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Computational Insight into the Reaction Intermediates in the Glycosylation Reaction Assisted by Donor Heteroatoms

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We studied the geometric and electronic structure of several cations (**9** and **18**−**23**) that are usually proposed as intermediates for glycosylation reactions using DFT methods. For ions **9** and **18**−**23** the geometries obtained corresponded to an open ion (**6b** type) irrespective of the exocyclic heteroatom (S, Se, I) and the size of the cycle (furanoses as well as pyranoses). We studied how substituents bonded to the exocyclic heteroatom (R in SR and SeR) affect the structure of ions and found that the geometry approached that of episulfonium and episelenonium ions (**6a** type) when the substituents were electron donors. The *tert*-butyl group and the 2,4,6-trimethyl- and 2,4,6-trimethoxyphenyl and trimethylsilyl groups produced the strongest of these effects. The presence of an electron-withdrawing group ($CO-CF_3$) bonded to the hydroxymethyl group produced a similar but weaker effect. We analyzed this behavior in terms of molecular orbital interactions.

Introduction

2′,3′-Dideoxynucleosides have attracted the attention of researchers because they have remarkable antiviral properties, especially against HIV viruses.[1] A common problem in the synthesis of these nucleosides through glycosylation reaction is how to control the stereoselectivity in the absence of a participating group at position 2 of the sugar ring. Several reports describe how this problem can be overcome by using electron-donor groups (such as iodo, phenylsulfanyl, and phenylselenenyl) at position 2 (**2**) (Scheme 1).[2] Once the corresponding nucleosides **7** have been obtained, they are further reductively removed to provide 2′-deoxynucleosides **8**. Glycosylation is therefore performed from furanoses **2** (Y = SPh,[3] SePh[4]) (Scheme 1, path 1), from glycals **3** by using NIS,[5] I_2,[5] PhSCl,[6] or PhSeCl[7] (Scheme 1, path 2, Y = I, SPh, SePh respectively), or from seleno-[8] or thio-glycosides[9] **5** under Mitsunobu conditions (Scheme 1, path 3, Y = SPh, SePh).

The stereoselectivity of the global process is determined by two different steps. The first step is to introduce the group bearing the heteroatom. This can be done by reacting a sulfur or selenium electrophile with the enolate of lactone **1**, then reducing lactone and activating the acetyl group to give **2** (path 1), or by adding the electrophile to enol ether **3** (path 2). The stereoselectivity of these processes is controlled by the substituent at position 4. Alternatively, the group bearing the heteroatom can be initially introduced at position 1 by forming a seleno- or thio-glycoside **5** (path 3), which will then further stereoselectively migrate to position 2 under glycosylation conditions.

For the second step (glycosylation), intermediate **6a** has been proposed for the three procedures to justify the stereoselectivity. However, although these reactions are highly stereoselective, an α/β mixture is always obtained, and intermediate **6b** has been suggested as a possible explanation for this.[8,9] Since the reaction is usually driven under kinetic conditions, the stereoselectivity should be controlled by the relative stability of intermediates **6a** and **6b**.

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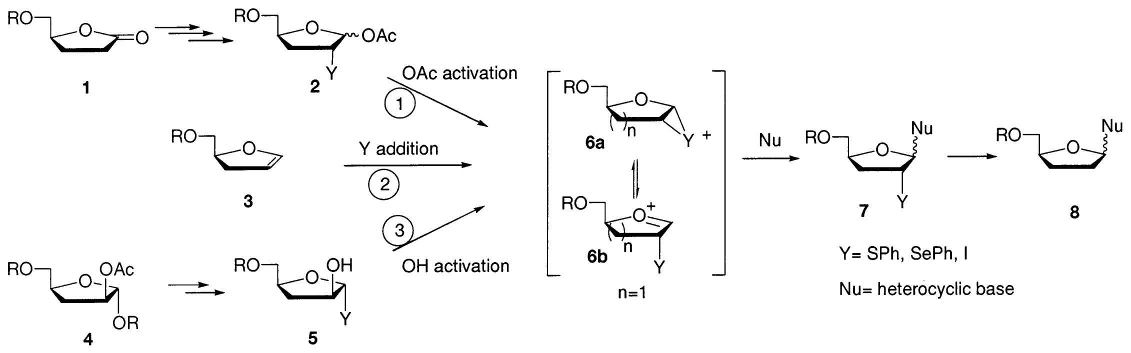
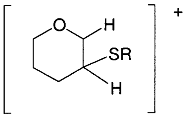
SCHEME 1



