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Using Nucleophilic Substitution Reactions to Understand How a Remote Alkyl or Alkoxy Substituent Influences the Conformation of Eight-Membered Ring Oxocarbenium Ions

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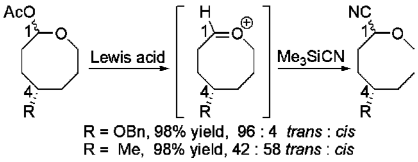
ABSTRACT



A remote alkoxy substituent strongly stabilizes one particular conformer of an eight-membered ring oxocarbenium ion by a through-space electrostatic effect. X-ray crystallographic analysis of a crystalline derivative proves that kinetically controlled nucleophilic substitution favors the 1,4-trans product. Nucleophilic substitution of the corresponding alkyl-substituted acetate, however, is unselective. A computational model has been developed and experimentally validated to predict the low-energy conformers of C3-, C4-, or C5-alkyl- or alkoxy-substituted eight-membered ring oxocarbenium ions.

Many of the methods employed to synthesize the substituted medium-ring ethers contained within cytotoxic natural products such as the ladder ether toxins[1] and Laurencia metabolites[2] rely on establishing stereochemistry prior to or during cyclization. Selective introduction of a substituent to a medium-ring oxocarbenium ion represents another powerful method for preparing this class of compounds.[2d] The stereoselectivities resulting from nucleophilic attack on medium-ring oxocarbenium ions, however, are largely undocumented,[1a,2d] in contrast to reactions of the more common five- and six-membered ring systems.[3] In this communication, we provide a systematic study of the influence of substituents on the selectivity of nucleophilic additions to eight-membered ring oxocarbenium ions. We demonstrate that steric effects alone are insufficient to obtain high selectivity. In contrast, electronic effects exhibited by remote alkoxy substituents in eight-membered rings can be powerful forces for the control of ring conformation, and therefore selectivity, mirroring results observed for five- and six-membered rings.[3]

Selective nucleophilic addition to monosubstituted eight-membered ring oxocarbenium ions[4] can be complicated by the presence of many accessible low-energy conformations of these intermediates. Furthermore, the distribution of

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[1] (a) Nicloaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136−4137. (b) Crimmins, M. T.; Cleary, P. A. *Heterocycles* **2003**, *61*, 87−92 and references cited therein.

[2] (a) Paquette, L. A.; Sweeney, T. J. *J. Org. Chem.* **1990**, *55*, 1703−1704. (b) Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386-4399. (c) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483−7498. (d) For an example of nucleophilic addition to a C7-alkyl-substituted eight-membered ring oxocarbenium ion, see: Rychnovsky, S. D.; Dahanukar, V. H. *J. Org. Chem.* **1996**, *61*, 7648−7649. (e) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653−5660 and references cited therein.

[3] (a) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521−15528 and references cited therein. (b) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209.

[4] Reactions of acetals with carbon nucleophiles likely proceed via oxocarbenium ion intermediates: Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915−7916.

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conformers cannot be predicted easily. Preference among the conformers is crucial for achieving highly selective reactions because nucleophilic attack should be slow relative to conformer interconversion.[2b,5,6] The unsubstituted intermediate exists as two low-energy conformations, boat-chair-2 (**1**) and boat-chair-3 (**2**), which are comparable in energy (Scheme 1).[7−10] When a remote substituent is appended to the ring, conformational control becomes even more complex. Selectivity upon nucleophilic attack depends not only on the preferred substituent orientation but also on the relative contribution of **1**, **2**, and other possible conformers to the overall energy profile.[7b] Each of these conformers should undergo attack by nucleophiles from the periphery as observed for electrophilic approach to medium- and large-ring olefins.[11]

