 2* **1972**, 906.

³⁶⁶This analysis is due to Ingold *Structure and Mechanism in Organic Chemistry*, 2d ed.; Cornell University Press: Ithaca, NY, 1969, pp. 457-463.

TABLE 10.11 Transition states for SN1 reactions of charged and uncharged substrates, and for SN2 reactions of the four charge types³⁶⁶

Reactants and transition states		Charge in the transition state relative to starting materials	How an increase in solvent polarity affects the rate
SN2	Type I $\text{RX} + \text{Y}^- \longrightarrow \text{Y}^{\delta-} \cdots \text{R} \cdots \text{X}^{\delta-}$	Dispersed	Small decrease
	Type II $\text{RX} + \text{Y} \longrightarrow \text{Y}^{\delta+} \cdots \text{R} \cdots \text{X}^{\delta-}$	Increased	Large increase
	Type III $\text{RX}^+ + \text{Y}^- \longrightarrow \text{Y}^{\delta-} \cdots \text{R} \cdots \text{X}^{\delta+}$	Decreased	Large decrease
	Type IV $\text{RX}^+ + \text{Y} \longrightarrow \text{Y}^{\delta+} \cdots \text{R} \cdots \text{X}^{\delta+}$	Dispersed	Small decrease
SN1	$\text{RX} \longrightarrow \text{R}^{\delta+} \cdots \text{X}^{\delta-}$	Increased	Large increase
	$\text{RX}^- \longrightarrow \text{R}^{\delta+} \cdots \text{X}^{\delta-}$	Dispersed	Small decrease

a greater solvent polarity slows the reaction. Even for solvents with about the same polarity, there is a difference between protic and aprotic solvents.³⁶⁷ SN1 reactions of un-ionized substrates are more rapid in protic solvents, which can form hydrogen bonds with the leaving group. Examples of protic solvents are water, alcohols, and carboxylic acids, while some polar aprotic solvents are dimethylformamide (DMF), dimethyl sulfoxide,³⁶⁸ acetonitrile, acetone, sulfur dioxide, and hexamethylphosphoramide [(Me₂N)₃PO], HMPA.³⁶⁹

For SN2 reactions, the effect of the solvent depends on which of the four charge types the reaction belongs to (p. 293). In types I and IV, an initial charge is dispersed in the transition state, so the reaction is hindered by polar solvents. In type III initial charges are *decreased* in the transition state, so that the reaction is even more hindered by polar solvents. Only type II, where the reactants are uncharged but the transition state has built up a charge, is aided by polar solvents. These effects are summarized in Table 10.11.³⁶⁶ Westaway has proposed a "solvation rule" for SN2 reactions, which states that changing the solvent will not change the structure of the transition state for type I reactions, but will change it for type II reactions.³⁷⁰ For SN2 reactions also, the difference between protic and aprotic solvents must be considered.³⁷¹ For reactions of types I and III the transition state is more solvated in polar aprotic solvents than in protic ones,³⁷² while (as we saw on p. 349) the original charged nucleophile is less solvated in aprotic solvents³⁷³ (the second factor is generally much greater than the first³⁷⁴). So the change from, say, methanol to dimethyl sulfoxide should greatly increase the rate. As an example, the relative rates at 25°C for the reaction between methyl iodide and Cl⁻ were²⁹⁸ in MeOH, 1; in HCONH₂ (still protic though a weaker acid), 12.5; in HCONHMe, 45.3; and HCONMe₂, 1.2 × 10⁶. The change in rate in going from a protic to an aprotic solvent is also related to the *size* of the attacking anion. Small ions are solvated best in protic solvents, since hydrogen bonding is most important for them, while large anions are solvated best in aprotic solvents (protic solvents have highly developed structures held together by hydrogen bonds; aprotic solvents have much looser

³⁶⁷See, for example Ponomareva; Dvorko; Kulik; Evtushenko *Doklad. Chem.* **1983**, 272, 291.

³⁶⁸For reviews of reactions in dimethyl sulfoxide, see Buncel; Wilson *Adv. Phys. Org. Chem.* **1977**, 14, 133-202; Martin; Weise; Niclas *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 318-334 [*Angew. Chem.* 79, 340-357].

