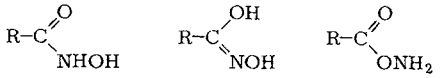
The Chemistry of Hydroxamic Acids and *N*-Hydroxyimides

By Ludwig Bauer and Otto Exner[*]

This progress report is concerned primarily with problems relating to the structure and reactions of hydroxamic acids and *N*-hydroxyimides, and also surveys some of the biological activities of these compounds. Particular significance attaches to the Lossen rearrangement of *O*-acylated hydroxamic acids, which leads to isocyanates or their reaction products.

1. Introduction

The chemistry of hydroxamic acids began in 1869 when *H. Lossen*, working in *W. Lossen*'s laboratory, isolated oxalohydroxamic acid from the reaction products of ethyl oxalate and hydroxylamine[1]. Later, when *W. Lossen* obtained a mixture of mono-, di-, and tribenzoyl derivatives from the reaction of hydroxylamine with benzoyl chloride, an era of tedious structural investigation commenced which was plagued by polymorphism, stereoisomerism, and tautomerism[2]. The pioneering efforts of investigators like *A. Werner*, *Lauder W. Jones*, and *C. D. Hurd* paved the way for a clearer understanding of structure and reactions in hydroxamic acid chemistry. In the absence of spectral data, the structure of the oxo form *(1)* was difficult to establish; many experimentalists believed that the hydroximic acid structure *(2)* represented hydroxamic acids correctly and that *(2)* would also exhibit geometrical isomerism akin to oximes. In his review in 1943, *Yale* brought some order to the state of confusion existing in the literature of hydroxamic acids[3]. Considerable progress was achieved in the last 30 years in understanding the chemistry of acyl derivatives of hydroxylamine[4], particularly with the evolution of spectral methods.



(1) *(2)* *(3)*

(1a), R = C_6H_5

Hydroxamic acids occupy relatively little space in textbooks. A noted exception is the Lossen rearrangement leading to isocyanates, which is usually mentioned as an appendage to the related Hofmann, Curtius, Schmidt, and Tiemann rearrangements[4]. Complexation of metal ions by hydroxamic acids is the basis of a number of analytical determinations[5]. The best known of these complexes is that with Fe^{3+} whose beautiful purple color forms the basis for the sensitive qualitative and quantitative determination of carboxylic acids and their derivatives[6,7].

This quick color test retains some value in the preparative work with hydroxamic acids and is unique for hydroxamic acids of structure *(1)*, although hydroxamic acids possessing either an NH or OH group may exhibit a red color with Fe^{3+} ion.

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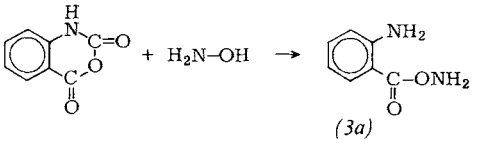
2. Structure of Hydroxamic Acids

Monoacylation of hydroxylamine should produce *N*- and *O*-derivatives, *(1)* and *(3)*, respectively. Members of both series are known, but thermodynamically controlled reactions usually yield only *(1)*.

2.1. *O*-Acylhydroxylamines *(3)*

It was shown in 1942 that hydroxylaminolysis of isatoic anhydride produces *O*-(2-aminobenzoyl)hydroxylamine *(3a)*[8], the first identified representative of class *(3)*, although the classical Wöhler synthesis produces both *N*-hydroxyurea *(1)*, R = NH_2, and "isohydroxyurea" *(3)*, R = NH_2. The structure of the latter was proved by chemical methods to be *O*-carbamoylhydroxylamine[9a], and this structure was confirmed recently by X-ray analysis[10].

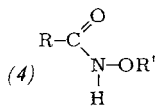


(3a)

Acylations of hydroxylamines frequently provide the primary kinetically controlled product *(3)*, which rearranges rapidly, particularly under the catalytic effect of hydroxylamine (α-effect)[9,11], to the thermodynamically stable hydroxamic acid *(1)*. Although it is possible to prove the structure of *(3)* by further acylation and subsequent Lossen rearrangements[8,9a], one can now readily distinguish between *(1)* and *(3)* by IR spectroscopy. The carbonyl stretching frequency in *(3)* is considerably higher (1760—1730 cm^{-1}) than that for the more amidic type of C=O in *(1)* (1670—1640 cm^{-1})[9b,12,13c]. Syntheses of *O*-acylhydroxylamines *(3)* are still being investigated and ingenious methods have been devised to prepare these types of compounds[9,13].

2.2. Hydroxamic Acids ("*N*-Acylhydroxylamines") *(1)*

Structure *(1)* represents hydroxamic acids in the solid state, as shown by X-ray analyses of crystalline acetohydroxamic acid hemihydrate[14] and *N*-hydroxyurea[15]. All spectral evidence indicates that *(1)* is the predominant species in solutions. Attempts to detect even minute amounts of the tautomeric oximino form *(2)* in solutions failed. UV studies on hydroxamic acids and the monoalkyl derivatives of type *(4)* and *(5)* support structure *(1)*[16], which is further substantiated by the C=O stretching frequency in their IR spectra[12,17]. Furthermore, ESR[18], mass[19], and NMR[20] spectra of hydroxamic acids agree with structure *(1)*.



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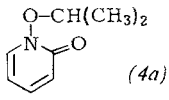
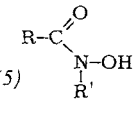


(4a)

(4b), R = CH_3, R' = Alkyl
(4c), R' = CH_3
(4d), R = C_6H_5, R' = CH_3
(4e), R = C_6H_5, R' = Alkyl



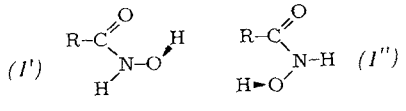
(5)

(5a), R = R' = C_6H_5
(5b), R = CH_3, R' = Alkyl
(5c), R' = CH_3
(5d), R = C_6H_5, R' = CH_3

Direct proof for the NH grouping in *(1)* was obtained only recently[20d] from the NMR spectrum of *p*-nitrobenzohydroxamic[^{15}N] acid in dimethyl sulfoxide, where a large spin-spin coupling constant between ^{15}N and H, $J_{N-H} = 102$ Hz, was observed[20d].

