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Nucleophilic Substitution Reactions of 2-Phenylthio-Substituted Carbohydrate Acetals and Related Systems: Episulfonium Ions vs. Oxocarbenium Ions as Reactive Intermediates

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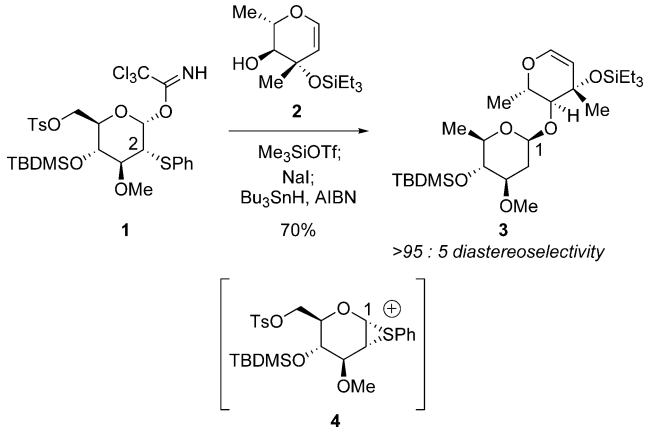
A powerful approach for controlling the stereochemistry of glycosylation reactions involves using a directing group at an adjacent carbon to influence the stereochemistry of nucleophilic attack. The use of substituents such as I, PhS, and PhSe has proven to be especially valuable because it enables the preparation of 2-deoxysugars after reductive removal of the directing group. The mechanisms of these reactions are generally considered to involve nucleophilic opening of bridged onium ions and to proceed with inversion. Onium ions, however, equilibrate with open cations, and these open forms can be favored when the cation is highly stabilized. Although the selectivities of reactions of carbohydrate-derived cations are consistent with the intermediacy of onium ions, the reactions of acyclic cations are not. Instead, consideration of the preferred conformations of the oxocarbenium ions and stereoelectronically favored additions to these intermediates provides a predictive model to explain the diastereoselectivities observed in reactions of oxocarbenium ions bearing proximal heteroatoms.

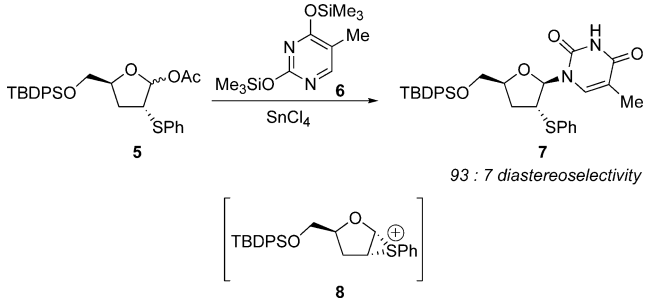
Introduction

The use of neighboring-group participation to control the stereoselectivity of a glycosylation reaction is a powerful method for the synthesis of glycosides.[1,2] This method provides an efficient synthesis of 2-deoxysugars, because after a substituent at the C-2 position has directed the stereochemistry at the anomeric position (C-1), the substituent can be removed.[1,2] Carbohydrate-derived acetals substituted with PhS groups undergo highly diastereoselective reactions, and substrates of this type have been applied in natural product synthesis,[3] as illustrated in Scheme 1.[4] Similar observations have been made in glycosylation reactions of furanose derivatives (Scheme 2).[5] Other substituents, such as PhSe groups[6,7] and halogens (particularly I[8–11]), have also been employed. The stereochemical outcomes of these reactions are typically considered to result from stereospecific ring-opening of bridged intermediates[2] such as **4** and **8** (Schemes 1 and 2) with inversion of configuration. The high selectivities exhibited by many of these processes make this explanation strongly compelling.[12]

Although mechanisms involving bridged intermediates such as the episulfonium ions **4** and **8** provide concise and satisfying explanations for observations such as those shown in Schemes 1 and 2, accumulating evidence suggests



Scheme 1. Stereoselective pyranosylation controlled by a phenylthio group.



Scheme 2. Stereoselective *N*-furanosylation controlled by a phenylthio group.

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that such intermediates may not be involved in stereoselective substitution processes. The fact that reactions that would be expected to proceed through episulfonium,[6,7,13–15] episelenonium,[13,16] or iodonium ions[9,10] (**9**, Figure 1) are not completely selective[17] indicates that these reactions may occur by a different pathway or through multiple pathways. The formation of the product that would not correspond to stereospecific opening of the onium ion **9** (i.e., the 1,2-*cis* product) is typically explained by invoking oxocarbenium ions **10** as reactive intermediates.[18] It is not common to consider that the formation of the major product could be the result of reactions of oxocarbenium ions **10**, which are perceived to undergo unselective reactions with nucleophiles.

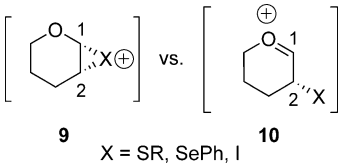

Figure 1. Onium ions vs. oxocarbenium ions.

This Microreview will focus on comparisons between episulfonium ions and related onium ions **9** and the corresponding oxocarbenium ions **10** (Figure 1) in the reactions of carbohydrate-derived acetals. The synthetic aspects of these transformations will only be presented briefly because glycosylation reactions of sulfur-, selenium- and halide-substituted glycosyl donors were recently reviewed,[1,2] as were 1,2-sulfur migrations,[19–21] which are conceptually related. Instead, key mechanistic issues will be discussed, which requires consideration of the reactivity of acetals not derived from carbohydrates. In addition, the assumption that the major products formed in glycosylation reactions such as those shown in Schemes 1 and 2 are the result of reactions of onium ions **9** will be addressed. Alternatively, both the major and minor products may be formed by reactions involving oxocarbenium ions **10** due to hyperconjugation both in the control of the conformation of the oxocarbenium ion as well as the transition state leading to product.

