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Investigations into the Role of Ion Pairing in Reactions of Heteroatom-Substituted Cyclic Oxocarbenium Ions

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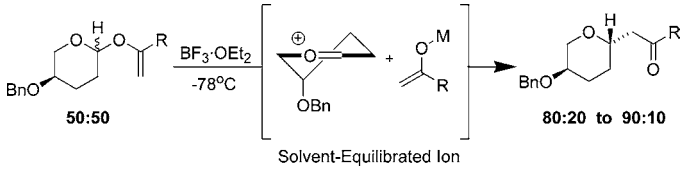
ABSTRACT



The O-to-C rearrangement of vinyl acetals is used to demonstrate that tight ion pairing is not involved in the stereoselective nucleophilic addition reactions of alkoxy-substituted cyclic oxocarbenium ions.

Although it is generally accepted that many organic transformations proceed via oxocarbenium ion intermediates,[1−4] the details of oxocarbenium ion reactivity continue to garner tremendous interest in both bioorganic[5−9] and synthetic organic chemistry.[10,11] For example, the rates of glycoside hydrolysis[12] and the high diastereoselectivities observed in the nucleophilic substitution reactions of 1,3-dioxanes[10] are attributed to the stability and conformational preferences of these ionic intermediates. We recently reported that tetrahydropyran acetals bearing alkoxy substituents undergo substitution reactions with opposite diastereoselectivities to those observed for pyrans bearing alkyl groups.[13,14] We attributed these results to the electronic preference[15,16] of heteroatom substituents to adopt pseudoaxial positions in the half-chair conformations of the incipient cyclic oxocarbenium ion intermediates.[17,18]

Recently, an intriguing report from Rovis and co-workers described an O-to-C vinyl acetal rearrangement in alkyl-

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(11) For a review on the nucleophilic substitution reactions of five-membered ring acetals, see: Harmange, J.-C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711−1754.
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(17) Other research groups have also reported nucleophilic addition to oxocarbenium ions with pseudoaxial alkoxy groups: (a) Chong, P. Y.; Roush, W. R. *Org. Lett.* **2002**, *4*, 4523−4526. (b) Saeeng, R.; Isobe, M. *Tetrahedron Lett.* **1999**, *40*, 1911−1914. (c) Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917−1920. (d) Roush, W. R.; Sebesta, D. P.; Bennet, C. E. *Tetrahedron* **1997**, *53*, 8825−8836.

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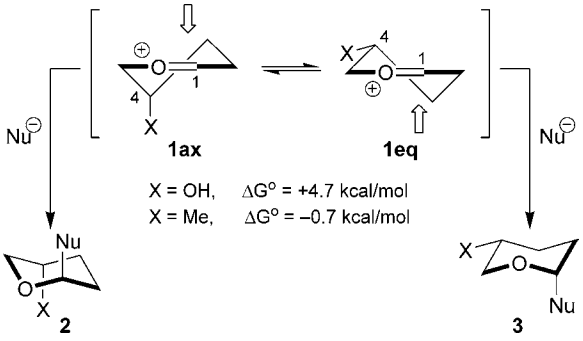
substituted pyrans in which the selectivity of the rearrangement was controlled by contact ion pairs.[19] In light of these results, we examined the role of ion-pairing in the reactions of heteroatom-substituted six-membered ring oxocarbenium ions with nucleophiles. In this paper, we document the use of the O-to-C vinyl acetal rearrangement as a mechanistic probe to prove conclusively that ion pairing is not a factor controlling the high selectivity of nucleophilic additions to heteroatom-substituted tetrahydropyran oxocarbenium ions.