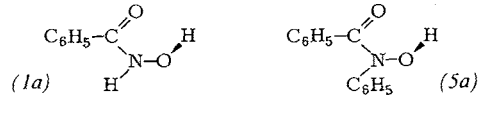
By way of comparison, thiohydroxamic acids are now believed to exist in the thioacylhydroxylamine form, R—CS—NHOH, both in solution and the solid state[20e,g]. Along those lines, it is interesting to note that amidoximes exist primarily as amino-oximino tautomers, R—C(=NOH)NH_2[20h]. All these types of molecules are strongly hydrogen bonded.

In the hydroxamic acid molecule *(1)* the oxygen, carbon, and nitrogen atoms belonging to the —C(O)—NO grouping are expected, by analogy with amides, to be in one plane; *a priori*, the OH group could assume two different spatial positions with respect to the C=O group: (1') and (1''). The NH—OH grouping is clearly not planar[14,15,21a]; for instance benzohydroxamic acid *(1a)* in dioxane approaches *(1')*[21a]. This conclusion was reached by determining the dipole moments of benzohydroxamic acid and suitable derivatives and by calculating dipole moments of these substances from suitable bond moments and angles[21].



(1') (1'')

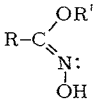
A similar conformation is postulated for the *N*-phenyl derivative *(5a)*[23]. No intramolecular hydrogen bond O—H···O is present in the crystal[14], probably due to unfavorable steric conditions, whereas such a bond is detected in dilute solutions by IR spectroscopy. This also explains the low C=O frequency[12,17c].



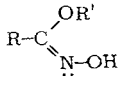
(1a) (5a)

Attempts to detect restricted rotation around the C···N bond of *(1)* due to partial carbon-nitrogen double bond character have not borne fruit. However, slightly restricted rotation about the C···N bond is reported for the highly substituted compound *(10a)* (see Section 3)[20b]. In a more recent report, NMR spectra of formohydroxamates HCO—N(R)OR' at low temperature clearly revealed restricted rotation about the C···N bond. The configuration of the rotamers was established by means of long range coupling constants[20g].

In order to study torsion about an N—O bond, the NMR spectra of 1-isopropoxy-2-pyridone *(4a)*, a cyclic hydroxamate, were examined and a certain barrier to rotation was found[22].



(E)-(6)



(Z)-(6)

(6a), R = C_6H_5, R' = $C_6H_5CH_2$
(6b), R' = C_2H_5
(6c), R = C_6H_5, R' = C_2H_5

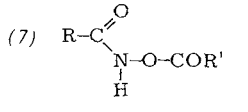
Since neither tautomerism nor partial double bond (C···N) character is detected in *(1)*, the configurations of the N—OH group pose no structural problem. A configurational problem arises, however, when fixed C=N bonds are present, as in structure *(6)*: (*E*) and (*Z*) isomers of type *(6)* have been differentiated by dipole moment measurements[26] which reversed the original literature assignments. These results were confirmed by X-ray analysis[24]. Dipole moment or NMR determinations were also useful in establishing the (*E*) and (*Z*) isomers of related *S*-alkyl thiohydroximates RC(=NOH)-SR'[25a,25b] and *O*-methylarenohydroximoyl chlorides ArC(=$NOCH_3$)Cl[25c].

3. Nomenclature

The hydroxamic or carbohydroxamic acid nomenclature (IUPAC Rule C-451.3) may be used for *(1)*. For example, CH_3CO—NHOH is named acetohydroxamic acid, *cyclo*-$C_6H_{11}CO$—NHOH, cyclohexanecarbohydroxamic acid, and 1,4-$C_{10}H_6(CO—NHOH)_2$ 1,4-naphthalenedicarbohydroxamic acid. Alternatively, compound of type *(1)* may be named as *N*-hydroxycarboxamides according to Rule C 841.3.

Monoalkyl derivatives *(4)* and *(5)* are esters and *N*-substituted hydroxamic acids, respectively; for example *(4b)*, CH_3CO—NHOAlkyl can be designated as alkyl acetohydroxamates (or *N*-alkoxyacetamide) and *(5b)*. CH_3CON(Alkyl)OH, as *N*-alkylacetohydroxamic or *N*-alkyl-*N*-hydroxyacetamide.

Compounds of type *(6)* are best named as derivatives of hydroximic acids *(2)*. For example, (*Z*)-*(6a)* would be benzyl (*Z*)-benzohydroximate.



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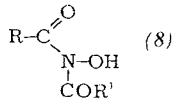
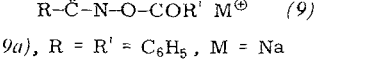


(8)

(7a), R = R' = CH_3
(7b), R = R' = C_6H_5

(8a), R = R' = CH_3



(9)

(9a), R = R' = C_6H_5, M = Na
(9b), R = $(C_6H_5)_3C$, R' = CH_3, M = K

The acyl derivatives *(7)* and *(8)* can be named as hydroxamic acid derivatives, *e.g. (7a)* and *(8a)* as acetohydroxamic acetic anhydride and *N*-acetylacetohydroxamic acid, respectively. This type of name is preferred to those such as *O*,*N*-diacetylhydroxylamine and *N*-hydroxydiacetylamine, which infer that

these compounds are bases. Salts of *(7)* [*viz. (9)*] can then be named as hydroxamates.