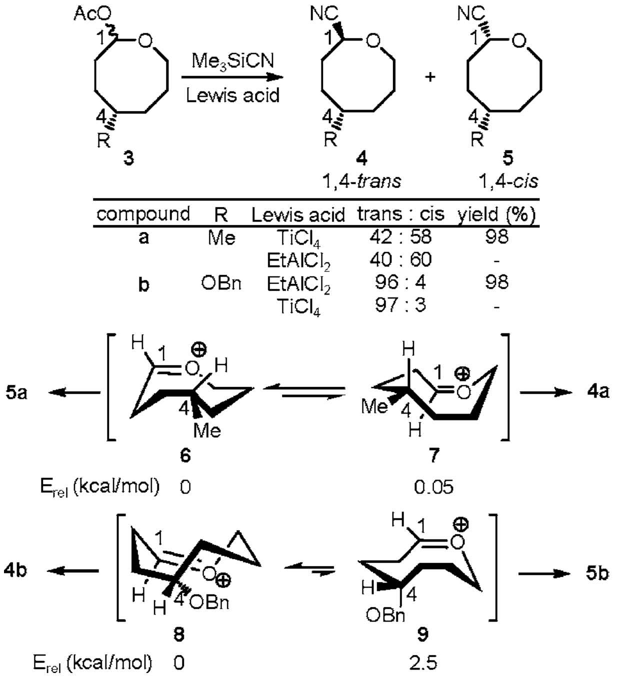
Scheme 1

1 **2**

E_{rel} (kcal/mol) 0 0.1

To elucidate the influence of remote substitution on selectivity, we compared nucleophilic substitution reactions of eight-membered ring oxocarbenium ion precursors bearing a C3-, C4-, or C5-alkyl or alkoxy substituent.[12,13] Nucleophilic addition to a C4-methyl-substituted eight-membered ring oxocarbenium ion, generated upon treatment of acetate **3a** with a Lewis acid, is unselective (Scheme 2).[14−16] The lowest energy conformers of this intermediate, **6** and **7**, bear a strong resemblance to the unsubstituted cations shown in Scheme 1. Although the steric preference for a methyl substituent to adopt a pseudoequatorial orientation seems to dominate, conformers **6** and **7** should be similar in energy.[10] As a consequence, selectivity is low because both diastereomeric faces of the oxocarbenium ion are presented to the nucleophile.

Scheme 2



compound	R	Lewis acid	trans : cis	yield (%)
a	Me	$TiCl_4$	42 : 58	98
		$EtAlCl_2$	40 : 60	-
b	OBn	$EtAlCl_2$	96 : 4	98
		$TiCl_4$	97 : 3	-

A C4-alkoxy substituent, however, does control the conformation of the charged intermediate.[10] The C4-benzyloxy-substituted acetate **3b** afforded high 1,4-trans diastereoselectivity upon nucleophilic substitution (Scheme 2).[14−16] This selectivity can be explained by a through-space electrostatic attraction[17,18] between the remote electronegative substituent and C-1[9a] that stabilizes conformer **8** (Scheme

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(5) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc*. **1985**, *107*, 2435−2441.

(6) Under certain conditions, solvent cage effects can exert strong influences on the selective reactions of oxocarbenium ions: Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc*. **2002**, *124*, 9720−9721.

(7) (a) Anet, F. A. L. In *Conformational Analysis of Medium-Sized Heterocycles*; Glass, R. S., Ed.; VCH: New York, 1988, Chapter 2. (b) Meyer, W. L.; Taylor, P. W.; Reed, S. A.; Leister, M. C.; Schneider, H.-J.; Schmidt, G.; Evans, F. E.; Levine, R. A. *J. Org. Chem*. **1992**, *57*, 291−298. (c) Yavari, I.; Tahmassebi, D.; Nori-Shargh, D.; Heydari, M. *Monatsh. Chem*. **1996**, *127*, 1021−1025.

(8) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 765−771.

(9) (a) Dudley, T. J.; Smoliakova, I. P.; Hoffmann, M. R. *J. Org. Chem*. **1999**, *64*, 1247−1253. (b) Liang, G.; Sorensen, J. B.; Whitmire, D.; Bowen, J. P. *J. Comput. Chem*. **2000**, *21*, 329−339.

(10) Details of calculations are provided as Supporting Information.

(11) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981−3996.

(12) Numbering in this paper considers the carbocationic carbon as C-1.

