Carbocation Intermediates

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Stereoelectronic Model To Explain Highly Stereoselective Reactions of Seven-Membered-Ring Oxocarbenium-Ion Intermediates

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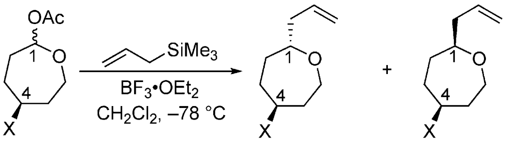
Abstract: *Nucleophilic attack on seven-membered-ring oxocarbenium ions is generally highly stereoselective. The preferred mode of nucleophilic attack forms the product in a conformation that minimizes transannular interactions, thus leading to different stereoselectivity as compared to that of reactions involving six-membered-ring oxocarbenium ions.*

Because of their biological significance and the challenges inherent to the synthesis of medium-ring compounds,[1] seven-membered-ring ethers (oxepanes) are important synthetic targets.[1,2] Substitution reactions of oxepane acetals, which probably proceed via oxocarbenium-ion intermediates, are particularly useful methods for the stereoselective construction of natural products and seven-membered-ring sugar derivatives.[3] The origin of stereoselectivity in these transformations remains poorly understood, however, because of the conformational complexity of seven-membered-ring systems.[4,5] No systematic study of nucleophilic addition reactions to simple seven-membered-ring oxocarbenium ions has appeared, and no general explanation has been forwarded to explain the reactions of these intermediates.[6]

We report herein that nucleophilic substitution reactions of oxepane acetals are highly stereoselective in most cases. We propose a model to explain these selectivities by considering that nucleophilic attack should occur from the face that minimizes transannular interactions in the first-formed product. We also demonstrate that acetal substitution reactions that proceed by S_N2-like mechanisms generally result in products with the opposite stereochemical configuration to that of products resulting from the corresponding S_N1-like reactions.

Initial studies revealed that nucleophilic substitution reactions of acetals that proceed via seven-membered-ring oxocarbenium ions are highly diastereoselective. Under dissociative (S_N1-like) conditions, the substitution reaction of acetal **1** (X = Me) occurred with high *trans* selectivity [Eq. (1)].[7] By contrast, the substitution reaction of alkoxy-substituted acetal **1** (X = OBn; Bn = benzyl) gave the product with the opposite relative configuration.[8,9] These selectivities are also opposite to those observed in reactions of six-membered-ring oxocarbenium ions:[8] in the six-membered-ring series, the alkyl-substituted acetal favored the 1,4-*cis* product, and the alkoxy-substituted acetal formed the 1,4-*trans* product.



(1)

1 *trans*-**2** *cis*-**2**

X	*trans*-**2** / *cis*-**2**
Me	99 : 1
OBn	6 : 94

Because the diverging stereochemical outcomes illustrated in Equation (1) are similar to observations regarding the reactions of five- and six-membered-ring oxocarbenium ions,[8,9] the factors that govern selectivity in those systems should apply to the seven-membered-ring system. Models used to explain selective reactions of oxocarbenium ions and iminium ions[8–12] consider the conformations of these reactive intermediates and how those conformations change in the transition state of nucleophilic attack, which, in the case of π-nucleophiles, is irreversible.[13] Although it would be desirable to model this step computationally,[14] calculations involving interactions of cations with electron-rich species are challenging.[15–17] Nevertheless, models derived by conformational analysis of the first-formed products that result from nucleophilic attack can be useful.[9,11,12]

A model to explain and predict the outcomes of reactions involving seven-membered-ring oxocarbenium ions is illustrated for oxocarbenium ion **3** [Eq. (2)]. The oxocarbenium ion probably adopts a chair-like conformation[18] with the methyl group in a pseudoequatorial position.[19,20] Steric interactions between the approaching nucleophile and the substituent should be minimal, so the major product is likely to be formed from this lowest-energy conformer.[21] The two different modes of nucleophilic attack, **A** and **B**, give the products in twist-chair-like conformations, but the interactions that develop in the two transition states are different. Nucleophilic attack along trajectory **A** would pyramidalize the carbon and oxygen atoms in opposite directions,[8,12] thus leading to an initial twist-chair conformation of product **4** (the TC6 conformation[5]). Conversely, attack along trajectory **B** would form product **5** in a different twist-chair conformation