(10) *(11)*

(10a), R = C_6H_5, R' = C_6H_5CO, R'' = $C_6H_5CH_2$

(10b), R = R' = R'' = CH_3

(10c), R = C_6H_5

(11a), R = C_6H_5

Dialkyl derivatives *(10)* are referred to as hydroxamates (*i.e.*, as esters). Therefore, *(10b)* can be named methyl *N*-methylacetohydroxamate; the possible names derived from *N*-hydroxyamides should also be borne in mind.

Like *(6)*, compounds *(11)* are derivatives of hydroximic acid; however, they can also be named as *N*-hydroxyimidic acid derivatives in analogy with the *N*-hydroxyamide nomenclature of hydroxamic acid derivatives.

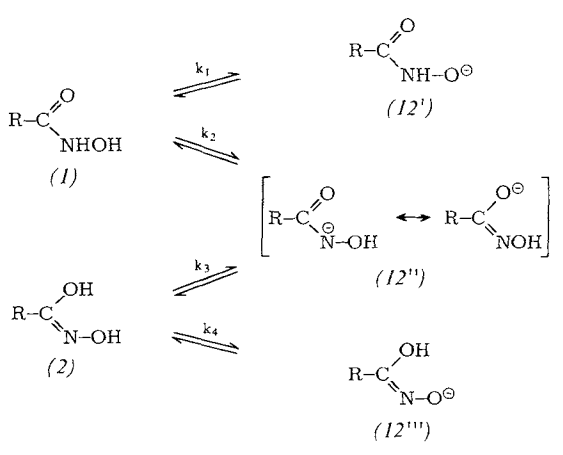
No attempt will be made to include the nomenclature of cyclic hydroxamic acids in which the functional groups become part of a heterocyclic system[4d, 27].

4. Ionization of Hydroxamic Acids *(1)*

4.1. Structure of the Hydroxamate Anion *(12)*

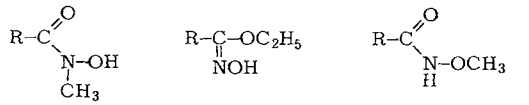
The unexpected relatively high acidity of hydroxamic acids *(1)* is one of their most striking properties. A number of pK_a values for RCO—NHOH are reported in the literature[28, 29] and these are of the order of 9 p*K* units, *i.e.*, approximately 6 units more acidic than amides $RCONH_2$. It should be noted that the difference between $NH_4^{\oplus}$ and $NH_3OH^{\oplus}$ is of the order of 3 p*K* units only. In a recent paper, the thermodynamic ionization constants were determined for a number of *p*-substituted benzohydroxamic acids and were found to correlate well with those calculated using Hammett's constants[28g, 29a].

The structure of the anion *(12)* is still the subject of some controversy. *A priori*, three possibilities *(12')*, *(12'')*, and *(12''')* are considered[29], and the ultimate aim is to determine



the four partial dissociation constants k_1 to k_4. At this point it is difficult to generalize beyond one hydroxamic acid and the solvent systems used for the particular study. Another difficulty lies in the detection of minute fractions; this problem also hindered the tautomerism studies alluded to in Section 2.2.

Nevertheless, some evidence has accumulated that *(12'')* best represents the structure of the anion of *(1)*. Measurements of dissociation constants could theoretically yield all the desired values k_1 to k_4 when the experimental p*K* values of such alkyl derivatives as *(5c)*, *(6b)*, and *(4c)* are considered as approximations of k_1, k_4 and $k_2k_3/(k_2+k_3)$, respectively[29]. This method can only lead to rather crude approximate values since the introduction of alkyl groups on N or O markedly effect these dissociation constants.



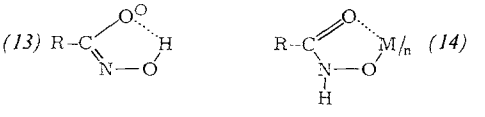
(5c) *(6b)* *(4c)*

(5d), R = C_6H_5 *(6c)*, R = C_6H_5 *(4d)*, R = C_6H_5

Although claims are made in the literature[29b, c] that the anions of aceto- and benzohydroxamic acids are composed of a mixture of *(12')* and *(12'')*, the proof based on UV measurements and pK_a values is not altogether convincing[29b, c, 30].

There is great disparity of values in the literature[29] resulting from pK_a determinations on hydroxamic acids *(1)* and their derivatives *(4)*, *(5)*, and *(6)*. For example, it would appear that benzohydroxamic acid *(1a)* and its methyl ester *(4d)* are stronger acids than *(5d)* or *(6c)*[29]. This is not unexpected, since resonance contributions [see *(12'')*] would enhance stabilization of the former, but not the latter two alkyl-substituted derivatives. In any one series, the acidity of either the NH or OH protons are affected to some degree by the nature of the substituents. For example, electron releasing substituents would reduce the relative acidity of the NH protons in *(4)* more than in *(5)*, since the inductive effect would be felt less by the more remote OH proton[5a, 29, 31].

An IR study of a salt of deuterated benzohydroxamic acid[31] in the solid state and in dioxane solution detected the O—D vibration frequency which could point to the presence of *(12'')* or, for that matter, *(12''')*. An intramolecular hydrogen bond, as in *(13)*, may also contribute to the stability of *(12'')*. An intramolecularly hydrogen-bonded species *(13)* could explain the stability of *(12'')* and the fact that nucleophilic reactions seem to take place preferentially on the NOH oxygen atom. The structure of complex salts of hydroxamic



(13) *(14)*

acids may differ from that of simple salts; the formula *(14)*[5] is supported already by the fact that *N*-alkylhydroxamic acids *(5)* form complexes, while *(4)* and *(6)* do not.