We employed the six-membered-ring oxocarbenium ion bearing a single substituent at C-4 as a model system to study the role of ion pairing.[20] The C-4-substituted system was appealing due to the simplicity in its reactivity with nucleophiles. Oxocarbenium ions bearing a C-4-substituent can adopt two diastereomeric half-chair conformations (**1eq** and **1ax**, Scheme 1).[21,22] Heteroatom-substituted oxocarbenium

Scheme 1

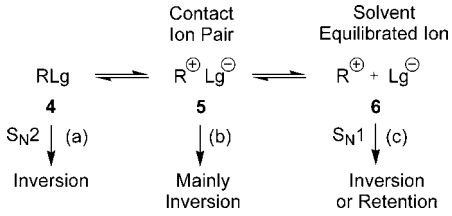


ions favor the pseudoaxial conformer by about 4 kcal/mol due to stabilizing electrostatic interactions between the partially negatively charged atom of the substituent and the positively charged carbon (Scheme 1).[15,16] As a consequence, nucleophilic addition to an oxocarbenium ion bearing a C-4 alkoxy substituent results in 1,4-trans selectivity (pyran **2**), while opposite diastereoselectivities are observed in additions to oxocarbenium ions bearing C-4 alkyl substituents (pyran **3**).[21,22] In both cases, the approaching nucleophile does not develop unfavorable steric interactions with the C-4 ring substituent, and consequently, the activation energies for the reactions of **1ax** and **1eq** are comparable.

Two assumptions are implicit in the analysis of the oxocarbenium ion reactivity depicted above. First, it is presumed that nucleophilic attack is slower than the conformational interconversion between the two half-chair conformers. Second, it is assumed that the cations **1ax** and **1eq** are fully disassociated from the leaving group of the oxocarbenium ion precursor. In principle, the existence of ion pairing should affect the diastereoselectivity of nucleophilic additions to these oxocarbenium ion intermediates. Ion pairing has been suggested to explain the unique selectivities observed in the substitution reactions of nucleophiles with glycosides and other six-membered ring oxocarbenium ions.[23,24]

In this paper, we use a modified version of the Winstein ion pair mechanism[25] for the analysis of ion pair intermediates (Scheme 2).[26] In this scheme, the leaving group forms

Scheme 2



a contact ion pair with the carbenium ion (**5**).[27] The limiting S_N2 pathway (a) is considered to be unlikely.[28] If ion pairing is involved, nucleophilic attack prior to ion pair disassociation requires the nucleophile to approach the carbenium ion stereospecifically from the side opposite the ion pair complex, leading to products with inversion of stereochemistry at the cationic center (pathway b). If ion pairing is not involved, the carbenium would be solvated and nucleophilic attack could occur from either face of the solvent-equilibrated carbenium ion **6** (pathway c).

To study the involvement of ion-pairing in the nucleophilic substitution reactions of heteroatom-substituted oxocarbenium ions, we first considered a case in which a nucleophile could attack the oxocarbenium ion irreversibly prior to the leaving group escaping the solvent cage (pathway b).[19] The formation of oxocarbenium ions **8eq** and **8ax** occur with the departure of the Lewis acid-bound vinyl ethers from *cis*-**7** and *trans*-**7**, respectively (Scheme 3). If these intermediates exist as contact ion pairs, the O-to-C vinyl acetal rearrangement should lead to *cis*- and *trans*-**9** by stereospecific recombination to the same face of the oxocarbenium ion from which they left.[19] Thus, the ratio of *cis*- to *trans*-**9** should be identical to the initial anomeric ratio of starting acetal **7**.[19]

(18) For an example of the electronic effects of axial hydroxyl groups on the rates of glycoside hydrolysis, see: Jensen, H. H.; Bols, M. *Org. Lett.* **2003**, *5*, 3419−3421.

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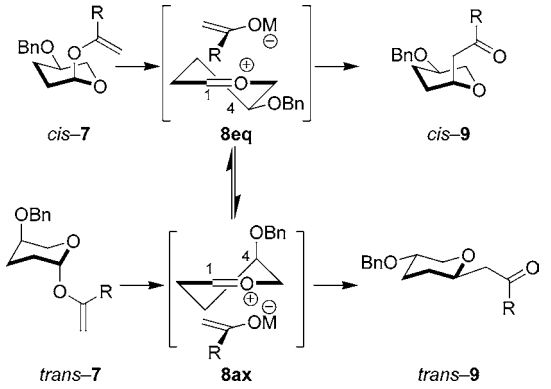
(26) Since the separation of the cation and leaving group by solvent would allow for the equilibration of the oxocarbenium ion intermediate, the "solvent-separated ion pair" intermediate in the Winstein scheme has been combined with the "dissociated carbenium ion" and deemed a "solvent-equilibrated cation." See: Shiner, V. J., Jr.; Dowd, W. *J. Am. Chem. Soc.* **1969**, *91*, 6528−6529.