Evidence for Episulfonium Ions

Episulfonium ion intermediates are often invoked to explain the reactions of phenylthio-substituted acetals[22] because they appear to be involved in numerous substitution reactions.[23–25] Structural studies support the plausibility of episulfonium ions (thiiranium ions),[26–29] thiirenium ions,[28,29] and related episelenonium ions.[30] For example, X-ray structures of episulfonium ions **11**,[30] **12**,[27] and **13**[28,29] have been reported (Figure 2). In addition, bromonium and iodonium ions have also been characterized

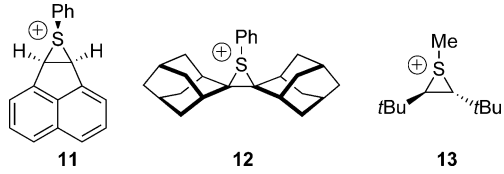

Figure 2. Episulfonium ions characterized by X-ray crystallography.

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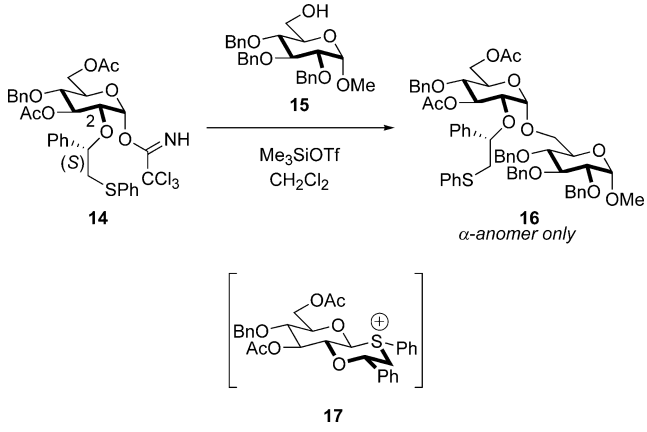
by X-ray crystallography.[31,32] Formation of an episulfonium ion has also been implicated in the deactivation of a proteinase, as determined by an X-ray crystal structure of a covalently bound inhibitor.[33]

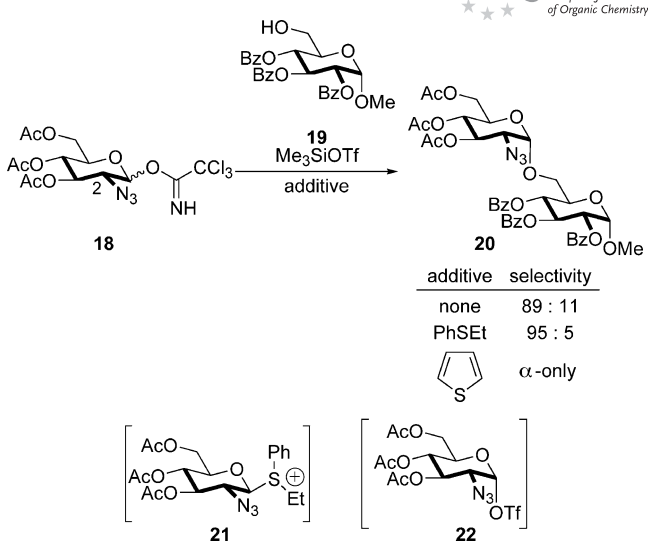
Although crystal structures of episulfonium ions in carbohydrate systems have not been obtained, carbohydrate-derived sulfonium ions have been observed spectroscopically. The Boons laboratory[34–36] has developed methods for 1,2-*cis* *O*-glycosylation, a challenging problem in carbohydrate chemistry.[37] The glycosyl donor **14**, which bears a pendant sulfide group at C-2, exhibited high α-selectivity in glycosylation reactions (Scheme 3).[35] The intermediate sulfonium ion **17** was observed by low-temperature NMR spectroscopy in the absence of a nucleophile. The stereochemical outcome of the glycosylation reaction implies a mechanism involving ring-opening of sulfonium ion **17** with inversion at the anomeric carbon. The Boons laboratory, however, noted that the precise structure of the sulfur-bearing directing group is critical. When the directing group possessed the (*R*)-configuration at the benzylic stereocenter, the disaccharide product was obtained with no selectivity. Consequently, the formation, stability, and reactivity of sulfonium ions resembling **17** are sensitive to the exact nature of the cation.



14 15 16 17

Scheme 3. 1,2-*cis* Glycosylations using a tethered sulfide.

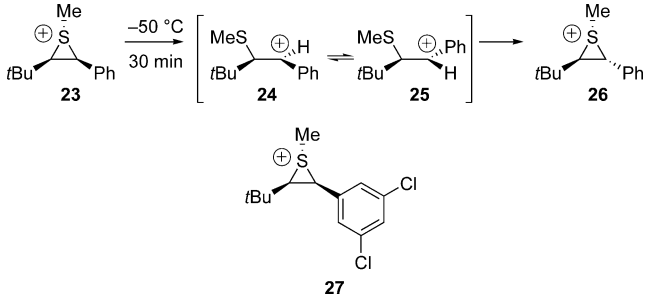
The addition of exogenous sulfides can increase the selectivity of some glycosylation reactions,[35] and sulfonium ion intermediates may be involved in these reactions[36] and related processes.[38] For example, the selectivities of reactions of the 2-azido sugar **18** can be enhanced with the appropriate choice of a sulfide additive (Scheme 4).[36] As with the glycosyl donor bearing a tethered sulfide (**14**, Scheme 3), a sulfonium ion **21** was observed by low-temperature NMR spectroscopy, along with the glycosyl triflate **22**.[36] The stereochemical course of this glycosylation reaction is also consistent with direct displacement of an anomeric sulfonium ion. The observation of inversion at the anomeric center, however, can also be the result of a transition state with considerable oxocarbenium ion character, as demonstrated for mannosyl triflates[39] and iodides.[40]



Scheme 4. 1,2-*cis* Glycosylations of 2-azidosugars using exogenous sulfides.