To summarize, the exact composition of salts of simple unsubstituted hydroxamic acids is not established with absolute certainty but there is good evidence that hydroxamic acids

bearing electron-attracting substituents dissociate exclusively to the anion *(12″)*, and thus belong to the *N*-acids.

4.2. Structure of the Hydroxamic Acid Cation

The structure of the cations of hydroxamic acids has received little attention, particularly since such salts are seldom isolated. Protonation of the carbonyl oxygen is suggested, by analogy with the behavior of amides; hence the cations are represented by the following formula[32]:

$$RC{=}\overset{\oplus}{O}H(NHOH) \leftrightarrow RC(OH){=}\overset{\oplus}{N}HOH$$

5. Reactions

It is not intended to survey all the reactions which have been reported for hydroxamic acids, but rather to restrict this section to recent studies in which the products have been well characterized.

5.1. Hydrolysis

Acid or base-catalyzed hydrolyses of hydroxamic acids *(1)* and their derivatives *(4)* or *(5)* to carboxylic acids and hydroxylamine derivatives proceed readily and it would appear logical to compare these hydrolyses with corresponding reactions of amides[29g, 32b, 32c]. Kinetic studies do indeed suggest that the mechanism of acid and base-catalyzed hydrolyses of benzohydroxamic acid resembles those of amides[32c].

By analogy to the hydrolysis of other carboxylic acid derivatives, the acid-catalyzed reaction is assumed to involve a cation whose structure is discussed in Section 4.2.

Attack by water leads to a tetrahedral intermediate of the kind usually associated with nucleophilic acyl substitution reactions; this intermediate yields the final products. First-order dependence on hydronium ion supports such a mechanism in a kinetic study of the hydrolysis of benzohydroxamic acid[32c]. For the acid-catalyzed hydrolysis of a number of aliphatic hydroxamic acids, polar and steric effects are found to be of comparable magnitude. This contrasts with the acid-catalyzed hydrolysis of amides or esters which show little or no dependence on polar effects. The observed rates correlate well with those calculated from the two-parameter Taft equation and thus support the above mechanism[29g].

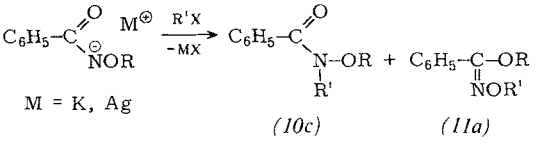
The base-catalyzed reaction is somewhat more complicated since the structure of hydroxamate anion *(12)* has not been settled. The question arises as to whether the unionized hydroxamic acid or its anion is attacked by hydroxide ion or water to produce the acid and hydroxylamine. Both first and second order dependence on hydroxide ion are inferred in the base-catalyzed reaction[32c], and further data are needed to establish these mechanisms.

5.2. Alkylation

Alkyl hydroxamates *(4)* are the major products resulting from the action of an alkylating agent on the hydroxamate ion *(12)*[33], in spite of the fact that three plausible sites exist for alkylation. One would expect the ambident anion *(12″)* to favor alkylation of the nitrogen or the carbonyl oxygen rather than the OH oxygen. However, the bifurcated anion species might be sufficiently hydrogen-bonded or coordinated to the accompanying cation that the oxygen attached to the nitrogen becomes the most nucleophilic and sterically least encumbered atom [see *(13)* and *(14)*] for attack on an electrophilic center.

The α-effect exerts a tremendous influence in effecting such a facile and selective reaction to form *(4)*. The anion *(12)* is rarely alkylated on the nitrogen to give *(5)*; these compounds are synthesized by another route, *viz.* acylation of R—NHOH[12, 33c–33e].

Further alkylation of *(4)* poses an interesting problem. The anion of *(4)* behaves more like an ambident anion and is subject to all the theories on this subject. The ratios of products are largely dependent upon the solvent, the nature of the accompanying cation, and the electrophilicity of the carbenium ion center in the alkylating agent. Alkylation of the potassium and silver salts of the alkyl esters C_6H_5CO—NHOR *(4e)* afforded a mixture of products from which the esters *(10c)* and the (*Z*) and (*E*) isomers of *(11a)* were isolated[33a]. The

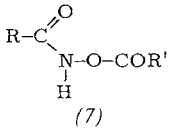


(10c) *(11a)*

isomer distribution is very much influenced by the alkyl halide R′X, the solvent (DMF/R′OH), the structure of R′ and the nature of the leaving group X. The isomers did not isomerize during work up and were thus formed under kinetically controlled conditions. Although the authors advance theories compatible with current thoughts on S_N reactions involving ambident anions, there are no predictions regarding the major products arising from the alkylations of *(4)*[33a].

5.3. Acylation

The reaction of hydroxamic acids *(1)* with acid halides or anhydrides produces mixed anhydrides ("*O*-acylhydroxamic acids") *(7)*[34]. More reactive acid halides, however such as sulfonyl or phosphoryl halides induce an almost spontaneous Lossen rearrangement of *(1)* presumably *via* *O*-sulfonyl or *O*-phosphoryl derivatives (see Section 6). The mixed anhydrides *(7)* are acids (p*K* in water would be *ca.* 7[29a]); they form



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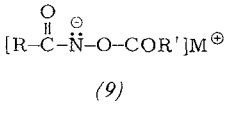

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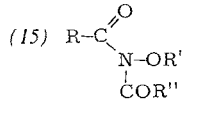
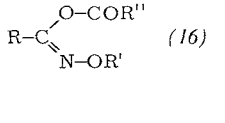




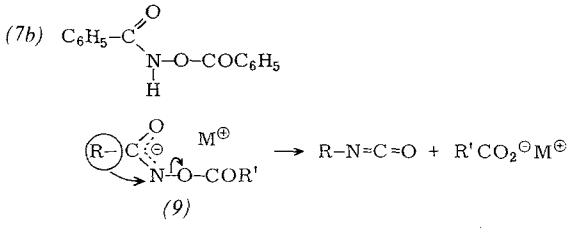
(16)

stable salts (in the cold) which rearrange on heating. Alkylation of these salts *(9)* and subsequent hydrolysis of the acyl residue produces either the (*Z*) or the (*E*) isomer of *(6)*[33a]. Acylation of the esters *(4)* yields the trisubstituted compounds *(15)*, and in certain instances also the isomers *(16)*[34c].