³⁶⁹For reviews of HMPA, see Normant *Russ. Chem. Rev.* **1970**, 39, 457-484. *Bull. Soc. Chim. Fr.* **1968**, 791-826. *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 1046-1067 [*Angew. Chem.* 79, 1029-1050].

³⁷⁰Westaway *Can. J. Chem.* **1978**, 56, 2691; Westaway; Lai *Can. J. Chem.* **1989**, 67, 345.

³⁷¹For reviews of the effects of protic and aprotic solvents, see Parker *Chem. Rev.* **1969**, 69, 1-32. *Adv. Phys. Org. Chem.* **1967**, 5, 173-235. *Adv. Org. Chem.* **1965**, 5, 1-46; Madaule-Aubry *Bull. Soc. Chim. Fr.* **1966**, 1456.

³⁷²However, even in aprotic solvents, the transition state is less solvated than the charged nucleophile; Magnera; Caldwell; Sunner; Ikuta; Kebabze *J. Am. Chem. Soc.* **1984**, 106, 6140.

³⁷³See, for example, Fuchs; Cole *J. Am. Chem. Soc.* **1973**, 95, 3194.

³⁷⁴See, however, Haberfield; Clayman; Cooper *J. Am. Chem. Soc.* **1969**, 91, 787.

structures, and it is easier for a large anion to be fitted in). So the rate of attack by small anions is most greatly increased by the change from a protic to an aprotic solvent. This may have preparative significance. The review articles in Ref. 371 have lists of several dozen reactions of charge types I and III in which yields are improved and reaction times reduced in polar aprotic solvents. Reaction types II and IV are much less susceptible to the difference between protic and aprotic solvents.

Since for most reactions S_N1 rates go up and S_N2 rates go down in solvents of increasing polarity, it is quite possible for the same reaction to go by the S_N1 mechanism in one solvent and the S_N2 in another. Table 10.12 is a list of solvents in order of ionizing power;³⁷⁵ a solvent high on the list is a good solvent for S_N1 reactions. Trifluoroacetic acid, which was not studied by Smith, Fainberg, and Winstein, has greater ionizing power than any solvent listed in Table 10.12.³⁷⁶ Because it also has very low nucleophilicity, it is an excellent solvent for S_N1 solvolyses. Other good solvents for this purpose are 1,1,1-trifluoroethanol CF_3CH_2OH , and 1,1,1,3,3,3-hexafluoro-2-propanol $(F_3C)_2CHOH$.³⁷⁷

We have seen how the polarity of the solvent influences the rates of S_N1 and S_N2 reactions. The ionic strength of the medium has similar effects. In general, the addition of an external salt affects the rates of S_N1 and S_N2 reactions in the same way as an increase in solvent polarity, though this is not quantitative; different salts have different effects.³⁷⁸ However, there are exceptions: though the rates of S_N1 reactions are usually increased by the addition of salts (this is called the *salt effect*), addition of the leaving-group ion often decreases the rate (the common-ion effect, p. 300). There is also the special salt effect of $LiClO_4$, mentioned on p. 303. In addition to these effects, S_N1 rates are also greatly accelerated when there are ions present that specifically help in pulling off the leaving group.³⁷⁹ Especially important are Ag^+ , Hg^{2+} , and Hg_2^{2+} , but H^+ helps to pull off F (hydrogen bonding).³⁸⁰ Even primary halides have been reported to undergo S_N1 reactions when assisted by metal ions.³⁸¹ This does not mean, however, that reactions in the presence of metallic ions invariably proceed

TABLE 10.12 Relative rates of ionization of *p*-methoxyneophyl toluenesulfonate in various solvents³⁷⁵

Solvent	Relative rate	Solvent	Relative rate
HCOOH	153	Ac₂O	0.020
H₂O	39	Pyridine	0.013
80% EtOH-H₂O	1.85	Acetone	0.0051
AcOH	1.00	EtOAc	6.7×10^{-4}
MeOH	0.947	Tetrahydrofuran	5.0×10^{-4}
EtOH	0.370	Et₂O	3×10^{-5}
Me₂SO	0.108	CHCl₃	} Lower still
Octanoic acid	0.043	Benzene	
MeCN	0.036	Alkanes	
HCONMe₂	0.029		

³⁷⁵Smith; Fainberg; Winstein *J. Am. Chem. Soc.* **1961**, 83, 618.