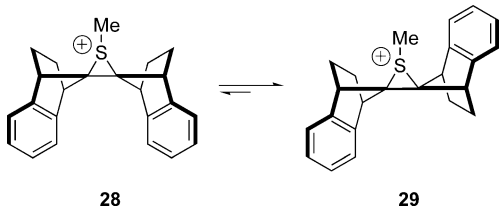
Dynamic Behavior of Sulfonium Ions

Although episulfonium ions can be observed in the solid state, they can be fluxional in solution. The stereochemical isomerization of *cis*- and *trans*-substituted episulfonium ions was established by examination of the addition of methylsulfenyl chloride to isomeric (*E*)- and (*Z*)-alkenes.[41] The formation of episulfonium ion intermediates was stereospecific at low temperatures (–78 °C) as determined by NMR spectroscopy.[41] Upon warming to –50 °C, however, the *cis* episulfonium ion **23** rapidly isomerized to the *trans* episulfonium ion **26** (Scheme 5). It is likely that isomerization occurred by ring-opening to form the benzylic cations **24** and **25** followed by rotation about the central carbon–carbon bond and closure to form the more stable *trans* episulfonium ion **26** (Scheme 5). Access to this reaction pathway depends upon the stability of the benzylic cation: episulfonium ion **27**, which bears electron-withdrawing groups on the aromatic ring, is configurationally stable even at 0 °C, presumably because the corresponding benzylic cation is too high in energy (Scheme 5). Isomerization has also been observed with episulfonium ions **28** and **29** (Scheme 6). These cations isomerize after days at room temperature ($\Delta G^{\ddagger}$ = 25.8 kcal/mol), and the positive entropy of activation ($\Delta S^{\ddagger}$ = 5.0 cal/mol·K for conversion of **28** to **29**)



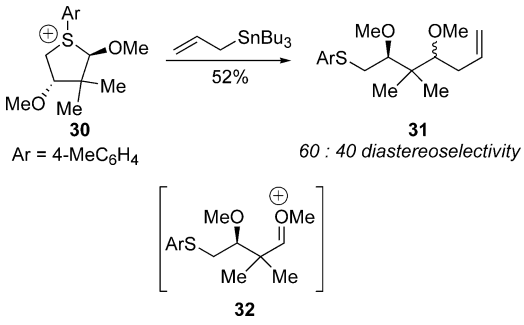
Scheme 5. Isomerizations of aryl-substituted episulfonium ions.

is consistent with a mechanism involving opening of the cation, analogous to the mechanism shown in Scheme 5.[42] These studies demonstrate that even if the bridged episulfonium ion intermediate is more stable than its open form (as in Scheme 5), the open forms are energetically accessible, leading to bond rotations and isomerizations.



Scheme 6. Isomerization of alkyl-substituted episulfonium ions.

The dynamic nature of sulfonium ions suggest that sulfonium ions may not be directly involved in nucleophilic substitution reactions. Even in a case where a sulfonium ion was observed, it did not appear to be the reactive intermediate. The sulfonium ion **30** was isolated, and its three-dimensional structures in the solid and solution phases were determined by X-ray crystallography and NMR spectroscopy, respectively (Scheme 7).[43] The preference for five-membered ring sulfonium ion **30** over the oxocarbenium ion **32** suggests that the significant enthalpic benefit to forming the carbon–sulfur bond of the onium ion (about 22 kcal/mol)[44] compensated for the ring strain of tetrahydrothiophene (about 6 kcal/mol).[45,46] Although the sulfonium ion is a single diastereomer, little stereoselectivity was observed upon nucleophilic attack of allyltributyltin (Scheme 7). In addition, the nucleophile attacked the more substituted secondary neopentyl position, which is typically less reactive than a primary electrophile.[47] The contrasteric regioselectivity and low diastereoselectivity of this reaction are not consistent with a direct displacement reaction on the sulfonium ion **30**. Instead, these results suggest reaction via oxocarbenium ion intermediate **32**.[43] In related examples using stronger nucleophiles, such as Grignard reagents, the major products do appear to be formed by direct displacement reactions.[48]

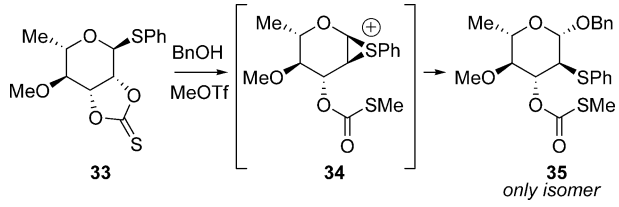


Scheme 7. Nucleophilic substitution reaction of a five-membered ring sulfonium ion.

The explanation of the results shown in Scheme 7 illustrate how the Curtin–Hammett principle can be used to analyze reaction mechanisms.[49] The lowest energy form of an intermediate need not be the species that reacts to form product.[49] It is not enough to know which form is favored: the relative reactivities of different forms must also be considered. The selectivity of the reaction described in Scheme 7 suggests that the higher energy oxocarbenium ion **32** was more reactive than the sulfonium ion **30**, providing an overall lower energy pathway for nucleophilic addition of the allylmetal reagent.[43] Consequently, if a reaction produced oxocarbenium ion and sulfonium ion intermediates in rapid equilibrium, the final products of these reactions could occur solely from trapping of the oxocarbenium ion intermediate.