(27) Since a Lewis acid would be required to activate **4** for solvolysis, the actual counterion involved in an ion pairing mechanism may involve a leaving group−Lewis acid complex.

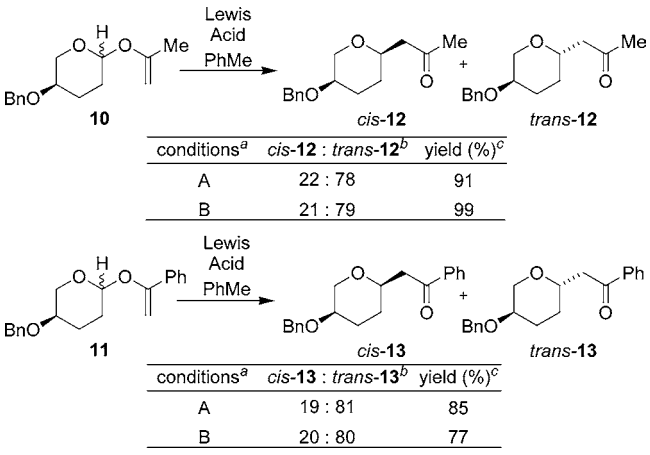
(28) Eliel, E. L.; Ro, R. S. *J. Am. Chem. Soc.* **1957**, *79*, 5995−6000.

Scheme 3



We tested this hypothesis by subjecting an anomeric mixture of vinyl acetals **10** and **11** to the reaction conditions outlined by Rovis et al. for generating contact ion pairs in the analogous alkyl-substituted pyran systems[19] and to the optimized conditions we generally use for nucleophilic substitution reactions to six-membered ring oxocarbenium ions.[14] Under both conditions, 1,4-trans selectivity was observed for both **10** and **11**, irrespective of the anomeric ratios of the starting vinyl acetals (Scheme 4).[29] The O-to-C

Scheme 4 [a]



conditions[a]	*cis*-**12** : *trans*-**12**[b]	yield (%)[c]
A	22 : 78	91
B	21 : 79	99

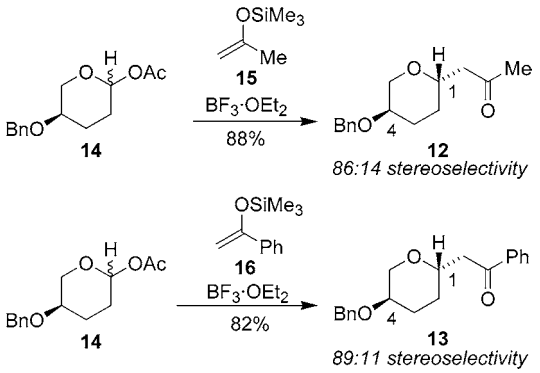
conditions[a]	*cis*-**13** : *trans*-**13**[b]	yield (%)[c]
A	19 : 81	85
B	20 : 80	77

[a] Typical reaction conditions: (A) $BF_3{\cdot}OEt_2$ (1.3 equiv), −78 to 25 °C, 30 min. (B) $AlMe_3$ (4.0 equiv), $BF_3{\cdot}OEt_2$ (1.1 equiv), −78 °C, 30 min. [b]Measured by GC analysis of unpurified reaction mixture. [c]Reported yields based on purified products.

vinyl acetal rearrangement appears to occur slower than the conformational interconversion of the cation intermediate; thus, the diastereoselectivities of the products represent the relative ground-state populations of the two half-chair conformers (**8eq** and **8ax**) as described by the Curtin−Hammet/Winstein−Holness concepts.[30]