A similar stereochemical behavior was recently observed in the synthesis of 4′-thionucleosides starting from thioglycals,[10,11] which suggests a similar trend for the different heteroatoms present in the ring.

Computational studies of the intermediates in the glycosylation of pyranoses with a sulfur at position 2 have recently been published, although similar studies in the furanose field have not been reported. A semiempirical study of ion **9** (R = Ph) (Figure 1) as a model for understanding the glycosylation starting from 2-deoxy-2-arylsulfanyl-pyranoses suggests that both intermediates (episulfonium and oxonium) are minima in the potential energy surface, but that oxonium ion is more stable than episulfonium (ESI) in pyranoses.[12]



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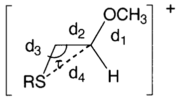

10

A more recent study based on ab initio methods (HF, MP2, and QCISD) in ions **9** and **10** (R = H, Me) as model systems shows that ions with an S−C−C−O backbone have an oxonium structure, but the presence in **10** of a methyl group bonded to sulfur makes this structure become more episulfoniun-like, although this was not confirmed in intermediate **9**.[13] These authors suggested that a deeper study was needed. Recent reports show evidence of episulfonium intermediates in electrophilic additions to alkenes and alkynes.[14]

In the glycosylation reaction starting from glycosyl donors **5** (3,5-tetraisopropyldisiloxane-α-arabino derivatives, Y = SR), we recently observed a change in the steroselectivity depending on R. Thus, the α/β ratio is 2 and 10 for R = Ph and ^{t}Bu, respectively.[9]

We therefore decided to carry out a general and systematic study of the intermediate in the glycosylation reaction, starting from 2′,3′-dideoxy-furanoses with donor heteroatoms at position 2 of the sugar ring, based on DFT calculations. To explain the general behavior of these systems, we considered 2,3-dideoxyfuranoses and cyclopentane derivatives which have as external heteroatoms sulfur, selenium, and iodine. For comparison purposes we also report some example models of pyranoses.

Computational Methods

The reported DFT calculations were carried out with the Amsterdam Density Functional (ADF) program system version 2.3 derived from the work of Baerends et al.[15] and developed at the Free University of Amsterdam[16] and the University of Calgary.[17] The atomic orbitals were described as an uncontracted double-ζ Slater function basis set with a single-ζ polarization function on all atoms taken from the ADF library. The 1s electrons on carbon and oxygen, the 1s2s2p on sulfur, and the 1s2s2p3s3p on selenium were assigned to the core and treated by the frozen core approximation. A set of s, p, d, f, g, and h Slater functions centered on all nuclei was used to fit the electron density, and to evaluate the Coulomb and exchange potentials accurately in each SCF cycle. The local part of the V_{xc} potential (LDA) was described by using the VWN parametrization,[18] in combination with the gradient corrected (GGA) Becke's functional[19] for the exchange and Perdew's function[20] for correlation (BP86). The GGA approach was applied self-consistently in geometry optimizations. Second derivatives were evaluated numerically by a two-point formula.