³⁷⁶Refs. 87, 125; Streitwieser; Dafforn *Tetrahedron Lett.* **1969**, 1263.

³⁷⁷Schadt; Schleyer; Bentley *Tetrahedron Lett.* **1974**, 2335.

³⁷⁸See, for example, Duynstee; Grunwald; Kaplan *J. Am. Chem. Soc.* **1960**, 82, 5654; Bunton; Robinson *J. Am. Chem. Soc.* **1968**, 90, 5965.

³⁷⁹For a review, see Kevill, in Patai; Rappoport, Ref. 88, pt. 2, pp. 933-984.

³⁸⁰For a review of assistance by metallic ions, see Rudakov; Kozhevnikov; Zamashchikov *Russ. Chem. Rev.* **1974**, 43, 305-316. For an example of assistance in removal of F by H^+ , see Coverdale; Kohnstam *J. Chem. Soc.* **1960**, 3906.

³⁸¹Zamashchikov; Rudakov; Litvinenko; Uzhik *Doklad. Chem.* **1981**, 258, 186; Zamashchikov; Rudakov; Bezbozhnaya; Matveev *J. Org. Chem. USSR* **1984**, 20, 424. See, however, Kevill; Fujimoto *J. Chem. Soc., Chem. Commun.* **1983**, 1149.

by the S_N1 mechanism. It has been shown that alkyl halides can react with AgNO₂ and AgNO₃ by the S_N1 or S_N2 mechanism, depending on the reaction conditions.³⁸²

The effect of solvent has been treated quantitatively (for S_N1 mechanisms, in which the solvent pulls off the leaving group) by a linear free-energy relationship³⁸³

$$\log \frac{k}{k_0} = mY$$

where *m* is characteristic of the substrate (defined as 1.00 for *t*-BuCl) and is usually near unity, *Y* is characteristic of the solvent and measures its "ionizing power," and *k*₀ is the rate in a standard solvent, 80% aqueous ethanol at 25°C. This is known as the Grunwald-Winstein equation, and its utility is at best limited. *Y* values can of course be measured for solvent mixtures too, and this is one of the principal advantages of the treatment, since it is not easy otherwise to assign a polarity arbitrarily to a given mixture of solvents.³⁸⁴ The treatment is most satisfactory for different proportions of a given solvent pair. For wider comparisons the treatment is not so good quantitatively, although the *Y* values do give a reasonably good idea of solvolysis power.³⁸⁵ Table 10.13 contains a list of some *Y* values.³⁸⁶

Ideally, *Y* should measure only the ionizing power of the solvent, and should not reflect any backside attack by a solvent molecule in helping the nucleofuge to leave (nucleophilic assistance; *k*_s, p. 317). Actually, there is evidence that many solvents do lend some nucleophilic assistance,³⁸⁷ even with tertiary substrates.^{387a} It was proposed that a better measure of solvent "ionizing power" would be a relationship based on 2-adamantyl substrates, rather than *t*-BuCl, since the structure of this system completely prevents backside nucleophilic assistance (p. 340). Such a scale, called *Y*_{OTs}, was developed, with *m* defined as 1.00 for 2-adamantyl tosylate.³⁸⁸ Some values of *Y*_{OTs} are given in Table 10.13. These values, which are actually based on both 1- and 2-adamantyl tosylates (both are equally impervious to nucleophilic assistance and show almost identical responses to solvent ionizing power³⁸⁹) are called *Y*_{OTs} because they apply only to tosylates. It has been found that solvent "ionizing power" depends on the leaving group, so separate scales³⁹⁰ have been set up for OTf,³⁹¹ Cl,³⁹² Br,³⁹² I,³⁹³ and other nucleofuges,³⁹⁴ all based on the corresponding adamantyl compounds.

³⁸²Kornblum; Jones; Hardies *J. Am. Chem. Soc.* **1966**, *88*, 1704; Kornblum; Hardies *J. Am. Chem. Soc.* **1966**, *88*, 1707.

³⁸³Grunwald; Winstein *J. Am. Chem. Soc.* **1948**, *70*, 846.

³⁸⁴For reviews of polarity scales of solvent mixtures, see Reichardt, Ref. 362, pp. 339-405; Langhals *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 724-733 [*Angew. Chem.* **94**, 739-749].

