A Stereoelectronic Model To Explain the Highly Stereoselective Reactions of Nucleophiles with Five-Membered-Ring Oxocarbenium Ions

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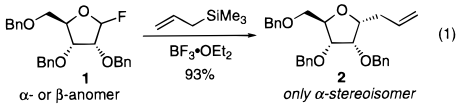
To date, no general stereoelectronic model has been offered to explain stereoselective reactions of five-membered-ring oxocarbenium and iminium ions. In contrast, the model used to understand the stereoselectivity of nucleophilic attack upon six-membered-ring cations is a powerful predictive tool used widely by synthetic organic chemists.[1,2] Because of the importance of five-membered-ring oxocarbenium ions as reactive intermediates in bioorganic[3] and synthetic organic chemistry,[4−6] a model that would provide insight regarding their reactivities would be an invaluable complement to the current understanding of stereoselective reactions. In this paper, we present a general stereoelectronic model (the "inside attack" model) to explain the stereoselective reactions of five-membered-ring oxocarbenium ions.

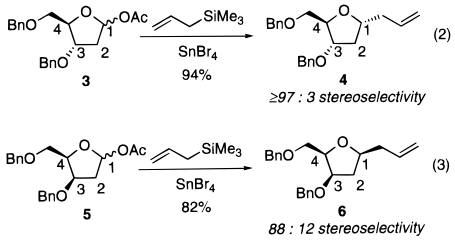
Previous models employed to explain stereoselective reactions of five-membered-ring oxocarbenium ions do not encompass a wide range of substrates, nucleophiles, and conditions. The most advanced model was proposed by Reissig based upon a systematic study of reactions of monomethyl γ-lactols.[7,8] This model, however, has limitations. For example, the stereoselective nucleophilic substitutions of carbon nucleophiles onto D-ribose acetals such as **1** (eq 1), reactions for which oxocarbenium ion



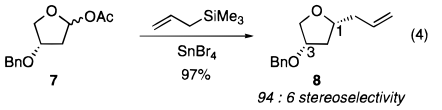
intermediates have been implicated,[9] are not readily explained by the Reissig model.[10] The stereoselectivities observed for these reactions have been attributed to steric hindrance provided by the counterion[11] or by the solvent.[12] These explanations are unsatisfying because comparable selectivities have been observed for a range of nucleophiles, Lewis acids, and solvents[11,13−15] as well as for reactions of closely related substrates.[16] We have demonstrated that highly substituted five-membered-ring oxocarbenium ions exhibit opposite stereoselectivities to what would be expected based upon consideration of simple steric effects alone.[17,18]

We chose to analyze the origin of stereoselectivity for *C*-glycosylation of ribose (eq 1) because of the importance of *C*-glycosidation[5,6] and because this reaction occurred with counterintuitive selectivity. Structural analogues of acetal **1** were prepared, and allylations were conducted under similar reaction conditions to ensure that selectivity could be correlated to structure. We concentrated on *C*-glycosylations with allyltrimethylsilane because nucleophilic attack of carbon nucleophiles is in many cases irreversible, in contrast to attack by heteroatom nucleophiles.[14] Each product was subjected to a rigorous proof of stereochemistry.[19]

The nucleophilic substitution reactions of tetrahydrofuran acetates without substituents at C-2 indicated that substitution at this position is not critical for high selectivity. Treatment of 2-deoxyribosyl acetate **3** (eq 2) with allyltrimethylsilane in the presence of a Lewis acid provided the α-isomer **4** with ≥97:3 stereoselectivity.[20] Other authors have also observed α-selective *C*-glycosylations of 2-deoxyribose acetals.[21] The reaction of the related cis-disubstituted acetate **5** afforded predominantly the all-cis product **6** (eq 3). In accord with Reissig's results,[7] substitution solely at C-4 was not sufficient to obtain high stereoselectivity for nucleophilic substitution reactions.[22]



Examination of the highly stereoselective reactions depicted in eqs 1−3 revealed that in all cases the nucleophile adds to the same face as the alkoxy substituent at C-3. These results led us to hypothesize that the alkoxy group at C-3 controls the approach of the nucleophile onto the same face of the oxocarbenium ion. The nucleophilic substitution of acetal **7** confirmed this prediction: the 1,3-cis product **8** was obtained with 94:6 stereoselectivity (eq 4).[23]



The 1,3-syn selectivities observed for acetals **3**, **5**, and **7** are reversed when the 3-alkoxy group is replaced with a methyl group. Nucleophilic substitution reactions with trans- and cis-disubsti-

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(23) The same magnitude of selectivity (94:6) was observed for the analogous *t*-$BuMe_2SiO$- and CH_3OCH_2O-substituted acetates. The stereochemistry was proven to be 1,3-cis for the silyloxy-substituted substrate.