Results and Discussion

To describe **6** as being similar to **6a** (episulfonium ion) or **6b** (oxonium ion) (Scheme 1), we compared **6** to oxonium and episulfonium ions as well as to neutral compounds of similar composition. Neutral compounds **11**−**15** and ions **16** and **17** are good models for these ions and provide reference geometrical data that will be used in the following discussion. Tables 1 and 2 show the most significant structural parameters of compounds **11**−**15**

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TABLE 1. Selected Geometrical Parameters for Compounds 11–15 and Ion 16[a]

	11	12	13	14	15	16
*d*1	1.437	1.440	1.436	1.385	1.376	1.265
*d*3	1.870	2.013	2.275	1.871	2.010	1.111
*d*4	2.850	2.965	3.173	1.905	2.078	2.079
τ	113.9	113.2	112.0	68.3	71.5	106.7

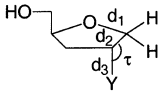
[a] Bond distances *d*1, *d*3, and *d*4 are given in Å and angles τ in deg.

TABLE 2. Selected Geometrical Parameters for Ions 17[a]

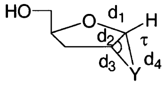
	SH	SeH	I
*d*1	1.507	1.506	1.494
*d*3	1.966	2.091	2.407
*d*4	1.947	2.090	2.383
τ	67.3	69.5	71.5

[a] Bond distances *d*1, *d*3, and *d*4 are given in Å and angles τ in deg.

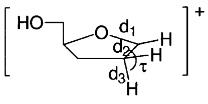
and ions **16** and **17**. The main differences are the distances *d*1 (close to a carbon–oxygen double bond for **16** and longer than a single carbon–oxygen bond for **11**), *d*3 and *d*4 (the difference between the *d*4 and the *d*3 bond distance ($d4 - d3$) is approximately 1 Å in the open compounds **11**–**13** and ion **16**, and practically zero in the cyclic compounds **14** and **15** and ions **17**), and the angle τ. This angle is >106° for compounds **11**–**13** and ion **16** and 70° for compounds **14** and **15** and ions **17**.



11 Y= SH
12 Y= SeH
13 Y=I



14 Y=S
15 Y=Se



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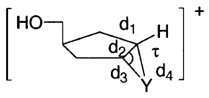
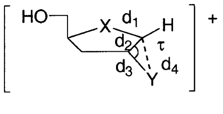
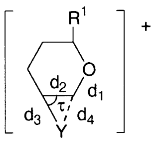


17 Y=SR, Y=SeR, Y=I

Table 3 shows the main parameters of the optimized geometry of ion **18** (X = O, Y = SR, SeR, I, for R = H, Me, Ph, and ^{t}Bu). From the comparison of the data in Tables 1, 2, and 3, it appears that the geometries of **18** (Y = SH, SeH, I) have many similar characteristics to those of oxonium ions (similar to **6b**), particularly the *d*1 distance. Moreover, τ is around 90°, which is larger than expected for episulfonium, episelenonium, or iodonium ions (70°).

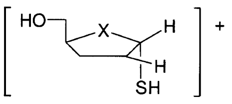


18 X=O, Y=SR, SeR, I



19 Y= SPh, R^1= CH_2OCOCF_3
20 Y= SeR, R^1= H
21 Y= SePh, R^1= CH_2OCOCF_3
22 Y= I, R^1= H
23 Y= I, R^1= CH_2OCOCF_3

We tried several times to obtain an energy minimum corresponding to an episulfonium ion and considered ion **24** with a thiol group at position 1. We actually performed a partial optimization in which we kept the S–C1–C2 (sugar numbering) angle frozen, but the structure, with a gradient norm of less than 0.01, evolved to the ion **18** (Y = SH) when the geometric constraints were released without an energy barrier.



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The nature of intermediates **18** was confirmed as true minima by calculating the harmonic vibrational frequencies that provided positive values in all cases (vide infra). The vibrational frequencies for **18** also support an oxonium ion character similar to that of **6b**.

We then considered the effects of replacing the substituents in sulfur and selenium. Table 3 shows that *d*1 increases and the difference between *d*3 and *d*4 decreased. Also, angle τ was lower when R = Ph, Me, and ^{t}Bu than when R = H. These values show that there was a large electronic effect that depended on the substituent in the sulfur or selenium. Therefore, the more electron donating is the substituent, the closer the 2-thio or 2-selenium group is to C1, i.e., the more **6a** character the reaction intermediate has.