³⁸⁵For a criticism of the *Y* scale, see Abraham; Doherty; Kamlet; Harris; Taft *J. Chem. Soc., Perkin Trans. 2* **1987**, 1097.

³⁸⁶*Y* values are from Fainberg; Winstein *J. Am. Chem. Soc.* **1956**, *78*, 2770, except for the value for CF₃CH₂OH which is from Shiner; Dowd; Fisher; Hartshorn; Kessick; Milakofsky; Rapp *J. Am. Chem. Soc.* **1969**, *91*, 4838. *Y*_{OTs} values are from Bentley; Llewellyn, Ref. 390, pp. 143-144. *Z* values are from Ref. 396. *E*_T(30) values are from Reichardt; Dimroth *Fortschr. Chem. Forsch.* **1969**, *11*, 1-73; Reichardt *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 98-110 [*Angew. Chem.* **91**, 119-131]; Reichardt; Harbusch-Görnert *Liebigs Ann. Chem.* **1983**, 721-743; Laurence; Nicolet; Reichardt *Bull. Soc. Chim. Fr.* **1987**, 125; Laurence; Nicolet; Lucon; Reichardt *Bull. Soc. Chim. Fr.* **1987**, 1001; Reichardt; Eschner; Schäfer *Liebigs Ann. Chem.* **1990**, 57. Values for many additional solvents are given in the last five papers. Many values from all of these scales are given in Reichardt, Ref. 384.

³⁸⁷A scale of solvent nucleophilicity (as opposed to ionizing power), called the *N*_T scale, has been developed: Kevill; Anderson *J. Org. Chem.* **1991**, *56*, 1845.

^{387a}For discussions, with references, see Kevill; Anderson *J. Am. Chem. Soc.* **1986**, *108*, 1579; McManus; Neamati-Mazreah; Karaman; Harris *J. Org. Chem.* **1986**, *51*, 4876; Abraham; Doherty; Kamlet; Harris; Taft *J. Chem. Soc., Perkin Trans. 2* **1987**, 913.

³⁸⁸Schadt; Bentley; Schleyer *J. Am. Chem. Soc.* **1976**, *98*, 7667.

³⁸⁹Bentley; Carter *J. Org. Chem.* **1983**, *48*, 579.

³⁹⁰For a review of these scales, see Bentley; Llewellyn *Prog. Phys. Org. Chem.* **1990**, *17*, 121-158.

³⁹¹Kevill; Anderson *J. Org. Chem.* **1985**, *50*, 3330. See also Creary; McDonald *J. Org. Chem.* **1985**, *50*, 474.

³⁹²Bentley; Carter *J. Am. Chem. Soc.* **1982**, *104*, 5741. See also Liu; Sheu *J. Org. Chem.* **1991**, *56*, 3021.

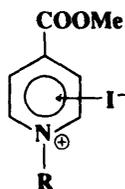
³⁹³Bentley; Carter; Roberts *J. Org. Chem.* **1984**, *49*, 5183.

³⁹⁴See Kevill; Bahari; Anderson *J. Am. Chem. Soc.* **1984**, *106*, 2895; Bentley; Roberts *J. Org. Chem.* **1985**, *50*, 4821; Takeuchi; Ika; Shibata; Tsugeno *J. Org. Chem.* **1988**, *53*, 2852; Kevill; Bahnke *Tetrahedron* **1988**, *44*, 7541; Hawkinson; Kevill *J. Org. Chem.* **1988**, *53*, 3857; **1989**, *54*, 154; Kevill; Hawkinson *J. Org. Chem.* **1990**, *55*, 5394.

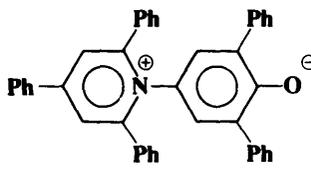
TABLE 10.13 Y , Y_{OTs} , Z , and $E_T(30)$ values for some solvents³⁸⁶