1,2-Sulfur Migrations and Episulfonium Ions

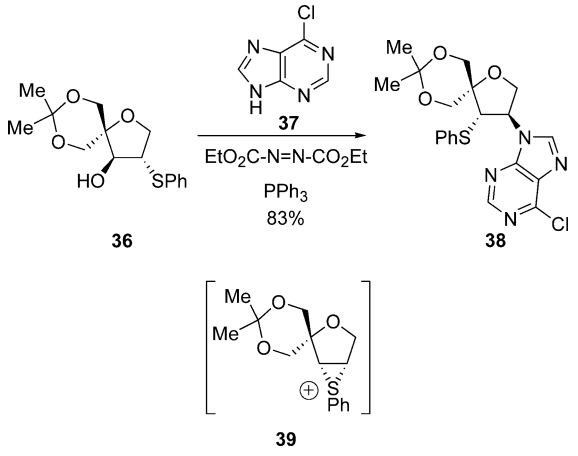
Since the original report of carbohydrate synthesis by a 1,2-sulfur migration,[50] related rearrangements have emerged as important synthetic transformations.[19–21] Many of these transformations are highly selective. For example, Yu and co-workers developed a synthetic method that involved 1,2-sulfur migration, stereoselective glycosylation, and differential protection of the different hydroxy groups of a sugar (Scheme 8).[51] This methodology can be employed for the synthesis of deoxyglycosides after reductive removal of the sulfur substituent.[52]



Scheme 8. 1,2-Sulfur migration/glycosylation reaction.

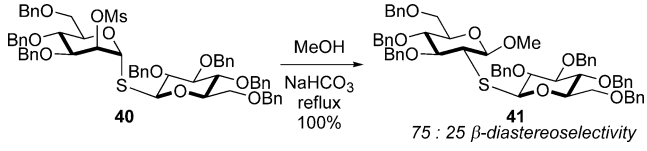
The 1,2-sulfur migration/glycosylation reaction can also be employed in the preparation of sugar-like structures where the glycosyl acceptor is connected at a position other than the anomeric center. Generation of a leaving group adjacent to a sulfide as in **36** (Scheme 9) resulted in a 1,2-migration reaction and ring-opening[19–21] to provide the isonucleoside **38**.[53] Formation of the proposed episulfonium ion **39** and its microscopic reverse, ring-opening, occurred with complete control of stereochemistry, as would be anticipated for stereospecific reactions. The regioselectivity of the ring-opening, which occurs away from the neopentyl position,[47] is also consistent with substitution of episulfonium ion intermediate **39**.

Not all 1,2-sulfur migrations/glycosylation reactions are stereoselective, however. In the course of synthesizing thiosugars, Pinto observed that although the sulfur migration proceeded with inversion of configuration at the carbon stereocenter, the stereoselectivity of the glycosylation step was low (Scheme 10).[14] This lack of stereospecificity at the anomeric center was also observed by Nicolaou in the original publication of this method.[50] These results suggested that oxocarbenium ions, not episulfonium ions, were important reactive intermediates in the glycosylation step.[14] Similar observations were reported during *N*-glyco-



Scheme 9. Synthesis of an isonucleoside by a 1,2-sulfur migration/glycosylation reaction.

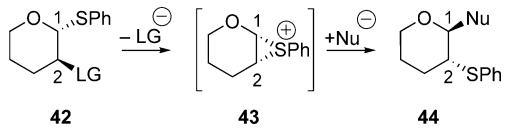
sylations of furanosides using anomeric sulfides and selenides.[13,16] With optimization, the sulfur system could be rendered diastereoselective, but only low selectivity was observed for the selenium series. From these results, the authors concluded that these reactions do not involve episulfonium or episelenonium ions.[13,16]



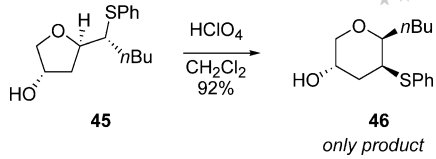
Scheme 10. Unselective 1,2-sulfur migration/glycosylation reaction.

Comparison of 1,2-Rearrangements of Sulfur and Silicon

The intermediacy of three-membered ring onium ions in 1,2-sulfur rearrangement/glycosylation reactions such as those shown in Schemes 8 and 9 is not unreasonable. These reactions involve three operations: (1) the sulfur atom promotes ejection of the leaving group *anti* to it, (2) the sulfur atom migrates on the same face of the cation without loss of stereochemical integrity, and (3) the nucleophile attacks the stabilized cation *anti* to the sulfur atom. A mechanism involving episulfonium ions satisfies these three stereochemical conditions (Scheme 11). This stereochemical consequence has also been observed in systems other than carbohydrates. For example, the ring expansion of tetrahydrofuran **45** follows the same three stereochemical rules, and these reactions are stereospecific (Scheme 12).[54]

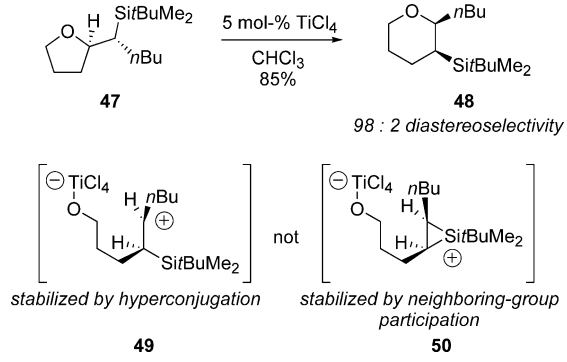


Scheme 11. General mechanism of the 1,2-sulfur migration/glycosylation reaction.



Scheme 12. Ring expansion by 1,2-sulfur migration.

Juxtaposition of the sulfur chemistry described above (Scheme 12) with its analogue in the silicon series is informative. When silane **47**, which closely resembles sulfide **45**, was treated with a Lewis acid, a comparable ring expansion by a 1,2-rearrangement occurred (Scheme 13).[55] This reaction was also stereospecific. The essential features of this reaction are the same as for the sulfide: (1) the leaving group departs *anti* to the silyl group, (2) migration of the silyl group is suprafacial, and (3) nucleophilic attack occurs *anti* to the silyl group.