To limit the involvement of oxygen electrons in the stabilization of the ion, an electron-acceptor group (trifluoroacetate) was introduced onto O5 (Y = S, R = Me; Y = Se, R = Me, ^{t}Bu) (Table 3). Effectively, the thio or selenenyl group and C1 slightly approached each other, as we can deduce from the decrease in *d*4 and τ.

Since the electronic effect that depended on the substituent at sulfur and selenium was relatively important, we decided to extend the study by introducing classical π or σ electron-donor and electron-acceptor groups in the selenium (Figures 1 and 2). In general, *d*4 was shorter when electron-donor groups were introduced. From Table 3 and Figures 1 and 2, $d4-d3$, which may indicate the tendency to form the oxonium ion, appears to increase as follows: R = Ph-$(Me)_3$ < Si$(Me)_3$ < Ph$(OMe)_3$ < ^{t}Bu < *m*Ph$(OMe)_2$ = *p*Ph-Sn$(Me)_3$ < Me < *p*Ph(OMe) < Ph < *p*PhNO_2 < H. Electron-donor and -withdrawing groups are clearly delimited by the phenyl group.

The previous data for Y = SR and SeR show that the high stereoselectivity in glycosylation to obtain nucleosides when R = S-2,6-di-^{i}PrPh[3a] and S^{t}Bu[9] is justified not only by steric factors but also by electronic factors (an intermediate that is closer to ESI, **6a**) (Scheme 1, via steps 2 and 3).

As we mentioned above, the structure of ion **10** has been determined by other authors.[13] As Table 4 shows, DFT and MP2/6-31G[13] provide quite similar structural data. Bond distances *d*1 and *d*2 are practically identical in both these studies, whereas our values for *d*3 are slightly longer. The largest discrepancy is for *d*4 when R = Me, which is directly reflected in the values of angle τ. The above authors also observed that τ was smaller and *d*1 was lengthened when R = Me, and suggested that a larger substituent in the sulfur, such as a phenyl group, may stabilize the ESI ion (**6a** type). Our results do not support this. Although our data show an increasing tendency toward episulfonium- or episelenonium-like

TABLE 3. Selected Geometrical Parameters for Ions 18[a]

	SH	SMe[b]	SPh	S^{t}Bu[b]	SeH	SeMe[b]	SePh	Se^{t}Bu[b]	I
*d*1	1.288	1.299 (1.303)	1.300	1.304 (1.310)	1.297	1.305 (1.310)	1.306	1.310 (1.315)	1.284
*d*3	1.895	1.888 (1.887)	1.914	1.880 (1.882)	2.039	2.035 (2.037)	2.059	2.030 (2.030)	2.284
*d*4	2.396	2.309 (2.293)	2.347	2.280 (2.251)	2.467	2.406 (2.362)	2.444	2.378 (2.356)	2.794
τ	90.1	86.2 (85.5)	87.3	85.4 (83.7)	88.1	85.0 (84.3)	86.5	84.4 (83.4)	94.1

[a] Bond distances *d*1, *d*3, and *d*4 are given in Å and angles τ in deg. [b] Values in parentheses correspond to the compounds with a trifluoroacetate group on O5 (oxygen exocyclic).

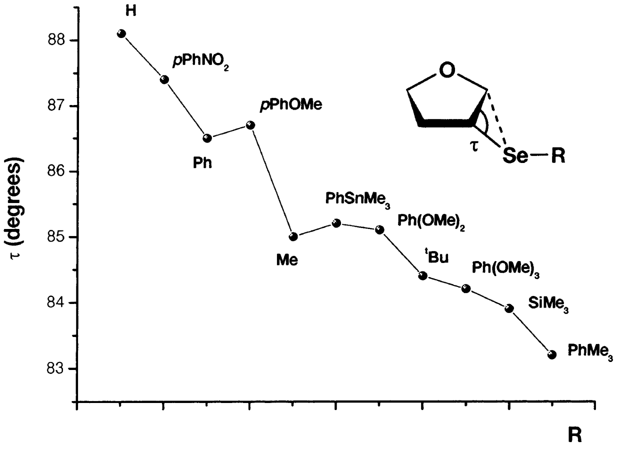

FIGURE 1. Variation of angle τ with R in ion **18**.

