Stereochemical Reversal of Nucleophilic Substitution Reactions Depending upon Substituent: Reactions of Heteroatom-Substituted Six-Membered-Ring Oxocarbenium Ions through Pseudoaxial Conformers

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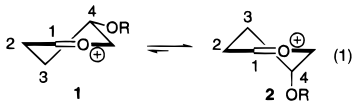
Although conformational preferences of neutral six-membered-ring systems are dominated by steric effects,[1] recent computational studies suggest that electronic effects exert a profound influence on the conformations of six-membered-ring oxocarbenium ions. In the process of analyzing rates of glycoside hydrolysis, Bowen and co-workers reported molecular mechanics calculations indicating that hydroxyl groups at C-4 and C-3 of a six-membered oxocarbenium ion[2] assume pseudoaxial positions in the half-chair conformation (eq 1).[3,4] The pseudoaxial preference has been

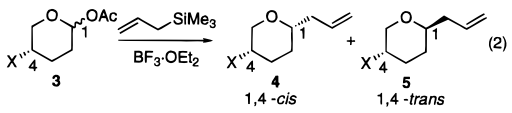


1 **2** (1)

attributed to a stabilizing electrostatic attraction between the partially negatively charged hydroxyl oxygen atom and the carbocationic carbon,[5] which are positioned closer together in a pseudoaxial conformer than in a pseudoequatorial conformer.[3,4] This phenomenon would have significant impact on bioorganic and synthetic chemistry if it could be confirmed by solution-phase experiments. For example, the mannosyl cation is believed to adopt a conformation in which alkoxy groups at C-3 and C-4 reside in pseudoaxial orientations.[6,7] The preference for pseudoaxial positions in oxocarbenium ions could also provide a means to control the stereochemical courses of synthetic transformations.[8,9] In this paper, we report evidence that oxocarbenium ions bearing electronegative substituents at C-3 and C-4 react through pseudoaxial conformers.

To investigate the influence of alkoxy groups on the conformations of oxocarbenium ions, we compared nucleophilic substitution reactions of analogous alkyl- and alkoxy-substituted acetals bearing a single substituent at various positions on the ring.[2,10] Because nucleophiles attack oxocarbenium and iminium ions along axial trajectories through chairlike transition structures,[11,12] the stereochemistries of the products reveal the reactive conformations of the oxocarbenium cations. These reactive conformations will be strongly influenced by effects that stabilize the ground state conformations, since the transition structures for nucleophilic attack should be early and thus reactant-like. The *C*-glycosylation[13,14] of an anomeric acetate with allyltrimethylsilane, which likely proceeds via an oxocarbenium ion,[15] is an excellent probe for determining reactive conformations since attack of this carbon nucleophile is irreversible and high-yielding.

The nucleophilic substitution of 4-substituted tetrahydropyran acetals **3** proceeded with opposite stereochemistry depending upon the substituent (eq 2). Alkyl-substituted acetals **3a** and **3c** provided

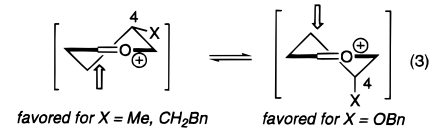


3 **4** 1,4 -*cis* **5** 1,4 -*trans* (2)

compound	X	cis : trans	yield (%)
a	Me	94 : 6	74
b	OBn	1 : 99	75
c	CH_2Bn	93 : 7	77

the 1,4-cis products **4a**,**c** whereas the presence of a benzyloxy group at C-4 in **3b** led to selective formation of the 1,4-trans product **5b**.[16,17]

The stereoselectivity observed for nucleophilic substitution of **3b** (eq 2) indicates that the alkoxy-substituted oxocarbenium ion intermediate[18] reacts through the pseudoaxial conformer **7** (eq 3),[8]



favored for X = Me, CH_2Bn *favored for X = OBn* (3)

6 **7**

since stereoelectronic effects[11,12] require that the 1,4-trans product arises from nucleophilic attack on this conformer of the cation. This conformational preference is in accord with computationally determined conformational preferences for substituted tetrahydropyran cations in their ground states.[3,4] The results also indicate that the alkyl-substituted oxocarbenium ions react through the pseudoequatorial conformer **6**.[3] Alternative explanations for these stereoselectivities do not account for the experimental data.