The 1,4-trans stereoselectivities obtained in the vinyl acetal rearrangements above indicate that nucleophilic attack occurs stereoselectively on the pseudoaxial conformer of a solvent-equilibrated oxocarbenium intermediate (pathway c, Scheme 2). Treating acetate **14** with the exogenous silyl enol ethers **15** and **16** in the presence of $BF_3{\cdot}OEt_2$ afforded the respective ketones **12** and **13** with comparable 1,4-trans selectivities to the intramolecular vinyl acetal rearrangements of **10** and **11** (Scheme 5).[31] These stereoselectivities indicate that the

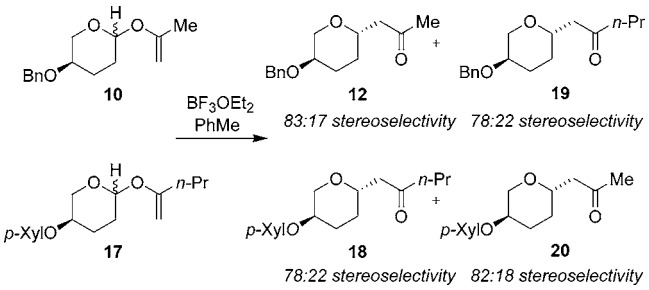
Scheme 5



benzyloxy-substituted oxocarbenium ion intermediate reacts through the solvent-equilibrated pseudoaxial conformer **8ax** (Scheme 3).

A crossover experiment provided conclusive evidence that the substitution reactions of C-4 alkoxy-substituted six-membered ring oxocarbenium ions proceed through fully solvent-equilibrated ionic intermediates. We used the C-4 benzyloxy vinyl acetal **10** and the C-4 *p*-xylyloxy vinyl acetal **17** shown in Scheme 6. If conformational interconversion

Scheme 6 [a]



[a] *p*-Xyl = (4-Me)$C_6H_4CH_2$

and recombination were faster than the dissociation of an ion pair, C-4 benzyloxy vinyl acetal **10** should give methyl ketone product **12** and C-4 *p*-xylyloxy vinyl acetal **17** should give *n*-propyl ketone product **18** exclusively, and the crossover products **19** and **20** should not be observed.

(29) Rovis and co-workers (ref 19) have shown that optimal selectivities for C-4-substituted oxocarbenium ions are observed when the reactions are performed at −25 °C. Performing the rearrangement reaction on the C-4 benzyloxy-substituted oxocarbenium ions at −25 °C or slowly warming the reaction mixture from −78 to −25 °C did not affect the diastereoselectivity of the reaction.

(30) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134.

Upon treating a 1:1 mixture of vinyl acetals **10** and **17** with $BF_3{\cdot}OEt_2$, all four ketone products were produced as detected by GC-MS and ^1H NMR analysis. In addition, all four ketone products were produced with 1,4-trans selectivity (Scheme 6). The observation of rearrangement products **19** and **20** conclusively indicated that the reaction proceeds through solvent-equilibrated oxocarbenium ion intermediates.[32]

In conclusion, our experiments indicate that ion pairing is not involved in the nucleophilic substitution reactions of alkoxy-substituted six-membered ring oxocarbenium ions. The analysis of product diastereoselectivities indicated that the stereoelectronic effects of C-4 alkoxy-substituted oxocarbenium ions dominated the stereochemical course of nucleophilic addition to these cations. The results of the crossover experiment confirm that ion pairing is not a factor controlling the high selectivity of nucleophilic additions to C-4 alkoxy-substituted oxocarbenium ion intermediates.

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

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(31) For all experiments, stereoselectivities were determined by GC and ^1H NMR spectroscopic analysis of unpurified reaction mixtures. The reported yields are based on purified products (see Supporting Information for further details).

(32) Performing the crossover experiment using the reaction conditions outlined by Rovis et al. (ref 19) for generating contact ion pairs in the analogous alkyl-substituted pyran systems also provided all four ketone products. The details of this crossover experiment are included in Supporting Information.