6. The Lossen Rearrangement

In 1872 *Lossen* discovered the rearrangement bearing his name when he observed that pyrolysis of the mixed anhydride *(7b)* affords phenyl isocyanate[2,3]. This rearrangement does not take place with hydroxamic acids RCO—NHOH *(1)*, as is stated erroneously in some textbooks. Preliminary *O*-acylation is essential for a smooth rearrangement. Even then, such acyl derivatives only undergo pyrolytic rearrangement under fairly stringent conditions; *e.g.* *O*-(acetoacetyl)benzohydroxamic acids form isocyanates, acetone, and carbon dioxide only at 300—400 °C[34d].

The usual mode is to convert compounds *(7)* by means of a strong base (preferably in nonhydroxylic solvents) at low temperature into the salt *(9)*, preferably in a medium from which the salt precipitates. Rearrangement of the anion of *(9)* to the isocyanate involves the departure of the carboxylate ion with concomitant migration of the group R from carbon to nitrogen.

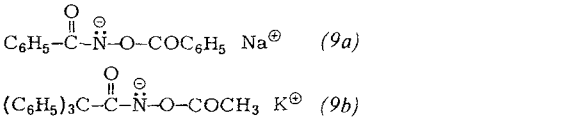


(7b)

(9)

The rate of this base-catalyzed Lossen rearrangement depends upon the electronic nature of the groups R and R'. *Hauser*'s kinetic data relate the rate of rearrangement to the strength of the acid $R'CO_2H$[35]. Thus, the rate increases as the departing group $R'CO_2^{\ominus}$ becomes more electron-attracting. This explains why *O*-sulfonyl or *O*-phosphoryl hydroxamic acids cannot be isolated: they rearrange extremely rapidly in a basic milieu (see below).

In another study, it was demonstrated that the rearrangement is facilitated as the electron-releasing power of R in *(9)* increases, provided no undue steric effects enter the picture[36]. The stereospecificity of the Lossen rearrangement supports this concerted mechanism since it is proven that the configuration of R in *(7)* remains unchanged during the rearrangement[37]. All attempts to show that nitrene intermediates are involved in nonphotolytic rearrangements have been unsuccessful. The ionic pathway indicated above with concomitant movement of group R from C to N as the anion departs therefore represents the best picture for the mechanism[34e].

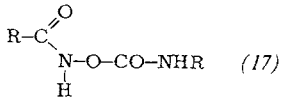


(9a)

(9b)

An example of the conventional rearrangement is that of *(9a)* in water at 95 °C to produce *N,N'*-diphenylurea. Presumably, the first product is phenyl isocyanate which hydrolyzes, in part, to aniline. The latter adds to residual isocyanate to produce the urea. As a matter of fact, *(9b)* is known to rearrange in water at room temperature to furnish trityl isocyanate.

Other activating groups inducing Lossen rearrangements have also been explored. 2,4-Dinitrofluorobenzene converts *(1)* into the *O*-2,4-dinitrophenyl derivatives, which rearrange in alkaline media to the amine RNH_2, 2,4-dinitrophenol, and carbon dioxide[38]. Another reagent for activating hydroxamic acids is sulfur trioxide (as the triethylamine complex) which forms the salts $RCO—NHOSO_3^{\ominus}$ $(C_2H_5)_3NH^{\oplus}$, in excellent yield. These derivatives are transformed into isocyanates, ureas, or urethanes under appropriate conditions[39].



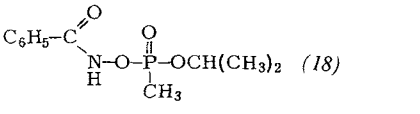
(17)

(17a), R = R' = C_6H_5

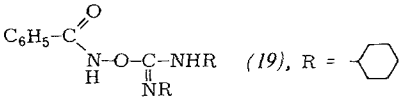
Unexpectedly, sulfonyl and phosphorus halides react vigorously with hydroxamic acids RCO—NHOH *(1)*. However, the products are not the *O*-sulfonyl or *O*-phosphoryl derivatives, but rather rearrangement products, *e.g.* *O*-carbamoyl hydroxamic acids *(17)*[40]. Thus, potassium benzohydroxamate is rearranged spontaneously by benzenesulfonyl chloride to give *(17a)* in one step.

A similar result is reported when benzohydroxamic acid *(1a)* was treated with the nerve gas "Sarin" (isopropyl methylphosphonofluoridate). In this reaction, the highly reactive intermediate *(18)* rearranges to phenyl isocyanate which in turn adds to unreacted benzohydroxamic acid to form *(17a)*.

The reaction of benzohydroxamic acid with benzenesulfonyl chloride or diisopropyl phosphofluoridate at pH 7.6 and 25 °C was investigated extensively in oxygen-18 labeled water[41]. The absence of oxygen-18 in any of the products expected from a Lossen rearrangement supports the mechanism involving initial formation of the *O*-sulfonyl- or *O*-phosphoryl hydroxamic acid. These hydroxamic acids then rearrange to phenyl isocyanate with simultaneous departure of the sulfonate *or* phosphate anion from the nitrogen. The isocyanate produced *in situ* now adds benzohydroxamic acid to produce the *O*-(phenylcarbamoyl)benzohydroxamic acid *(17a)*[41].