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(2) The numbering used in this paper considers the carbocationic carbon as C-1.

(3) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859−864.

(4) Other calculations (HF/6-31G*) indicate that oxocarbenium ion **2** (R = Me) is favored over **1** by 4.1 kcal/mol: Miljkovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597−7604.

(5) Dudley, T. J.; Smoliakova, I. P.; Hoffmann, M. R. *J. Org. Chem.* **1999**, *64*, 1247−1253.

(6) Winkler, D. A.; Holan, G. *J. Med. Chem.* **1989**, *32*, 2084−2089.

(7) Blériot, Y.; Genre-Grandpierre, A.; Imberty, A.; Tellier, C. *J. Carbohydr. Chem.* **1996**, *15*, 985−1000.

(8) This counter-intuitive conformational preference has been invoked to explain stereoselective reactions of acetoxy-substituted vinyloxocarbenium ions: Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917−1920.

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(12) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 209−221.

(13) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, FL, 1995.

(14) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Tarrytown, NY, 1995; Vol. 13.

(15) Reactions of acetals with carbon nucleophiles have been shown to proceed via carbocation intermediates. See, for example: (a) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915−7916. (b) Matsutani, H.; Ichikawa, S.; Yaruva, J.; Kusumoto, T.; Hiyama, T. *J. Am. Chem. Soc.* **1997**, *119*, 4541−4542. Other reactions of acetals do not appear to involve free cations. See, for example: (c) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089−8110.

(16) In all cases, stereoselectivities were determined by GC or GCMS analysis of unpurified reaction mixtures. These selectivities were corroborated by ^{1}H and ^{13}C NMR spectroscopy. The relative stereochemistries of the products were determined using combinations of ^{1}H NMR coupling constant data and NOE measurements. The yields are reported for purified products.

(17) The addition of the enoxysilane derived from acetophenone to **3b** in the presence of BF_3·OEt_2 provided the corresponding ketone with 93:7 diastereoselectivity, favoring the 1,4-trans isomer. This preference for **3b** to form the 1,4-trans product does not change (±3%) as a function of solvent (CH_2Cl_2, toluene, $EtNO_2$, EtCN) or Lewis acid ($SnBr_4$).

(18) Except for **13a** (which is prepared as only the cis isomer), mixtures of anomeric acetates were employed. For the acetate **18** (eq 8), the two anomers of starting material are separable. Control experiments indicate that both anomers give the same product with the same degree of selectivity.

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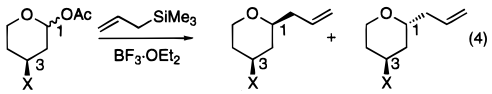
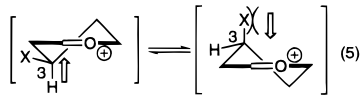
Substituents at C-4 are too far away from the cationic carbon atom to impede approach of the nucleophile. Anchimeric assistance from the benzyloxy group can be discounted by examination of selectivities exhibited for other substitution patterns (vide infra). Because both methyl-substituted acetal **3a** and phenethyl-substituted acetal **3c** undergo substitution with 1,4-cis selectivity, participation by the phenyl group on the benzyloxy substituent cannot be responsible for the reversal of selectivity.[19]

The reversal of selectivity exhibited by C-4 substituted acetals was also observed for C-3 substituted systems. Nucleophilic substitution on methyl-substituted acetal **8a** provided the 1,3-trans product **10a** with high selectivity,[20] and the alkoxy-substituted analogue **8b** provided 1,3-cis product **9b** (eq 4).