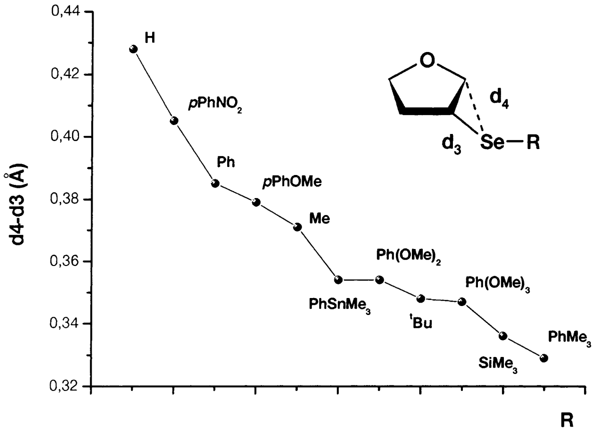

FIGURE 2. Variation of distance *d*4−*d*3 with R in ion **18**.

TABLE 4. Comparison of Geometrical Parameters of Compound 10[a] **Obtained by Using DFT (this study) and MP2/6-31G(d)**[13]

	H		Me	
	DFT	MP2	DFT	MP2
*d*1	1.285	1.275	1.301	1.301
*d*2	1.460	1.462	1.455	1.457
*d*3	1.876	1.845	1.870	1.842
*d*4	2.386	2.409	2.260	2.147
τ	90.5	92.8	84.7	80.3

[a] Bond distances *d*1, *d*2, *d*3, and *d*4 are given in Å and angles τ in deg.

intermediates when electron-donor substituents are present in sulfur and selenium, these ions do not seem to be clearly formed.[21]

We identified the normal mode corresponding to the C−X vibration in the computed harmonic vibrational frequencies. For ion **16**, in which we formally found a double $C_1{=}O$ bond, the vibrational frequency was 1549 cm^{-1}. The harmonic vibrational frequencies calculated for ions **18** (Y = SH, SeH, I) confirmed a partial double bond $C_1{=}O$ for each of them (1474, 1459, and 1477 cm^{-1} respectively), although the bond order was smaller. Finally, we extended our study to pyranoses[22] **9** and **19**−**23**, which are related to the above furanose systems and to the six-membered-ring model described in the literature.[12] DFT calculations on ions **18** provided no evidence of a stable intermediate corresponding to an episulfonium-like structure. This result supports the earlier semiempirical[12] and ab initio[13] calculations for pyranose **9** (R = H). For comparison purposes, we also considered ions **20** and **22**. The general trends of these pyranose rings (Table 5) were similar to those of furanoses. Trifluoroacetate derivatives **19**, **21**, and **23**, which are more closely related to the common pyranosyl donors, had a similar geometry to **9**, **20**, and **22**, respectively, although *d*1 was slightly longer, and *d*4 was slightly shorter, than in **19**, **21**, and **23**. Despite the long distance from the trifluororacetate to the endocyclic oxygen, the effect was still clear. We have so far presented a discussion mainly based on geometrical parameters.

The electronic structure of ion **18** is best visualized as a set of resonant structures (Figure 3) in which the positive charge is stabilized by an oxygen lone pair (oxonium) or by an external heteroatom electron pair. From a theoretical point of view, the relative weight of each structure can be obtained via a valence-bond treatment. This is, however, beyond the scope of this paper. The atomic population analysis carried out in the framework of the molecular orbital theory indicates the average electronic distribution in the system. Table 6 shows the relative values of Mulliken atomic charges, which are more appropriate for our discussion than the absolute values. In this study (Table 6), all Mulliken atomic charges for oxygen were negative, as Dudley et al.[13] also found for model system **10**. We should therefore conclude that the oxonium resonant structure does not contribute significantly to the stabilization of the carbenium ion. However, as we have already seen, if we analyze the geometrical parameters we reach the opposite conclusion.