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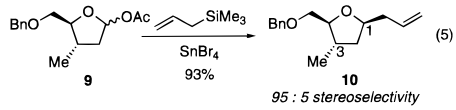
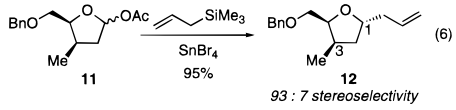
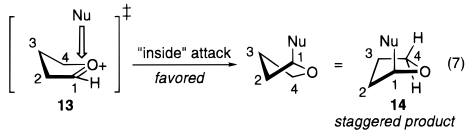
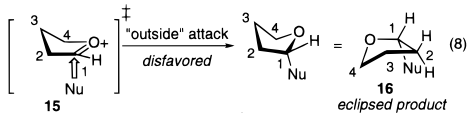
tuted acetates **9**[24] and **11** revealed that a methyl group at C-3 biases nucleophiles to attack with high 1,3-anti stereoselectivity (eqs 5 and 6). As observed for the 3-alkoxy acetal **7**, substitution at C-4 is not necessary to obtain high selectivity: Reissig reported that allyltrimethylsilane reacted with the methyl analogue of **7** with 95:5 stereoselectivity, favoring the anti product.[7]



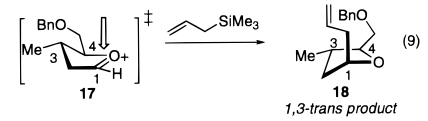


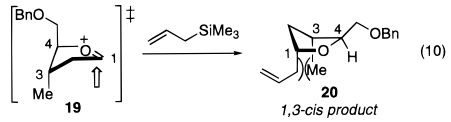
The stereoselective reactions of five-membered-ring oxocarbenium ions can be understood by evaluation of the preferred conformations of both reactants (oxocarbenium ions) and products in their newly formed conformations.[1,2,25] The preferred conformation of a five-membered-ring oxocarbenium ion, much like a cyclopentene ring,[26] is an envelope conformation where the C=O$^+$ unit resides in the flattened portion of the envelope. Approach of the nucleophile onto the cation can occur from either side, namely attack from "inside" the envelope (**13**, eq 7) or attack from "outside" the envelope (**15**, eq 8). Nucleophilic attack, as with the six-membered systems,[1,2] leads to the product tetrahydrofuran in two different conformations. Attack from "inside" the cation forms the all-staggered conformer **14** (eq 7). Attack from "outside" results in a conformer (**16**) that suffers from eclipsed interactions between substituents on C-1 and C-2 (eq 8). Because the staggered product **14** is lower in energy than the eclipsed product **16**, attack from "inside" the envelope should be favored.



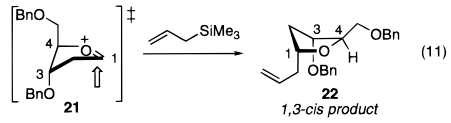


We propose that the relative stereochemistry exhibited by substituted five-membered-ring oxocarbenium ions arises from stereoelectronically controlled "inside attack" to form the product in the lowest energy conformation. This model provides an explanation of the selectivities reported above (eqs 1−6). For example, the cation derived from 3-methyl-substituted acetal **9** (eq 5) could exist as two conformers, namely **17** (eq 9) and **19** (eq 10). Attack from "inside" the cation **17** would lead to the 1,3-trans product as first-formed conformer **18** (eq 9). Alternatively, "inside attack" on the diaxial conformer **19** would be disfavored because of developing, destabilizing 1,3-diaxial interactions between the nucleophile and the alkyl group in the product **20** (eq 10).[27,28] Therefore, the 1,3-trans product would be expected to predominate, as shown by experiment (eq 5).





The formation of 1,3-cis products when alkoxy substituents are present at C-3 is also consistent with the "inside attack" model. We have demonstrated that certain alkoxy-substituted six-membered-ring oxocarbenium ions assume conformations in which the alkoxy group resides in a pseudoaxial position.[28,29] This conformational preference is consistent with computational investigations.[30,31] If five-membered-ring systems adopt conformations with pseudoaxial alkoxy groups, then the opposite stereoselectivities observed for 3-alkoxy and 3-alkyl tetrahydrofuran cations become clear. For example, ionization of deoxyribosyl acetate **3** (eq 2) results in oxocarbenium ion **21**, and "inside attack" would form the 1,3-cis product as conformer **22** (eq 11).[32] Developing 1,3-diaxial interactions upon formation of **22** would be less destabilizing for this substrate than for the alkyl analogue **20** (eq 10).[28]



In conclusion, we have introduced a general model that explains the stereoselective reactions of five-membered-ring oxocarbenium ions, including the ribosyl and deoxyribosyl cations. This model postulates that nucleophilic attack occurs by stereoelectronically controlled "inside attack" on the lower energy conformer of the cation to provide the product in its lower energy conformer. The "inside attack model" allows for reinterpretation of other data, including our own work on oxasilacyclopentane[17] and tetrahydrofuran cations,[18] Reissig's selectivities with substituted γ-lactols,[7] and the selectivities of *N*-acyliminium ions.[33]

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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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