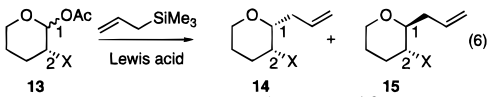
compound	X	cis : trans	yield (%)
a	Me	<1 : >99	69
b	OBn	89 : 11	94

The selectivities observed for 3-substituted acetals **8** (eq 4) are consistent with calculations of ground-state conformations of oxocarbenium ions in which an alkyl group at C-3 favors pseudoequatorial conformer **11**, while an alkoxy group favors pseudoaxial conformer **12** (eq 5).[3,21] Unlike the C-4 substituted



systems, the pseudoaxial substituent at C-3 of **12** is close enough to inhibit approach of the nucleophile. Evidently, the alkoxy substituent is not large enough to force the reaction to occur via the less stable conformer **11** (X = OBn). The stereochemistry observed for the alkoxy-substituted acetal **8b** demonstrates that anchimeric assistance by the alkoxy group does not occur. If this group were to participate in this way, the 1,3-trans product would be formed from **8b**, contrary to the experimental result (eq 4).

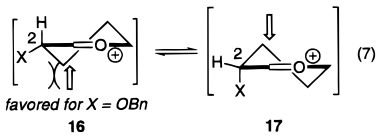
To complete our studies, we examined the influence of substitution adjacent to the acetal carbon. An alkyl substituent confers little stereochemical differentiation between the two sides of the intermediate oxocarbenium ion (eq 6), consistent with



compound	X	Lewis acid	cis : trans	yield (%)
a	Me	BF_3·OEt_2	52 : 48	57
b	OBn	$SnBr_4$	83 : 17	84

observations on 2-methyl-substituted tetrahydrofuran acetals.[22] The reaction of the 2-alkoxy acetal **13b**, on the other hand, was cis-selective.[23]

The selectivities shown in eq 6 are the result of conformational bias and steric approach control working in opposition to each other. Although the pseudoequatorial conformer should be modestly favored for the 2-methyl oxocarbenium ion **16** (X = Me),[3,24] this conformer is less reactive than the axial conformer **17** (X = Me) since approach of the nucleophile to **16** must occur along a trajectory over the methyl group. The low selectivity observed for this substrate indicates that steric inhibition of nucleophilic attack opposes conformational control. These forces are not balanced for the alkoxy-substituted oxocarbenium ion, however. Alkoxy substituents exhibit a larger preference for the pseudoequatorial conformer than the alkyl-substituted cation,[24] likely due to hyperconjugation between the electron-donating C−H bond and the 2p orbital on the electrophilic carbon atom.[5] Because an alkoxy group is less sterically demanding than an alkyl group, the nucleophile can approach from the same face as the substituent to provide predominantly the 1,2-cis product **14b**. As with the 3-substituted oxocarbenium ion, cis selectivity is inconsistent with anchimeric assistance.



The preference for C-4 substituted oxocarbenium ions to react with alkoxy groups in pseudoaxial orientations extends to other electronegative heteroatom substituents. Nucleophilic substitution on 4-chloro acetal **18** provided the 1,4-trans product **19** preferentially (eq 8). This result may be understood by considering nucleophilic attack on the pseudoaxially substituted oxocarbenium ion **7** (X = Cl, eq 3).[25]

In conclusion, the stereoselective reactions of tetrahydropyran acetals with nucleophiles demonstrate that oxocarbenium ions bearing electronegative substituents at C-3 and C-4 react through pseudoaxial conformers. These experiments show that for substitution at both C-3 and C-4, alkyl- and alkoxy-substituted oxocarbenium ions provide products with opposite stereochemistries. In these cases, the conformer of the intermediate that undergoes nucleophilic attack is the lower energy conformer as determined using computational methods. The preference for heteroatom-substituted oxocarbenium ions to react through pseudoaxial conformers likely operates in other carbocationic systems such as *N*-acyliminium ions.[26]

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Supporting Information Available: Complete experimental procedures, product characterization, and stereochemical proofs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The use of BF_3·OEt_2 resulted in lower selectivity (66:34, 85% yield). Using TMSOTf as the Lewis acid with the corresponding methyl acetal results in no stereoselectivity: Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263−6276.

(24) Calculations (B3LYP/6-31G*//HF/6-31G*) show that conformer **16** is favored by only 0.5 kcal/mol when X = Me, but is preferred by 1.6 kcal/mol for X = OMe.

(25) Ab initio calculations (HF/3-21G*) show that the pseudoaxial oxocarbenium **7** (X = Cl) is favored over the pseudoequatorial cation **6** by 2.5 kcal/mol.

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