(13) For these reactions, a small nucleophile, trimethylsilyl cyanide (Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem*. **1974**, *39*, 914−917), was chosen to minimize steric effects in the transition state that might perturb the inherent conformational preferences of the charged intermediates. Lewis acid-mediated nucleophilic substitution of **10a** and **15a** with another small nucleophile, diethyl-2-phenylethynylalane, gave selectivities comparable to those reactions using trimethylsilyl cyanide as the nucleophile.

(14) Mixtures of diastereomeric acetates (the syntheses of acetates are contained in Supporting Information) were used in these reactions. Control experiments indicate that diastereomeric acetates give the same product with largely the same degree of selectivity. These control experiments strongly suggest that the reaction operates by a dissociative mechanism. If direct displacement occurred, the selectivity should reflect the initial acetate ratio.

(15) In all cases, diastereoselectivities were determined by GC or single-scan ^{1}H NMR spectra of unpurified reaction mixtures. The relative stereochemistry of the major product was not proven for unselective reactions (C4- and C5-methyl) but was postulated to be cis on the basis of computational results (ref 10). For nitrile **4b**, the relative stereochemistry was proven by X-ray crystallography.

(16) Control experiments indicate that cyanide addition is irreversible, so these reactions are kinetically controlled. These reactions require the presence of Lewis acid, and the selectivity of product formation is independent of the solvent (CH_2Cl_2, toluene, or Et_2O) and Lewis acid ($EtAlCl_2$ or $TiCl_4$) employed. A table of comparative selectivities appears in Supporting Information.

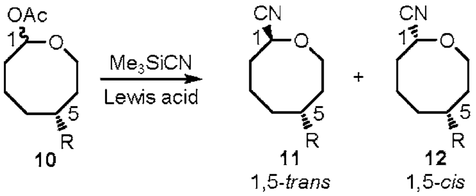
(17) (a) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc*. **1992**, *114*, 859−864. (b) Miljković, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem*. **1997**, *62*, 7597−7604. (c) Jensen, H.; Bols, M. *Org. Lett*. **2003**, *5*, 3419−3421.

(18) The border between anchimeric assistance and electrostatics is not a clear one. On the basis of B3LYP/6-31G* calculations, the oxygen of the benzyloxy group and the carbocationic carbon are approximately 2.6 Å apart in the optimized geometry of **8**. Although this separation is less than the van der Waals contact distance (3.2 Å, as found in: Bondi, A. *J. Phys. Chem*. **1964**, *68*, 441−451), it is considerably greater than a standard carbon−oxygen bond (1.4 Å) and longer than the bond distance in a trivalent oxonium ion such as the Et_3O cation (1.5 Å, as found in: Watkins, M. I.; Ip, W. M.; Olah, G. A.; Bau, R. *J. Am. Chem. Soc*. **1982**, *104*, 2365−2372). In addition, the C4−OBn bond and the C1═O$^+$ bond are of standard lengths (1.4 and 1.27 Å, respectively, ref 9b).

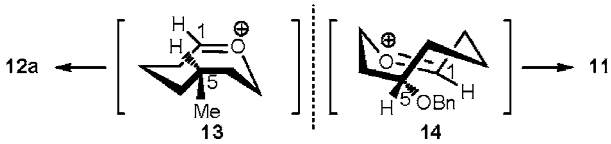
2).[19,20] This counterintuitive interaction occurs despite the inherent preference for substituents at this position to reside outside the ring, avoiding transannular strain.[11] Conformer **9** is higher in energy than **8** because the benzyloxy substituent is too far away from the cationic carbon[9a] to stabilize this conformer effectively. It is likely that nucleophilic addition to **9** provides the minor 1,4-cis product **5b**.