Solvent	Y	Y_{OTs}	Z	$E_T(30)$
CF₃COOH		4.57		
H₂O	3.5	4.1	94.6	63.1
(CF₃)₂CHOH		3.82		65.3
HCOOH	2.1	3.04		
H₂O—EtOH (1:1)	1.7	1.29	90	55.6
CF₃CH₂OH	1.0	1.77		59.8
HCONH₂	0.6		83.3	56.6
80% EtOH	0.0	0.0	84.8	53.7
MeOH	-1.1	-0.92	83.6	55.4
AcOH	-1.6	-0.9	79.2	51.7
EtOH	-2.0	-1.96	79.6	51.9
90% dioxane	-2.0	-2.41	76.7	46.7
iso-PrOH	-2.7	-2.83	76.3	48.4
95% acetone	-2.8	-2.95	72.9	48.3
<i>t</i>-BuOH	-3.3	-3.74	71.3	43.9
MeCN		-3.21	71.3	45.6
Me₂SO			71.1	45.1
HCONMe₂		-4.14	68.5	43.8
Acetone			65.7	42.2
HMPA				40.9
CH₂Cl₂				40.7
Pyridine			64.0	40.5
CHCl₃			63.2	39.1
PhCl				37.5
THF				37.4
Dioxane				36.0
Et₂O				34.5
C₆H₆			54	34.3
PhMe				33.9
CCl₄				32.4
<i>n</i> -Octane				31.1
<i>n</i> -Hexane				31.0
Cyclohexane				30.9

In order to include a wider range of solvents than those in which any of the Y values can be conveniently measured, other attempts have been made at correlating solvent polarities.³⁹⁵ Kosower found that the position of the charge-transfer peak (see p. 79) in the uv spectrum of the complex (**87**) between iodide ion and 1-methyl- or 1-ethyl-4-carbometh-

**87**

R = Me or Et

**88**

³⁹⁵For reviews of solvent polarity scales, see Abraham; Grellier; Abboud; Doherty; Taft *Can. J. Chem.* **1988**, *66*, 2673-2686; Kamlet; Abboud; Taft *Prog. Phys. Org. Chem.* **1981**, *13*, 485-630; Shorter *Correlation Analysis of Organic Reactivity*; Wiley: New York, 1982, pp. 127-172; Reichardt, Ref. 386; Reichardt; Dimroth, Ref. 386; Abraham *Prog. Phys. Org. Chem.* **1974**, *11*, 1-87; Koppel; Palm, in Chapman; Shorter *Advances in Linear Free Energy Relationships*; Plenum: New York, 1972, pp. 203-280; Ref. 384. See also Chastrette; Carretto *Tetrahedron* **1982**, *38*, 1615; Chastrette; Rajzmann; Chanon; Purcell *J. Am. Chem. Soc.* **1985**, *107*, 1.

oxypyridinium ion was dependent on the polarity of the solvent.³⁹⁶ From these peaks, which are very easy to measure, Kosower calculated transition energies that he called *Z* values. *Z* values are thus measures of solvent polarity analogous to *Y* values. Another scale is based on the position of electronic spectra peaks of the pyridinium-*N*-phenolbetaine **88** in various solvents.³⁹⁷ Solvent polarity values on this scale are called $E_T(30)$ ³⁹⁸ values. $E_T(30)$ values are related to *Z* values by the expression³⁹⁹

$$Z = 1.41E_T(30) + 6.92$$

Table 10.13 shows that *Z* and $E_T(30)$ values are generally in the same order as *Y* values. Other scales, the π^* scale,⁴⁰⁰ the π_{azo}^* scale,⁴⁰¹ and the Py scale,⁴⁰² are also based on spectral data.⁴⁰³

The effect of solvent on nucleophilicity has already been discussed (pp. 349-350).

Phase Transfer Catalysis and Ultrasound

A difficulty that occasionally arises when carrying out nucleophilic substitution reactions is that the reactants do not mix. For a reaction to take place the reacting molecules must collide. In nucleophilic substitutions the substrate is usually insoluble in water and other polar solvents, while the nucleophile is often an anion, which is soluble in water but not in the substrate or other organic solvents. Consequently, when the two reactants are brought together, their concentrations in the same phase are too low for convenient reaction rates. One way to overcome this difficulty is to use a solvent that will dissolve both species. As we saw on p. 358, a dipolar aprotic solvent may serve this purpose. Another way, which is used very often, is *phase transfer catalysis*.⁴⁰⁴

In this method, a catalyst is used to carry the nucleophile from the aqueous into the organic phase. As an example, simply heating and stirring a two-phase mixture of 1-chlorooctane for several days with aqueous NaCN gives essentially no yield of 1-cyanooctane. But if a small amount of an appropriate quaternary ammonium salt is added, the product

³⁹⁶Kosower *J. Am. Chem. Soc.* **1958**, *80*, 3253, 3261, 3267; Kosower; Wu; Sorensen *J. Am. Chem. Soc.* **1961**, *83*, 3147. See also Larsen; Edwards; Dobi *J. Am. Chem. Soc.* **1980**, *102*, 6780.