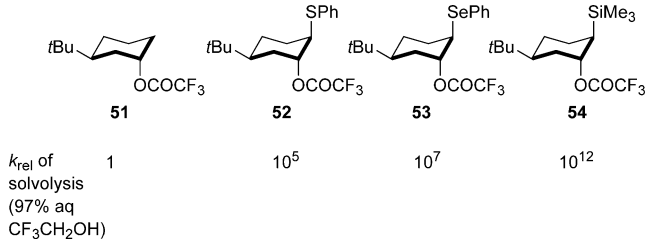
Scheme 13. Ring expansion by 1,2-silyl migration.

Analysis of the reaction in the silicon series is facilitated by extensive experimental and theoretical studies of silicon-stabilized cations.[56,57] The preponderance of evidence indicates that β-silyl carbocations are open cations stabilized by hyperconjugation from the high-energy σ_{C-Si} orbital (as in **49**, Scheme 13), not siliranium ions such as **50**.[57] This conclusion, supported by theoretical calculations,[58,59] is consistent with the high barriers to rotation about the central carbon–carbon bond of β-silyl carbocations[56,57] that result in stereospecific transformations of these cations.[60,61] Consequently, the mechanism for the rearrangement of tetrahydrofuran **47** to tetrahydropyran **48** (Scheme 13) most likely involves open cation **49**, which is stabilized by hyperconjugation.

The comparison between the sulfur and silicon series (Schemes 12 and 13) provides an alternative analysis of the reactions of acetals bearing heteroatoms such as sulfur at C-2. It is not necessary that three-membered rings be involved in these stereospecific transformations. Intermediates stabilized by hyperconjugation, as shown in Scheme 13, react with similar stereochemical outcomes. Consequently, hyperconjugation of the C–SPh bond (σ_{C-S})[62] could be responsible for stabilizing the cation and maintaining its stereochemical integrity. The competing hypotheses of neighboring-group participation and hyperconjugation

should lead to the design of experiments to differentiate between the possible intermediates.[63]

White and Lambert have provided evidence that hyperconjugation plays a significant role in the formation of cations substituted with sulfur and selenium substituents.[64] Solvolysis of a series of constrained trifluoroacetate esters indicates that ionization is considerably faster for the silyl-substituted ester **54** than for the sulfide **52** or selenide **53** (Scheme 14). Ionization of the silyl ester **54** involves only hyperconjugation,[65] but the sulfide and selenide could benefit from anchimeric assistance. The lone pairs of sulfur and selenium, however, do not accelerate ionization. Instead, the rates of solvolysis follow the donor ability of the σ_{C-X} bond, with σ_{C-Si} being the strongest donor, and σ_{C-S} the weakest.[62] The bond lengths and angles in X-ray crystal structures of esters related to **52** and **53** are also more consistent with hyperconjugative interactions than they are with anchimeric assistance.[64]



Scheme 14. Relative solvolysis rates of constrained esters.

Episulfonium Ions vs. Stabilized Cations

The structure of a β-silyl carbocation depends upon the stabilization of the cation by other substituents (Figure 3). The lowest-energy structure of the primary β-silyl carbocation was calculated to be the siliranium ion **55** by about 2 kcal/mol, but the corresponding secondary β-silyl carbocation favored the open form **56**; the siliranium ion form was not an energy minimum in this case.[58,59] As the carbocation becomes more stabilized, the influence of the bridging atom diminishes, shifting the equilibrium to the open form of the cation.

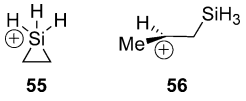
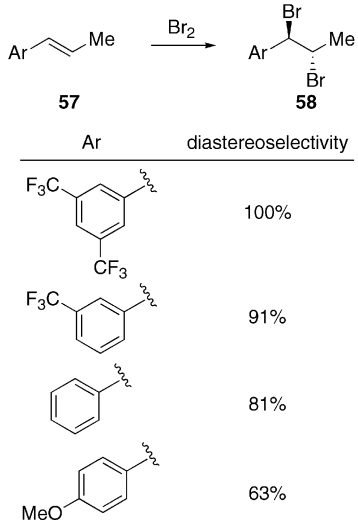
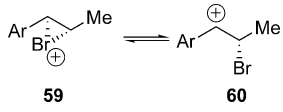


Figure 3. Calculated lowest-energy structures of primary and secondary β-silyl carbocations.

Other cations exhibit the same trend as the β-silyl carbocations: as the open-form of the carbocation becomes more stabilized, the contribution from neighboring-group participation may become less important. This trend was observed with the bromination of alkenes, a transformation that likely proceeds via bromonium ions, which have been characterized.[31] As the alkene **57** becomes more electron-rich, the stereospecificity of bromination decreases (Scheme 15).[66] These results imply that with electron-rich systems, bromonium ion **59** opens to form the benzylic cation **60** (Scheme 16). Similar observations have been made for the chlorination of styrenes.[67] Spectroscopic evidence indicates that β-bromo- and β-chloro tertiary carbocations exist in the open form, not the halonium ion.[68] These observations are consistent with the spectroscopic studies of episulfonium ions, which undergo ring-opening and isomerization reactions at rates that correlate to the stability of the corresponding open cations (vide supra, Schemes 5 and 6).[41,42]

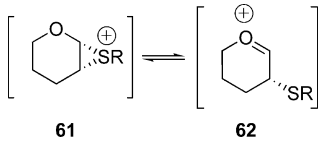


Scheme 15. Bromination of substituted β-methylstyrenes.



Scheme 16. Bromonium ion vs. benzylic cation.