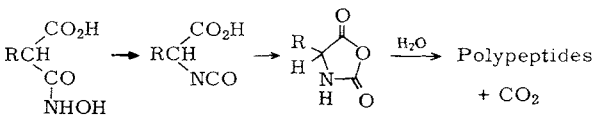


(18)



(19), R =

Interestingly, dicyclohexylcarbodiimide also reacts with benzohydroxamic acid to produce *(17a)*[42a]. The intermediate *(19)* from the addition of the hydroxamic acid to the diimide loses *N,N'*-dicyclohexylurea with concomitant rearrangement to phenyl isocyanate. Again isocyanate then adds a mole of benzohydroxamic acid to furnish the product. The rearrangement of the *anion* of *(17a)* is typical; the resulting carbamate anion loses CO_2 to yield aniline, which adds to phenyl isocyanate affording the isolated product *N,N'*-diphenylurea[42a]. An unusual Lossen rearrangement was observed when benzohydroxamic acid was treated with thionyl chloride, followed by thallium(I) phenoxide. The isolated triphenyl isocyanurate

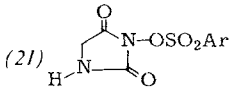


(20)

(23%) presumably arises from trimerization of phenyl isocyanate[42b].

Neighboring groups frequently react with an isocyanate group produced during a Lossen rearrangement. The Lossen degradation of half-malonohydroxamic acids *(20)* provides polypeptides, presumably *via* the route shown.

Since such polypeptides are prepared entirely in a basic medium, it becomes possible to synthesize an acid-sensitive polypeptide such as polytryptophan[43]. A hydroxamic acid group adds to a neighboring nitrile group when α-cyano esters react with hydroxylamine to form 5-amino-3-isoxazolones[44a]. Salicyclo- and anthranilohydroxamic acids react with benzenesulfonyl chloride to yield 2-benzoxazolone and 2-benzimidazolone, respectively[44]. Along these lines, a hydroxamic acid group can add to an adjacent isocyanate group to form a cyclic *N*-hydroxyimide. Thus, sulfonyl halides transform malonohydroxamic acids into *(21)*[45], and succino- and phthalohydroxamic acids into *(22)* and *(23a)* respectively[46].



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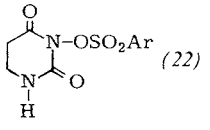

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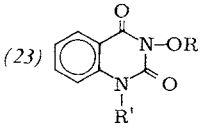
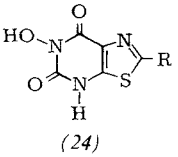


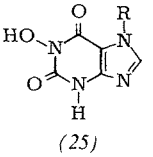
(23)

(23a), R = SO_2Ar, R' = H
(23b), R = $SO_2C_6H_5$, R' = H
(23c), R = $SO_2C_6H_5$, R' = CH_3

An extension of this method of fusing an *N*-hydroxyuracil ring onto five- or six-membered heteroaromatic systems resulted in the synthesis of various heterocycles of biochemical interest[47-51]. These include 3-hydroxylumazine, fused pyridopyrimidinediones, thiazolouracils, *e.g. (24)*, 1-hydroxyxanthines, *e.g. (25)*, and a number of *N*-hydroxypyrazolouracils represented by the selected structure *(26)*.



(24)



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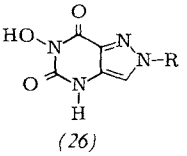


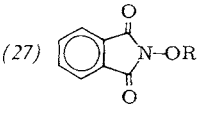
(26)

7. The Chemistry of Cyclic *N*-Hydroxyimides

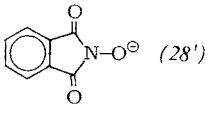
Cyclic *N*-hydroxyimides[52], particularly *N*-hydroxyphthalimide *(27a)*, have been known for a long time. Their synthesis has been discussed in Section 6. They may be formally regarded as *N*-acylhydroxamic acids of type *(8)*.

7.1. Structure and Alkylation

The assumption that *(27a)* exists in a colorless and a yellow modification proved to be erroneous. The yellow hue of the otherwise colorless crystals is caused by a minute amount of the intensely red anion *(28)*. One would expect the anion *(28')* of *N*-hydroxyphthalimide to be colorless [like the anion of *N*-hydroxysuccinimide]. It has therefore been suggested that the contribution of the highly chromophoric isomer *(28'')* is responsible for the intense color. In aqueous medium, the red solution of the salts of *N*-hydroxyphthalimide turns colorless due to their hydrolysis to *(29)*. The identity of *(29)* is established by its deep purple coloration with ferric chloride and by its isolation as the hydroxylammonium salt[52c]. Furthermore, *(29)* can be degraded by benzenesulfonyl chloride to anthranilic acid[52c].

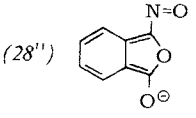


(27)

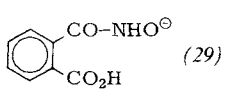


(28')

(27a), R = H
(27b), R = SO_2Ar



(28'')

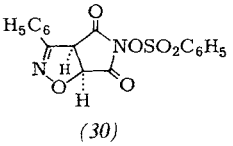


(29)

The stable triethylammonium salt of *(28')* can be alkylated in benzene to furnish *N*-alkoxyphthalimides, which readily yield *O*-alkylhydroxylamines on acid hydrolysis[53].