³⁹⁷Dimroth; Reichardt; Siepmann; Bohlmann *Liebigs Ann. Chem.* **1963**, *661*, 1; Dimroth; Reichardt *Liebigs Ann. Chem.* **1969**, *727*, 93. See also Haak; Engberts *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 307.

³⁹⁸The symbol E_T comes from *energy, transition*. The (30) is used because the ion **88** bore this number in the first paper of Ref. 397. Values based on other ions have also been reported: See, for example Reichardt; Harbusch-Görnert; Schäfer *Liebigs Ann. Chem.* **1988**, 839.

³⁹⁹Reichardt; Dimroth, Ref. 386, p. 32.

⁴⁰⁰Kamlet; Abboud; Taft *J. Am. Chem. Soc.* **1977**, *99*, 6027; Doherty; Abraham; Harris; Taft; Kamlet *J. Org. Chem.* **1986**, *51*, 4872; Kamlet; Doherty; Abboud; Abraham; Taft *CHEMTECH* **1986**, 566-576, and other papers in this series. See also Doan; Drago *J. Am. Chem. Soc.* **1982**, *104*, 4524; Kamlet; Abboud; Taft, Ref. 395; Bekárek *J. Chem. Soc., Perkin Trans. 2* **1986**, 1425; Abe *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2328.

⁴⁰¹Buncel; Rajagopal *J. Org. Chem.* **1989**, *54*, 798.

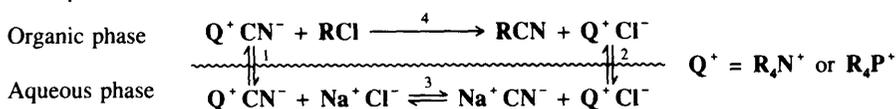
⁴⁰²Dong; Winnik *Can. J. Chem.* **1984**, *62*, 2560.

⁴⁰³For a review of such scales, see Buncel; Rajagopal *Acc. Chem. Res.* **1990**, *23*, 226-231.

⁴⁰⁴For monographs, see Dehmlow; Dehmlow *Phase Transfer Catalysis*, 2nd ed.; Verlag Chemie: Deerfield Beach, FL, 1983; Starks; Liotta *Phase Transfer Catalysis*; Academic Press: New York, 1978; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*; Springer: New York, 1977. For reviews, see Mąkosza; Fedoryński *Adv. Catal.* **1987**, *35*, 375-422; Gallo; Mąkosza; Dou; Hassanaly *Adv. Heterocycl. Chem.* **1984**, *36*, 175-234; Montanari; Landini; Rolla *Top. Curr. Chem.* **1982**, *101*, 147-200; Alper *Adv. Organomet. Chem.* **1981**, *19*, 183-211; Gallo; Dou; Hassanaly *Bull. Soc. Chim. Belg.* **1981**, *90*, 849-879; Dehmlow *Chimia* **1980**, *34*, 12-20, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 493-505, **1974**, *13*, 170-174 [*Angew. Chem.* **89**, 521-533; **86**, 187-196]; Mąkosza *Surv. Prog. Chem.* **1980**, *9*, 1-53; Starks, *CHEMTECH* **1980**, 110-117; Sjöberg *Aldrichimica Acta* **1980**, *13*, 55-58; McIntosh *J. Chem. Educ.* **1978**, *55*, 235-238; Gokel; Weber *J. Chem. Educ.* **1978**, *55*, 350-354; Weber; Gokel *J. Chem. Educ.* **1978**, *55*, 429-433; Liotta, in Izatt; Christensen *Synthetic Multidentate Macrocyclic Compounds*; Academic Press: New York, 1978, pp. 111-205; Brändström *Adv. Phys. Org. Chem.* **1977**, *15*, 267-330; Jones *Aldrichimica Acta* **1976**, *9*, 35-45; Dockx *Synthesis* **1973**, 441-456.

is quantitatively formed in about 2 hr.⁴⁰⁵ There are two principal types of phase transfer catalyst. Though the action of the two types is somewhat different, the effects are the same. Both get the anion into the organic phase and allow it to be relatively free to react with the substrate.