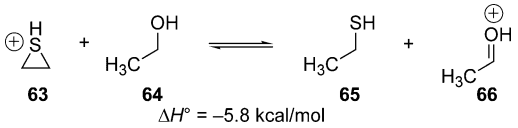
The equilibrium between episulfonium ions **61** and oxocarbenium ions **62** (Scheme 17) would likely follow the same trend. If anchimeric assistance from the sulfur atom stabilizes the cation more than donation of the non-bonding orbital on oxygen (n_O) to the vacant orbital on carbon (n_{C+}), then the episulfonium ion **61** would be favored. If donation from the oxygen lone pair is more stabilizing, then the oxocarbenium ion **62** would be favored.



Scheme 17. Episulfonium ion vs. oxocarbenium ion.

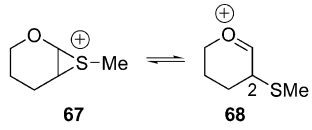
Experimental data in the gas phase suggests that for simple systems, an episulfonium ion is less stable than an oxocarbenium ion, indicating that donation from an oxygen lone pair stabilizes a cation more than anchimeric assistance by sulfur. The amount of energy liberated upon

quenching cations with hydride ions was measured in the gas phase,[69] and these values can be compared to suggest that oxocarbenium ion **66** is more stable than the episulfonium ion **63** (Scheme 18).[69] Because two other entities (alcohol **64** and thiol **65**) are present in the equation, it is not possible to compare the two cations directly, but it is likely that the position of the equilibrium is dominated by the cationic species, not the neutral ones.[69]



Scheme 18. Gas-phase stabilities of an episulfonium ion vs. an oxocarbenium ion.

An estimate combining computational studies also suggests a preference for the oxocarbenium ion form (Scheme 19). The relative energies of the episulfonium ion **67** and its open form, oxocarbenium ion **68**, can be estimated using enthalpies of formation of sulfonium ions and oxocarbenium ions (about 22 kcal/mol)[44] and the most recently determined ring strain of thiirane (about 26 kcal/mol).[70] The estimate that oxocarbenium ion **68** is about 4 kcal/mol more stable than episulfonium ion **67** compares favorably to the value obtained from analysis of gas-phase hydride affinities of the cations (Scheme 18).[69] Even if an older estimate of the ring strain of episulfides is employed (20 kcal/mol[45,70]), the conclusion remains: the ring strain of the three-membered ring episulfonium ion dramatically attenuates the enthalpic benefit of forming the carbon–sulfur bond.

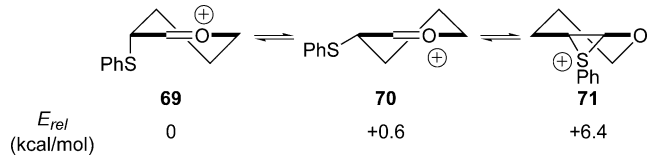


ΔH° for acyclic sulfonium versus oxocarbenium (kcal/mol)	Relief of ring strain of monocyclic episulfide (kcal/mol)	$\Delta H°_{reaction}$ (kcal/mol, estimated)
+21.6	–25.5	–3.9

Scheme 19. Estimate of relative stabilities of an episulfonium ion and an oxocarbenium ion.

Computational Studies on Episulfonium Ions

Theoretical studies not only demonstrate that oxocarbenium ions are favored over episulfonium ions, but they also illustrate a conformational preference for the oxocarbenium ion.[71–73] Jones and Liotta performed MNDO calculations to generate the reaction energy surfaces for the interconversion between episulfonium and oxocarbenium ion intermediates of 2-thioalkyl pyranosides (Scheme 20).[71] These calculations revealed that the half-chair oxocarbenium ion conformers **69** and **70** were more stable than the corresponding episulfonium ion **71** by about 6 kcal/mol, consistent with the estimates shown in Schemes 18 and 19. These calculations also indicated that the pseudoaxial conformer **69** was the lowest energy conformer of the cation, which would not be anticipated based upon consideration of steric effects.



Scheme 20. Semi-empirical calculations (MNDO) comparing episulfonium ions and oxocarbenium ions.

Other computational studies of these systems provided additional insight into the structure of sulfur-substituted cations. Using high-level ab initio calculations (including electron correlation), Hoffmann showed that the minimum energy form of the model cation **72** (Figure 4) more closely resembled the open oxocarbenium ion form **72** than the episulfonium ion form **73**; similar results were observed for a tetrahydropyran cation.[72] Differentiation between the open and closed forms requires careful analysis because of the relatively minor geometric differences between the two cations.[9] A strong vibrational frequency was present in the region of a carbonyl stretch, suggesting that the cation had significant oxocarbenium ion character. In addition, the bond lengths around the oxygen atom closely matched those of a cation without a sulfur atom. The perpendicular orientation of the carbon–sulfur bond of cation **72** suggests stabilization by hyperconjugation of the strongly donating σ_{C-S} into the vacant orbital on carbon (n_{C+}), analogous to the observations in the β-silyl carbocation series (vide supra, Schemes 13 and 14 and Figure 3). This analysis also indicates a preference for the axial conformer of the tetrahydropyran cation, in accord with the predictions of Jones and Liotta (Scheme 20).[71] Density functional theory calculations reported by Bo and Castillón on tetrahydrofurans and tetrahydropyrans bearing HS, HSe, and I groups also show only oxocarbenium ion forms with axial orientations of the substituent at C-2.[73]

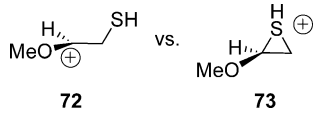
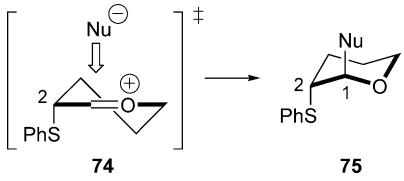


Figure 4. Computational studies of α-alkoxy-β-hydrosulfido carbocations.