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(21) For azasugar derivatives (see structure **18** for, X = NH, Y = PhS, PhSe, I) the calculated geometrical parameters indicate the presence of an iminium ion (**6b** type, Scheme 1). For tetrahydrothiophene ions (see structure **18** for X = S, Y = SR, SeR, I) the more stable structure involves the formation of a sulfonium cation by participating the endocyclic sulfur. The effect of substituents (Y) is similar to that observed for ions **18**. When X = SO, SO, (Y = SeH), the optimized geometry corresponds to that of episelenonium cations.

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TABLE 5. Selected Geometrical Parameters of Ions 9 and 19−23[a]

	9					**20**						
	H	Me	Ph	^{t}Bu	**19**	H	Me	Ph	^{t}Bu	**21**	**22**	**23**
$d1$	1.283	1.295	1.296	1.301	1.302	1.292	1.300	1.300	1.306	1.305	1.282	1.285
$d3$	1.890	1.892	1.921	1.894	1.924	2.045	2.036	2.068	2.039	2.070	2.307	2.307
$d4$	2.397	2.300	2.335	2.257	2.311	2.458	2.411	2.455	2.384	2.433	2.770	2.767
τ	90.2	85.5	86.3	83.4	85.1	87.4	85.5	86.6	84.1	85.6	92.0	91.9

[a] Bond distances $d1$, $d3$, and $d4$ are given in Å and angles τ in deg.

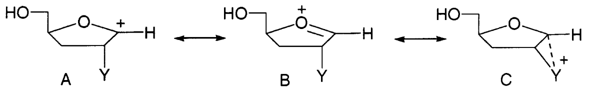

FIGURE 3. Resonant structures for cations **18**.

TABLE 6. Relative Mulliken Atomic Charges of Compounds 11, 14, 16, and 18 (Y = SH, ^{t}Bu)

	q(O-endocyclic)[a]	q(C1)[a]	q(S)[a]	overlap[b]
11	0 (−0.70)	0 (+0.32)	0 (−0.21)	−0.074
14	+0.04	+0.09	−0.05	+0.168
16	+0.31	+0.47		
18 (Y = SH)	+0.13	+0.31	+0.23	−0.018
18 (Y = S^{t}Bu)	+0.12	+0.26	+0.28	−0.004

[a] Relative Mulliken atomic charges (absolute values for **11** in parentheses). [b] Interatomic populations between S and C1.

In other words, the positive charge is delocalized between the endocyclic oxygen, C-1, and the external heteroatom (Figure 3).

Table 6 also shows the relative Mulliken atomic charges for C-1 and for the external heteroatom group, evaluated for the neutral model system **11**, **14** and for ions **16**, **18** (R = H, ^{t}Bu). We can see that the oxygen was less negatively charged in the ions than in the neutral compounds. Similarly, the positive charges in C-1 and sulfur increased in the same way. Interestingly, when H was substituted by ^{t}Bu in **18**, both oxygen and C-1 were less positively charged, whereas sulfur was more positively charged. This must be interpreted as an increasing contribution of resonance structure C (Figure 3), which is obviously reflected in the geometrical parameters $d1$, $d3$, $d4$, and τ (see Tables 3 and 6). Another proof of the increasing S/C-1 interaction is provided by the interatomic overlap population (Table 6). In **14**, S−C1 is a single bond and the overlap population reaches 0.168, whereas for the open compound **11** the overlap population is −0.074. Values for ions **18** lie between these limits, and when Y = S^{t}Bu they are closer to **14** than they are for SH. We can therefore conclude that there is some kind of interaction between sulfur and C-1 that helps to stabilize the ion. The theory of Atoms in Molecules (AIM),[23] based on the topological analysis of the charge density, provides a procedure for characterizing bonds between atoms. So, if two atoms interact directly, a bond critical point exists between them. In our study, for the greatest Y−C1 interaction (Y = Se^{t}Bu), we found no critical point between Se and C1. However, many examples in the literature, e.g. metal−metal bonds[24a] and agostic interactions,[24]reflect the fact that weak interactions are sometimes difficult to characterize.