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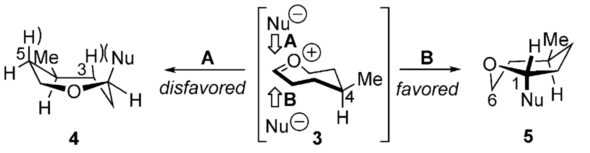
(TC5). Attack by mode **B** is preferred because the resulting product is formed with the carbon atom bearing the nucleophile (C1) in a position that minimizes steric interactions.[22] In the first-formed product **5**, the nucleophile and the hydrogen atom at C1 would occupy isoclinal positions, so neither group is axial. As a result, steric interactions with the other atoms of the ring are minimized.[4] By contrast, conformer **4** is higher in energy because it places C1 in a more sterically hindered position,[4] with destabilizing interactions between the nucleophile and axial hydrogen atoms at C3 and C5 [Eq. (2)].[4,5,22] As a result, the transition state leading to conformer **4** should be higher in energy than that leading to **5**.[23,24]

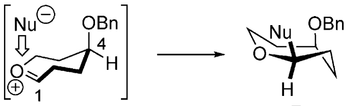


(2)

4 **3** **5**

develops transannular interactions *minimizes transannular interactions*

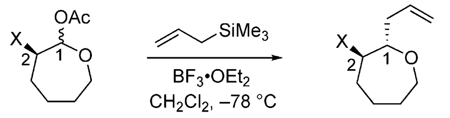
The preferred attack on the oxocarbenium ion along trajectory **B** also explains the selective formation of the 1,4-*cis* product when an alkoxy group is located at C4. The cation should adopt a pseudoaxial conformation **6** [Eq. (3)] to maximize electrostatic attraction between the positively charged carbon atom and the partially negatively charged oxygen atom of the benzyloxy group.[8,16,25,26] Computational studies reinforce this prediction: **6** was calculated to be favored by 1.4 kcal mol^{-1} as compared to an equatorial conformer.[19] Nucleophilic attack from the torsionally favored direction would form the 1,4-*cis* product **7** in the preferred twist-chair conformation.



(3)

6 **7**

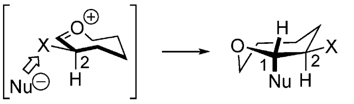
Other results support the prediction that the favored transition state for nucleophilic attack develops the fewest transannular interactions. Nucleophilic addition reactions to oxocarbenium ions bearing an alkyl or an alkoxy group at C2 are highly *trans*-selective [Eq. (4)], in contrast to results with five- and six-membered-ring acetals, for which selectivity is low.[8,9] These reactions probably proceed via an equatorially substituted oxocarbenium ion **10** [Eq. (5)]. In the case of X = OBn, this conformation, which computational studies indicate is favored by 2.5 kcal mol^{-1},[19] maximizes hyperconjugative stabilization from the pseudoaxial σ_{C-H} orbital.[8,16] Attack along the preferred trajectory leads to the twist-chair product **11**.[27]



(4)

8 *trans*-**9**

X	diastereoselectivity
Me	≥97 : 3
OBn	≥97 : 3

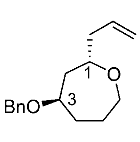


(5)

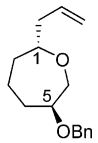
10 **11**

1,2-*trans* product

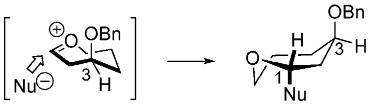
Considering the importance of seven-membered-ring sugars in glycobiology,[2,28] we examined the substitution reactions of two additional alkoxy-substituted seven-membered-ring acetals. The lower selectivity for the formation of the 1,3-*trans* product *trans*-**12** probably results from the low axial preference for the oxocarbenium ion **14** (calculated to be 0.3 kcal mol^{-1})[19] owing to competing electrostatic stabilization and steric destabilization [Eq. (6)]. The selectivity observed for the formation of *trans*-**13** results from the preference[8,9,16,25,26] for the alkoxy group to adopt a pseudoaxial orientation in the oxocarbenium ion **16** [Eq. (7)], which is consistent with the calculated preference of 0.8 kcal mol^{-1} for this conformer.[19]



trans-**12**
d.r. 75 : 25
(86%)



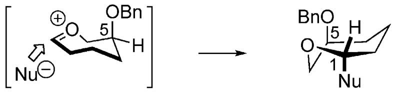
trans-**13**
d.r. 92 : 8
(86%)



(6)