The greater stability of the axially substituted oxocarbenium ion resembling **69** rather than the episulfonium ion **71** (Scheme 20)[71–73] suggests an alternative explanation for the diastereoselectivities of reactions of sulfur-substituted acetals. If the episulfonium ion were not an intermediate, then the product would be formed from the oxocarbenium ion **69**. The major product could be a result of stereoelectronic effects and conformational preferences of the oxocarbenium ion. Nucleophilic addition to the lower-energy axial oxocarbenium ion intermediate **69** through the stereoelectronically preferred chair transition state **74**[74–76] would provide the 1,2-*trans* product **75** that is the major product

of reactions of sulfur-substituted acetals (Scheme 21). This mode of attack would also minimize steric interactions between the incoming nucleophile and the axially disposed sulfur substituent.[72] The lack of stereospecificity for these reactions is also consistent with this explanation. The minor product could be formed if any of the equatorial oxocarbenium ion **70** were present. *Consequently, the existence of bridged onium ions is not required to explain the reactions of sulfur-substituted acetals*,[77] just as it was not required to explain the reactions of silyl-substituted cations (vide infra, Schemes 13 and 14 and Figure 3).

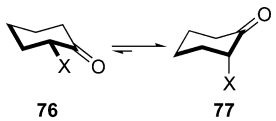


Scheme 21. Stereoelectronically controlled addition to an axially substituted oxocarbenium ion.

Although these computational studies used simple tetrahydropyran model systems to determine the influence of the sulfur atom on the cationic intermediate, the conclusions of these studies are likely to be relevant in fully elaborated carbohydrate-derived systems. In a related series, the influence of individual alkoxy groups on the conformational preferences and reactions of oxocarbenium ions have been examined in detail.[78–80] The conclusions of those studies are relevant to fully elaborated carbohydrate derivatives.[79,81,82]

Comparisons Between Substituted Oxocarbenium Ions and Ketones

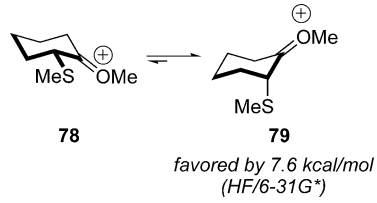
Examination of the structures of heteroatom-substituted ketones provides a valuable reference point for analyzing the behavior of oxocarbenium ions. 2-Halocarbonyl[83–86] and 2-thiocarbonyl[84,87] compounds show pronounced biases for axial conformers in some systems (Scheme 22). For example, 2-(phenylthio)cyclohexanone prefers the axial conformer **77**, presumably to maximize overlap of σ_{C-S} with π^* of the carbonyl group.[84,87] The preference for the axial conformer of these ketones mirrors the axial preference calculated for the oxocarbenium ion (vide supra, Scheme 20 and Figure 4).[71–73]



X	76 / 77 ($CDCl_3$)
Cl	45 : 55
I	12 : 88
SMe	15 : 85

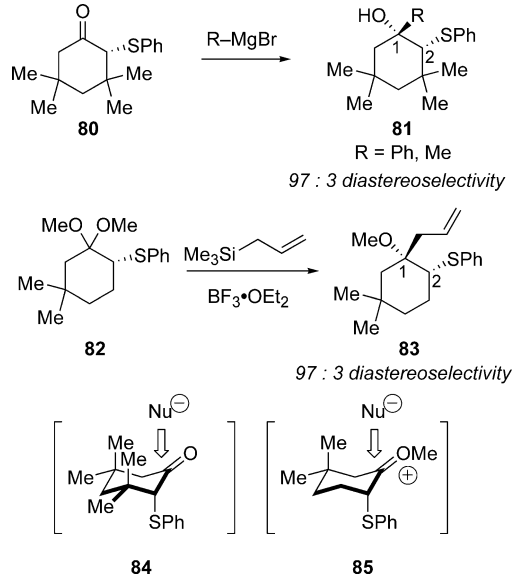
Scheme 22. Conformational preferences for heteroatom-substituted cyclohexanones.

Computations performed in our laboratory suggest a correlation between the conformational biases of ketones and those of oxocarbenium ions derived from these ketones (Scheme 23).[77] The axial conformer **79** was found to be considerably lower in energy than the equatorial isomer. No episulfonium ions were observed as energy minima, as noted by others.[72,73] The larger preference for the axial conformer of the oxocarbenium ion compared to the ketone can be understood by considering that the $\pi^*_{C=O}$ should be lower energy for the cation than for the ketone.[77]



Scheme 23. Calculated conformational preferences for methylthio-substituted cyclohexanone oxocarbenium ions.

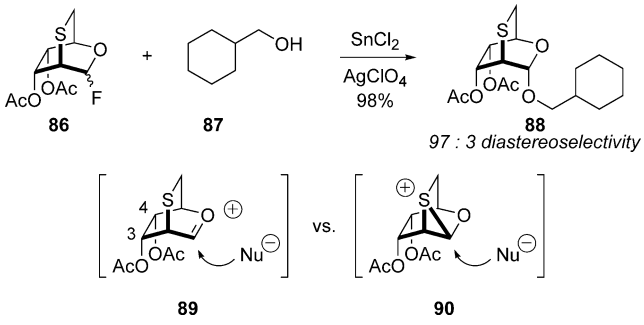
In addition to the related conformational biases, ketones and their analogous oxocarbenium ions exhibit similar selectivities.[77] Results such as those shown in Scheme 24 are representative. Both the ketone **80** and the oxocarbenium ion derived from acetal **82** were calculated to reside primarily in axial conformations (**84** and **85**, respectively). Nucleophilic addition to the axial ketone **84** was anticipated to be *anti* to the sulfur (controlled by a Felkin–Anh-type addition[88–91]), as has been observed for other 2-thioalkyl-substituted ketones.[92–94] Even with considerable steric hindrance to attack from the axial faces, additions to electrophiles **84** and **85** afforded *trans* products **81** and **83**, respectively. We concluded that additions to sulfur-substituted oxocarbenium ions occur to axial conformers, which are preferred due to strong hyperconjugative stabilization, and



Scheme 24. Comparison of reactions of phenylthio-substituted cyclohexanones and related acetals.

these conformers were favorably oriented to react through lower-energy Felkin–Anh-like transition states.