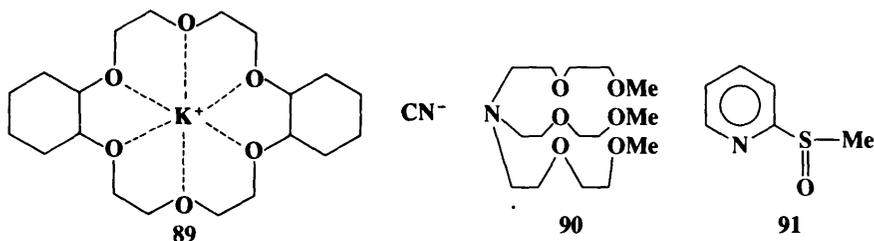
1. *Quaternary ammonium or phosphonium salts.* In the above-mentioned case of NaCN, the uncatalyzed reaction does not take place because the CN⁻ ions cannot cross the interface between the two phases, except in very low concentration. The reason is that the Na⁺ ions are solvated by the water, and this solvation energy would not be present in the organic phase. The CN⁻ ions cannot cross without the Na⁺ ions because that would destroy the electrical neutrality of each phase. In contrast to Na⁺ ions, quaternary ammonium (R₄N⁺)⁴⁰⁶ and phosphonium (R₄P⁺) ions with sufficiently large R groups are poorly solvated in water and prefer organic solvents. If a small amount of such a salt is added, three equilibria are set up:



The Na⁺ ions remain in the aqueous phase; they cannot cross. The Q⁺ ions do cross the interface and carry an anion with them. At the beginning of the reaction the chief anion present is CN⁻. This gets carried into the organic phase (equilibrium 1) where it reacts with RCl to produce RCN and Cl⁻. The Cl⁻ then gets carried into the aqueous phase (equilibrium 2). Equilibrium 3, taking place entirely in the aqueous phase, allows Q⁺ CN⁻ to be regenerated. All the equilibria are normally reached much faster than the actual reaction (4), so the latter is the rate-determining step.

In some cases, the Q⁺ ions have such a low solubility in water that virtually all remain in the organic phase.⁴⁰⁷ In such cases the exchange of ions (equilibrium 3) takes place across the interface. Still another mechanism (*the interfacial mechanism*) can operate where OH⁻ extracts a proton from an organic substrate.⁴⁰⁸ In this mechanism, the OH⁻ ions remain in the aqueous phase and the substrate in the organic phase; the deprotonation takes place at the interface.⁴⁰⁹

2. *Crown ethers and other cryptands.*⁴¹⁰ We saw in Chapter 3 that certain cryptands are able to surround certain cations. In effect, a salt like KCN is converted by dicyclohexano-18-crown-6 into a new salt (**89**) whose anion is the same, but whose cation is now a much larger species with the positive charge spread over a large volume and hence much less



⁴⁰⁵Starks; Liotta, Ref. 404, p. 2.

⁴⁰⁶Bis-quaternary ammonium salts have also been used: Lissel; Feldman; Nir; Rabinovitz *Tetrahedron Lett.* **1989**, 30, 1683.

⁴⁰⁷Landini; Maia; Montanari *J. Chem. Soc. Commun.* **1977**, 112; *J. Am. Chem. Soc.* **1978**, 100, 2796.

⁴⁰⁸For a review, see Rabinovitz; Cohen; Halpern *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 960-970 [*Angew. Chem.* **98**, 958-968].

⁴⁰⁹This mechanism was proposed by Mąkosza *Pure Appl. Chem.* **1975**, 43, 439. See also Dehmlow; Thieser; Sasson; Pross *Tetrahedron* **1985**, 41, 2927; Mason; Magdassi; Sasson *J. Org. Chem.* **1990**, 55, 2714.

⁴¹⁰For a review of this type of phase transfer catalysis, see Liotta, in Patai, Ref. 336, pp. 157-174.