14 **15**

1,3-*trans* product

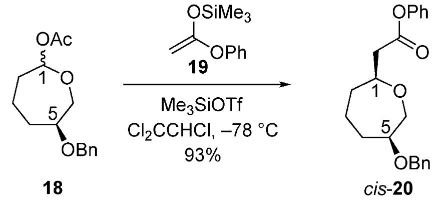


(7)

16 **17**

1,5-*trans* product

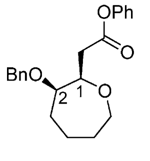
Because many substitution reactions in carbohydrate chemistry utilize stronger nucleophiles with either ion pairs or covalent intermediates,[29–31] we examined reactions under similar conditions. For example, the use of a highly reactive nucleophile (silyl ketene acetal **19**) in the presence of triflate ions in a nonpolar solvent (trichloroethylene)[31] gave the *cis* isomer in the case of 5-benzyloxy acetal **18** [Eq. (8)].[32] The relative configuration of the product is opposite to that observed for the allylation (see *trans*-**13**). The switch in selectivity for the S_N2-type C-glycosylation reactions as compared to S_N1-type reactions was also observed for reactions of 2- and 3-alkoxyoxepane acetals (see products *cis*-**21** and *cis*-**22**) and parallels observations for six-membered-ring systems.[31] In the case of the 4-benzyloxy acetal **1** (X = OBn), however, the *cis* isomer is the major product regardless of the reaction type [*cis*-**2**, Eq. (1) and *cis*-**23**]. The benzyloxy group at C4 may be too far from the oxygen and carbon atoms of the oxocarbenium-ion intermediate to destabilize it inductively,[33] so reactions proceed via oxocarbenium ions even in the presence of the triflate ion.[31]



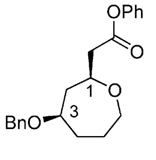
(8)

18

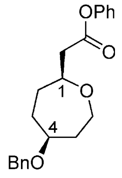
cis-**20**
≥ 97 : 3 diastereoselectivity



cis-**21**
d.r. ≥ 97 : 3
(92%)

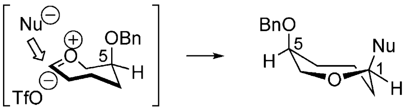


cis-**22**
d.r. 72 : 28
(97%)



cis-**23**
d.r. 80 : 20
(90%)

Selective substitution reactions to form *cis*-**20**, *cis*-**21**, and *cis*-**22** are consistent with the stereochemical model adapted for reactions under S_N2-like conditions.[31] As illustrated for the preparation of *cis*-**20**, a contact ion pair between the oxocarbenium ion and triflate anion, **24** (or the anomeric triflate[29,30]), would position the triflate where the nucleophile approaches in the S_N1-like process [Eq. (9)].[31] Displacement of the triflate would occur from the opposite face, thus leading to the observed products.



(9)

24 **25**

In conclusion, the substitution reactions of seven-membered-ring acetals occur with generally high diastereoselectivity, regardless of whether reactions involve free ions or intermediates with close contact between the electrophile and the leaving group. The reactions are selective because of strong conformational preferences of oxepanes, which favor one conformer of the product as it is formed upon nucleophilic attack.

Acknowledgements

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[20] Calculations indicate that the equatorial oxocarbenium ion **3** is favored over the axial conformer by 2.4 $\mathrm{kcal\,mol^{-1}}$.

[21] In cases in which the nucleophile approaches a substituent closely, such as C2-substituted systems, transition-state effects can be important (see, for example, Ref. [8]).

[22] The computed structures for **4** and **5** (Nu = Me) illustrate the different steric interactions in the two conformers. In **4**, transannular interactions occur between the nucleophile and two hydrogen atoms of the ring. The distance between the carbon atom of Nu and 3-H is 2.71 Å, and the distance to 5-H is 2.88 Å. In **5**, there is only one transannular interaction (with 6-H), and the distance is 2.90 Å.

[23] A model assuming that selectivity is controlled by attack *trans* to the axial hydrogen atom at C3 would not be consistent with the models used to explain selectivities in five- and six-membered-ring systems (see Refs. [9,12]).

[24] Computational studies also suggest that attack by mode **B** should be favored. A methyl group was used as the carbon nucleophile to simplify the calculation. The twist-chair isomer **5** was found to be lower in energy than **4** by 4.7 $\mathrm{kcal\,mol^{-1}}$, so transition states leading to this conformer should be lower in energy.

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