The combination of a conformational preference for the axial conformer of sulfur-substituted oxocarbenium ions (vide supra, Schemes 20 and 23 and Figure 4) and a stereoelectronic preference for attack *anti* to the sulfur atom (vide supra, Schemes 21 and 24) provides a model to explain the reactions of various sulfur-substituted acetals. For example, the highly stereoselective glycosylation of the thiabicyclic acetal **86** (Scheme 25)[95] can be explained by a Felkin–Anh-like *anti*-attack onto the bicyclic oxocarbenium ion **89**, not ring-opening of a highly strained tricyclic episulfonium ion **90**. This analysis appears to be applicable for systems with substituents other than sulfur: Díaz, Castillón, and coworkers explained the reactions of 2-phenylselenenyl glycosyl donors as the result of a conformational bias of an oxocarbenium ion and stereoelectronically controlled addition to it.[96]



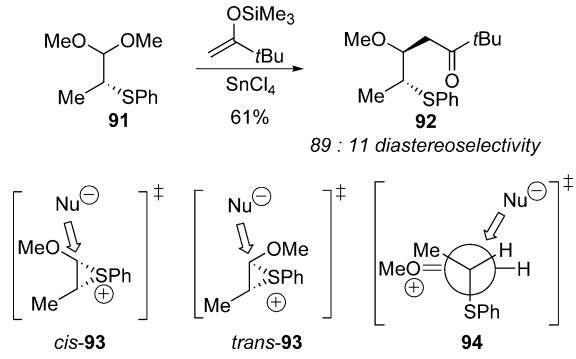
86 87 88 89 90

Scheme 25. Glycosylation of a bicyclic glycosyl donor.

Acyclic Acetals Bearing Heteroatoms

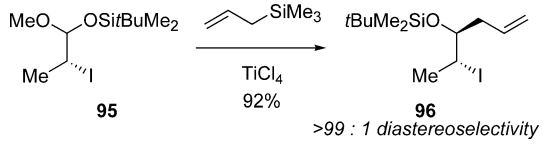
The concept that the reactions of sulfur-substituted cyclic acetals occur through oxocarbenium ions by Felkin–Anh-type additions rather than by direct displacement reactions of episulfonium ions is supported by the reactions of acyclic acetals. Whereas the stereochemical courses of reactions of cyclic cations are consistent with reactions through either onium ion intermediates or oxocarbenium ions, the reactions of the corresponding acyclic acetals cannot be readily explained by onium ions.

The substitution reactions of acyclic 2-phenylthio acetals and their related iodine analogues are generally diastereoselective (Schemes 26 and 27).[97,98] For example, the substitution of acetal **91** formed ketone **92** preferentially (Scheme 26). Similar selectivities were observed with iodine-substituted acetals (Scheme 27).[98] If an episulfonium ion were the reactive intermediate in Scheme 26, then the selectivity could only be rationalized by proposing that nucleophilic substitution occurred on the *cis*-substituted ion *cis*-**93**. The *cis*-substituted cation *cis*-**93** is topographically similar to the episulfonium ion required by the constraints of cyclic systems (such as **71**, Scheme 20), which explains the stereochemical similarities between the products formed. Unlike the cyclic systems, however, the acyclic substrates are conformationally flexible, and the *trans* sulfonium ion *trans*-**93** is expected to be more stable, as demonstrated for other systems (vide supra, Scheme 5).[41] The ion *trans*-**93** cannot be involved, however, because reactions of this ion would lead to a product with the opposite relative stereochemistry to that observed. Any explanation for the formation of product **92** involving episulfonium ions would need to account for why the *cis* ion *cis*-**93** was the reactive species. These reactions are better considered to proceed via open oxocarbenium ions such as **94** with the sulfur substituent aligned to maximize hyperconjugation with the cationic center. Additions to these cations by Felkin–Anh-like transition states[88–90] (favoring **94**)[97,98] provide results that coincide with the conclusions presented for exocyclic oxocarbenium ions (Scheme 24).[77]



91 92 *cis*-93 *trans*-93 94

Scheme 26. Reactions of acyclic phenylthio-substituted acetals.



95 96

Scheme 27. Reactions of acyclic iodine-substituted acetals.

Conclusions

Glycosyl donors substituted with groups such as PhS at C-2 undergo diastereoselective reactions in which the major product is formed by attack *anti* to the substituent. Although episulfonium ions are logical intermediates for such reactions, the available evidence demonstrates that episulfonium ions are less stable than the corresponding oxocarbenium ions due to ring strain. In addition, the oxocarbenium ion appears to be more reactive than the episulfonium ion.

Mechanisms involving oxocarbenium ion intermediates provide alternative explanations of the stereochemical courses of reactions of glycosyl donors bearing groups such as PhS at C-2. The oxocarbenium ion has a strong preference for a conformation that places the substituent in the axial position, likely due to hyperconjugation. The resulting oxocarbenium ions undergo stereoelectronically favored attack to form products in which the nucleophile is installed *trans* to the substituent. This analysis allows the reactions

of cyclic and acyclic acetals to be explained by the same analysis that has been employed to explain the conformational preferences and reactions of sulfur-substituted ketones. Considering oxocarbenium ions to be the intermediates in glycosylation reactions also explains why minor isomers are formed in many cases, a fact that is not readily accommodated by mechanisms involving episulfonium ions. In addition, an explanation involving oxocarbenium ions avoids invoking unstable episulfonium ions that have not been observed in high-level computational studies and are likely disfavored based upon thermodynamic considerations.

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