7.2. The Lossen Degradation of *N*-Hydroxyimides

Although hydroxamic acids RCO—NHOH *(1)* fail to form stable *O*-sulfonyl derivatives, *N*-hydroxyimides form isolable *N*-sulfonyloxy and *N*-phosphoryloxy derivatives[52,54]. The Lossen rearrangement of these sulfonates to amino acids has been performed for aliphatic and aromatic systems. Thus reaction of *cis*-*N*-benzenesulfonyloxyhexahydrophthalimide with 10% aqueous NaOH solution produced *cis*-2-aminocyclohexanecarboxylic acid which is isolated as the benzenesulfonate[37c]. *N*-Sulfonyloxyphthalimides *(27b)* are degraded by amines to anthranilic acid derivatives[52,54a]. By a similar mechanism, *N*-benzenesulfonyloxynaphthalimide is converted by hydroxide ion to naphthostyril[55]. In the same vein, *cis*-*N*-benzenesulfonyloxy-3-phenyl-2-isoxazoline-4,5-dicarboximide *(30)* reacts with aqueous ammonia to yield only one ureido acid *(31)* which was further cyclized, in a separate step, by dilute hydrochloric acid to *(32)*[56].



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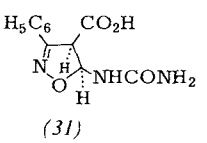
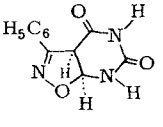


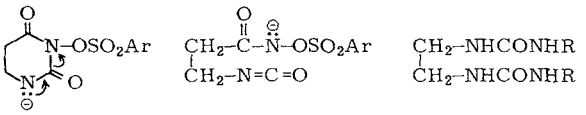
(31)



(32)

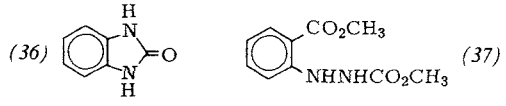
Interesting Lossen rearrangements are observed with *(22)*: treatment with one equivalent of NaOH produces ethylenediamine[46b], and degradative reduction to *N*,*N'*-dimethylethylenediamine occurs with $LiAlH_4$[57]. Both rearrangements are initiated by formation of *(33)* [the anion of *(22)*] which opens to give the anion *(34)* of *O*-arenesulfonyl-3-isocyanatopropionohydroxamic acid. The latter is the logical precursor for 1,2-ethylenediisocyanate, which can be hydrolyzed to ethyl-

enediamine or reduced to *N,N*-dimethylethylenediamine. The reaction of *(22)* with ammonia or amines produces ureas *(35)*, presumably *via* the diisocyanate[58].



(33) *(34)* *(35)*

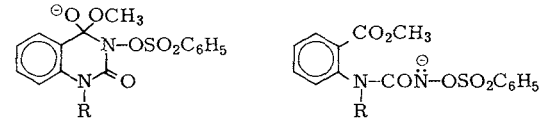
In a series of surprising Lossen rearrangements, 3-benzenesulfonyloxy-2,4-quinazolinedione *(23b)* rearranges either to benzimidazolone *(36)* or *o*-hydrazinobenzoic acid derivatives *(37)*[59a].



(36) *(37)*

The reaction of *(23b)* with NaH in DMF yields *(36)*. Presumably, neutralization of the acidic ring NH proton forms the anion [cf. *(33)*] which opens to produce *O*-benzenesulfonyl-2-isocyanatobenzohydroxamic acid. The latter rearranges to phenylene diisocyanate, from which *(36)* is created.

Lossen degradation to *(37)* is brought about by sodium methoxide in methanol. Attack by methoxide ion at the highly electrophilic C-4 atom of *(23b)* gives rise to a tetrahedral intermediate *(38a)* which opens to form *(39a)*. This second intermediate then rearranges to give *(40a)* which can add methanol to furnish *(37)*.



(38) *(39)*

(38a), R = H *(39a)*, R = H

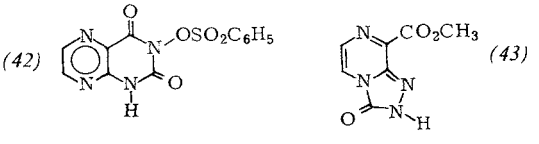
(40) *(41)*

(40a), R = H

It was therefore not surprising that the 1-methyl analog of *(23b)* [*(23c)*] is degraded by methoxide ion to 1-methyl-3-indazolone derivatives *(41)*, R = H or CO_2CH_3[59].

When the *pyridine* analogs of *(23a)* are treated with sodium methoxide, a series of *pyridine* analogs of *(37)* is obtained[59b]. An unusual product is encountered when the *pyrazine* analog *(42)* is exposed to sodium methoxide in methanol: the triazolopyrazine *(43)* is formed.

The mechanism of this reaction follows that suggested for the transformation of *(23)* into *(40)*, with the difference that

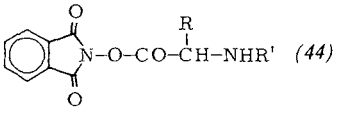


(42) *(43)*

the isocyanate cyclizes onto the pyrazine ring nitrogen in preference to adding methanol.

7.3. *N*-Hydroxyimides in Peptide Syntheses

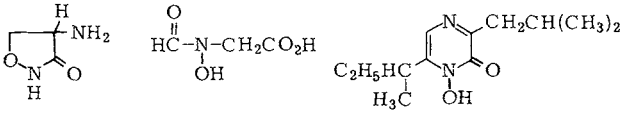
A number of investigators have explored the use of *N*-acyloxyimides as precursors for peptide syntheses[60]. The method commences with the preparation of esters of amino acid derivatives *(44)*, followed by attack by another amino acid on the activated ester carbonyl group to form a peptide link, with release of the *N*-hydroxyimide anion.



(44)

8. Brief Survey of Some of the Biological Activities of Hydroxamic Acids

Recent progress in hydroxamic acid chemistry has been stimulated by the isolation of several naturally occurring and the synthesis of a number of medicinally active hydroxylamine derivatives[4d]. Notable among these are the antibiotic cycloserine *(45)*[61], the antitumor antibiotic hadacidin *(46)*[62], and the heteroaromatic antibiotic aspergillic acid *(47)*[63].