The conformational preferences with substitution at C-5 resemble those observed when a C-4 substituent is present. For example, nucleophilic substitution of acetate **10a** afforded a nearly equal ratio of diastereomeric products **11a** and **12a** (Scheme 3). The presence of two low-energy conformers (**13**, and the C5-pseudoequatorial analogue of **6**) again leads to an unselective nucleophilic substitution reaction.[10,18,19] A C5-alkoxy-substituted eight-membered ring oxocarbenium ion also exists as a mixture of conformers in which the remote alkoxy group stabilizes the charged intermediate. Nucleophilic substitution reactions of C5-benzyloxy acetate **10b** mainly provided 1,5-trans product **11b** (Scheme 3). Because the energy difference among the three low-energy conformers of the intermediate (only the lowest, **14**, is shown) leading to **11b** or **12b** is less than that between **8** and **9**,[10] the trans:cis selectivity is reduced.

Scheme 3

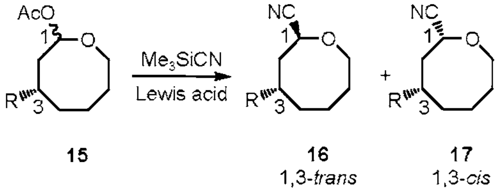


compound	R	Lewis acid	trans : cis	yield (%)
a	Me	$TiCl_4$	48 : 52	83
		$EtAlCl_2$	50 : 50	-
b	OBn	$EtAlCl_2$	80 : 20	89

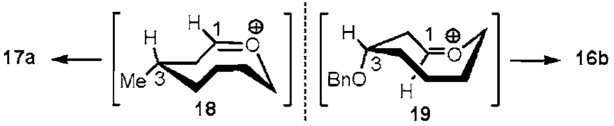


Alkyl or alkoxy substituents at C-3 do not exert significant control for reactions of eight-membered ring oxocarbenium ions. Conformers possessing a pseudoaxial or a pseudoequatorial substituent at a corner position of the eight-membered ring are close in energy because the substituents experience similar gauche−gauche interactions with the ring.[7a,11] Because each conformer can react to give one of two diastereomeric products, the overall selectivities for nucleophilic substitution reactions of acetates **15a** and **15b** are modest (Scheme 4). As before, steric preferences likely govern the distribution of conformers with alkyl substitution at C-3. The 1,3-cis isomer **17a** is the major product of nucleophilic substitution of acetate **15a**, arising primarily from addition to low-energy conformer **18** (Scheme 4). While a pseudoaxial benzyloxy substituent at the 3-position likely stabilizes the carbocation in conformers **19** and the pseudoaxial C3-alkoxy analogue of conformer **2**, the electrostatic attraction is attenuated by the less than optimal geometry of the interaction.[10] Nucleophilic addition to these conformers affords the major 1,3-trans isomer **16b**. Other low-energy conformers of the charged intermediate contain a pseudoequatorial C-3 alkoxy substituent and provide the minor 1,3-cis isomer **17b** upon nucleophilic addition.

Scheme 4



compound	R	Lewis acid	trans : cis	yield (%)
a	Me	$TiCl_4$	18 : 82	94
b	OBn	$EtAlCl_2$	77 : 23	89
		$TiCl_4$	70 : 30	-



In conclusion, the strong electrostatic (alkoxy) or more subtle steric (alkyl) effects exerted by remote substituents in monosubstituted eight-membered ring oxocarbenium ions govern the distributions of conformers in solution. These distributions were predicted on the basis of a computational[10] assessment of the low-energy conformers of these intermediates. Nucleophilic addition to these oxocarbenium ions affords disubstituted oxocanes. Highly selective reactions occur when a remote electronegative substituent can stabilize one oxocarbenium ion conformer over all others prior to nucleophilic attack.

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Supporting Information Available: Complete experimental procedures and characterization data for new compounds, details of control experiments and theoretical experiments, stereochemical proofs, GC and spectral data for selected compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Theoretical experiments suggest that a bridged bicyclic oxonium ion is the global minimum of this intermediate, but we do not believe that this conformation can be used to explain the diastereoselectivity of this reaction. Further explanation is provided within Supporting Information.

(20) An extreme example of transannular stabilization is seen for μ-hydrido bridged carbocations. See: Ponec, R.; Yuzhakov, G.; Tantillo, D. J. *J. Org. Chem.* **2004**, *69*, 2992−2996 and references cited therein.