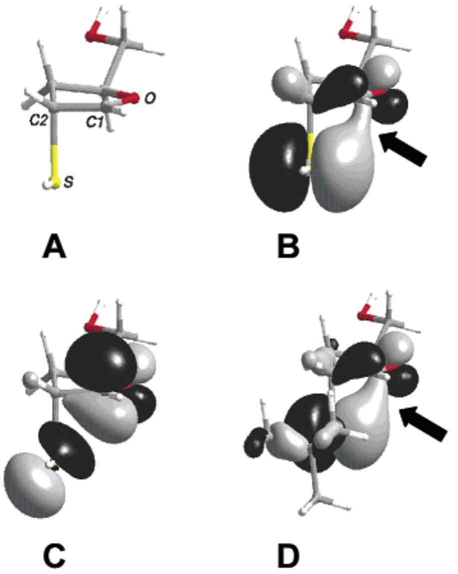

FIGURE 4. Molecular orbitals (MO) for ion **18**. (A) 3D view of the geometric structure for R = H. All MOs are represented in the same orientation. (B) HOMO-1 for R = H. (C) LUMO for R = H. (D) HOMO-1 for R = ^{t}Bu.

Figure 4 shows plots of the preferred conformation for **18** (Y = SH) and molecular orbitals (Y = SH, S^{t}Bu). The HOMO of both ions is the lone pair of the exocyclic oxygen, so it does not contribute to this discussion. However, the HOMO-1 and LUMO molecular orbitals, which are the bonding and antibonding combinations of a π*(O═C1) and sulfur lone pair, provide much more information. The overlap between the sulfur lone pair and the π*(O═C1) orbital lobule centered in C-1 is clearly visible in the HOMO-1 when R = SH (Figure 4B). This overlap is higher when R = S^{t}Bu (Figure 4D), which confirms the previous observation that sulfur contributes to the stabilization of the positive charge in C-1. The LUMO (Figure 4C) indicates that the nucleophilic attack takes place over C-1, but there is no great difference in the C-1 p-atomic orbital contributions above and below the ring plane. It appears, therefore, that above the plane the lobule on C-1 is slightly greater than it is below the plane, but it is not enough to justify the direction of the nucleophilic attack.

Conclusion

In conclusion, DFT calculations are a simple and efficient method for determining the geometry of reaction intermediates in glycosylation reactions. Our results

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(24) (a) Bo, C.; Costas, M.; Poblet, J. M.; Rohmer, M.-M.; Bénard, M. *Inorg. Chem.* **1996**, *35*, 3298−3306. (b) Popelier, P. L. A.; Logothetis, G. *J. Organomet. Chem.* **1998**, *555*, 101−111.

support a **6b** structure for the ion intermediates **9**, **18**, and **19**−**23**, irrespective of the presence of S, Se, or I at position 2. Electron-donor substituents bonded to the external heteroatom (R in SR and SeR), or electron-withdrawing groups bonded to exocyclic oxygen, produced a change in the geometry of the reaction intermediate that approached that of an episulfonium, episelenonium, or iodonium ion (closer to **6a**, both for $n = 1$ and for $n = 2$; see Scheme 1). The *tert*-butyl group and the 2,4,6-trimethylphenyl, 2,4,6-trimethoxyphenyl, and trimethylsilyl were the electron-donor groups that produced the strongest such effect. This may be due to the weak interaction between the heteroatom and C-1, which helped to stabilize the ion. As well as steric hindrance, therefore, the electronic factors produced by the donor substituent at position 2 and the acceptor groups at position 4/5 (for furanoses and pyranoses, respectively) should also be taken into account when controlling the stereoselectivity of the heteroatom-assisted glycosylation.

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Supporting Information Available: Tables of optimized geometries for compounds **11**−**15** and ions **9** and **17**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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