(45) *(46)* *(47)*

A wide spectrum of biological activities has been reported and a full recent review exists[4d]. A few recent examples will now be considered. A series of *o*-, *m*-, and *p*-alkoxybenzohydroxamic acids was found to be highly effective against pathogenic fungi[64], while salicohydroxamic acids and derivatives are effective antibacterial and antifungal agents[65]. β-Alkylaminopropionohydroxamic acids show hypotensive properties[66], and a number of hydroxamic acids and *N*-hydroxyureas possess hypocholesteremic activity[67]. *p*-Butoxyphenylacetohydroxamic acid (Bufexamac) is in actual use as an antiinflammatory agent in humans[68]. A series of terephthalohydroxamic and other dicarbohydroxamic acids have been investigated as potential antimalarials[69].

In a quantitative structure-activity relationship study, using the Hansch approach, a series of aliphatic and *m*- and *p*-substituted benzohydroxamic acids were investigated for their relative power to inhibit urease activity[72]. Among the alkylhydroxamic acids, maximum activity was observed with heptanohydroxamic acid *(1)*, R = C_6H_{13}, which the authors attribute to stereospecific "hydrophobic bonding". They concluded that electronic effects do not play a significant role in this activity. However, the steric effect of a bulky substituent becomes very clear in a series of aliphatic hydroxamic acids in which a phenyl group is moved along the fatty acid chain: a remarkable decrease of inhibitory power is observed as the phenyl group approaches the hydroxamic acid group.

Hydroxamic acids number among the few compounds effective as nucleophilic reactivators of sarin-inactivated chymotrypsin[71] or acetylcholine esterase[28d]. *N*-Hydroxyurea has been investigated extensively since it exhibited antileukemic activity in mice and spurred extensive pharmacological screening of many *N*-hydroxyureas and urethans[4d]. Hydroxyurea (Hyd-

rea) is available to the medical profession as an approved drug for the treatment of melanoma, myelocytic leukemia, and carcinoma of the ovary[70].

One of the metabolites of the carcinogenic *N*-(2-fluorenyl)acetamide is *N*-(2-fluorenyl)acetohydroxamic acid[72]. This points to the potentially important biological oxidation of amides by *N*-hydroxylation and it is conceivable that other compounds containing monosubstituted amide groups can form similar metabolites.

9. Conclusions

While tremendous progress has been made over the past 30 years in understanding and applying the chemistry of hydroxamic acids and *N*-hydroxyimides, a number of problems remain to be solved. Although the structures of hydroxamic and hydroximic acids and derivatives are fairly well established, the fine structure of the anion of hydroxamic acid, as well as its hydrolysis and behavior on nucleophilic substitution, remain to be clarified. Perhaps, the greatest endeavor in the next decade will be in the area of the biological evaluation of hydroxamic acid derivatives. In the meantime the study of hydroxamic acids will remain a viable part of chemistry[*].

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German version: Angew. Chem. *86*, 419 (1974)

[*] *Note added in proof* (May 24, 1974): Meanwhile an interesting rearrangement of *N*-hydroxyureas to *O*-carbamoylhydroxylamines, in solution, has been reported:
RNH—CO—NR'OH ⇌ [RNHOH + R'NCO] → RNH—CO—ONHR'
The reaction has been shown to proceed *via* the sterically induced dissociation of the urea to a hydroxylamine and an isocyanate which recombine to give the product [*H. G. Aurich* and *H.-G. Scharpenberg*, Chem. Ber. *106*, 1881 (1973)].

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[2] *W. Lossen*, Liebigs Ann. Chem. *161*, 347 (1872); *186*, 1 (1877); *252*, 170 (1889); *281*, 169 (1894).

[3] *H. L. Yale*, Chem. Rev. *33*, 209 (1943).

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[5] a) *S. Mizukami* and *K. Nagata*, Coord. Chem. Rev. *3*, 267 (1968); b) *T. J. King* and *P. G. Harrison*, J. C. S. Chem. Comm. *1972*, 815.

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[7] A variation of this test is the Angeli-Rimini reaction in which aldehydes are transformed into hydroxamic acids by benzenesulfohydroxamic acid, $C_6H_5SO_2NHOH$ [see *G. Di Maio* and *P. A. Tardella*, Gazz. Chim. Ital. *96*, 526 (1966)].

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Mass Transport in Solids

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Two aspects are especially important in connection with mass transport in solids; these are the phenomenological description of the diffusion process and the discussion of the transport mechanism. In addition to the self-diffusion of the constituent ions or atoms of a solid, which can be followed only with the aid of radioactive or stable isotopes, other known types of diffusion are the diffusion of trace elements, which can in principle be treated in the same way as self-diffusion, and chemical diffusion, in which the diffusion partners differ in their chemical composition. Processes of this type are being increasingly studied with the electron beam microprobe. Regardless of the crystallinity and the type of bonding, problems concerned with diffusion in solids can be discussed from a single standpoint by slight adaptation to suit the particular situation in question.

1. Introduction

Diffusion processes in solids provide information about the mobility of the particles that constitute the solid or that react with it. In the former case, *i.e.* in self-diffusion, the intrinsic mobility of the atoms or ions is determined; an insight into the dynamic structure of solids can be gained from measurements on this process. In the second case, *i.e.* chemical diffusion, one follows true chemical reactions, exchange processes, *etc.* between one solid and another solid, a liquid, or a gas. Chemical diffusion and self-diffusion are uniquely related to each other.

It is not purely on their own account that diffusion processes are interesting. There are many processes in which mass transport of this nature is involved or is even rate-determining. Some examples are crystallization, oxidation or scaling processes, corrosion phenomena on metals or oxides under the

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