

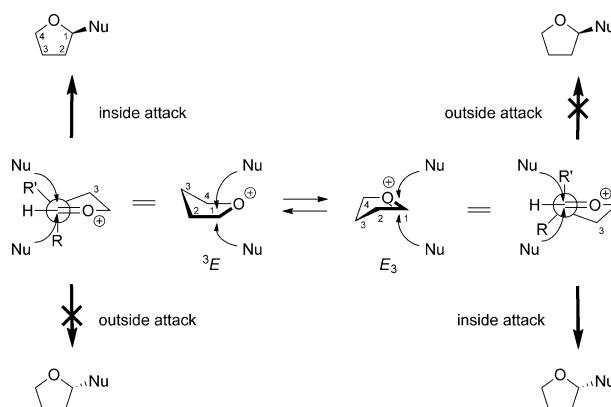
Furanosyl Oxocarbenium Ion Stability and Stereoselectivity**

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Abstract: Lewis acid mediated substitution reactions using [D]triethylsilane as a nucleophile at the anomeric center of the four pentofuranoses, ribose, arabinose, xylose, and lyxose, all proceed with good to excellent stereoselectivity to provide the 1,2-*cis* adducts. To unravel the stereoelectronic effects underlying the striking stereoselectivity in these reactions we have mapped the energy landscapes of the complete conformational space of the oxocarbenium ions of the four pentofuranoses. The potential energy surface maps provide a detailed picture of the influence of the differently oriented substituents and their mutual interactions on the stability of the oxocarbenium ions and the maps can be used to account for the observed stereoselectivities of the addition reactions.

Furanoses, five-membered ring carbohydrates, are ubiquitous in nature. They form characteristic motifs in many bacterial and plant oligo- and polysaccharides, while they are absent in mammalian oligosaccharides.^[1] Furanose-containing bacterial oligosaccharides are therefore attractive targets to use in vaccine applications and the enzymes involved in their assembly and degradation are appealing therapeutic targets.^[2] Furanosyl oxocarbenium ions play crucial roles in both the chemistry and biology of glycosyl furanoses, and insight into the structure of such ions is instructive to both the design of mimics to inhibit furanose-processing enzymes^[3] and to effect stereoselective transformations at the anomeric center of furanosides. Over the years several examples have been reported for furanosylations of conformationally unbiased furanosyl donors, which bear no apparent stereochemistry controlling functionalities, and proceed with striking stereoselectivity to provide 1,2-*cis* glycosides.^[4]

To account for the stereochemical outcome of reactions involving substituted tetrahydrofuran oxocarbenium ions as intermediates, Woerpel and co-workers have proposed a two-conformer model, in which the equilibrium between the ³*E* and *E*₃ oxocarbenium ions is decisive (Scheme 1).^[5] Both envelopes are preferentially attacked at the inside, because



Scheme 1. The two-conformer model. The two furanosyl ³*E* and *E*₃ envelope oxocarbenium ions are preferentially attacked by the incoming nucleophile along an inside trajectory to provide different epimeric products.

this mode of attack leads to a transition state devoid of eclipsing interactions with substituents at C2, and provides a product featuring a favorable staggered C1–C2 conformation.^[5a,d] Therefore reaction on the ³*E* conformer occurs on the top face, where the *E*₃ envelope is approached at the bottom face.^[5a,d,6] The nature and orientation of the substituents on the tetrahydrofuran ring play an all-important role in determining the stability of the oxocarbenium ion. Alkoxy substituents at the C2-position preferentially adopt a pseudoequatorial position to allow hyperconjugative stabilization of the oxocarbenium ion by the pseudoaxial C2–H2 bond, while a C3-alkoxy substituent can stabilize the electron-depleted anomeric center in a pseudoaxial position. The orientation of an alkyl group at C4 has been reported to be of little influence on the stability of the oxocarbenium ion.^[5d] This model explains well the stereochemical outcome of the addition of C nucleophiles, such as allyltrimethylsilane, to monosubstituted tetrahydrofuran cores. For multiple substituted systems, such as genuine furanosyl oxocarbenium ions, the interplay between the ring substituents becomes important and prediction of the relative preferences of the envelope oxocarbenium ions is very difficult.

Herein we report a complete survey of the energy landscape of the entire conformational space of the furanosyl oxocarbenium ions for the four possible pentoses, ribose, arabinose, xylose, and lyxose, and present a clear picture of how multiple ring substituents on a furanosyl oxocarbenium ion influence its stability, and therefore its reactivity and stereoselectivity in addition reactions. We have complemented this study with a set of substitution reactions to experimentally validate the theoretical results.

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Table 1: Results of the substitution reaction of [D]TES with the various furanosides.

$\text{BnO-CH}_2\text{-O-CH}_2\text{-OAc} \xrightarrow[\text{CH}_2\text{Cl}_2, -78^\circ\text{C}]{[\text{D}]\text{TES, TMSOTf}} \text{BnO-CH}_2\text{-O-CH}_2\text{-O-D}$				
Entry	Furanosyl acetate	Product	1,2- <i>cis</i> / 1,2- <i>trans</i> ^[a]	Yield [%] ^[b]
1	Ribose 1	5	> 98:2	50
2	Arabinose 2	6	> 98:2	62
3	Xylose 3	7	85:15	40
4	Lyxose 4	8	> 98:2	100

[a] Ratio determined by ¹H NMR spectroscopy. [b] Yield of isolated furanosides after column chromatography. The remainder of the mass balance consists of recovered and hydrolyzed starting material.

We initially investigated the Lewis acid mediated addition of a model nucleophile, [D]triethylsilane ([D]TES), to the four perbenzylated furanosyl acetates D-ribofuranosyl acetate **1**, D-arabinofuranosyl acetate **2**, D-xylofuranosyl acetate **3**, and D-lyxofuranosyl acetate **4** (Table 1). [D]TES was used as a nucleophile because the α- and β-deuterium epimeric products are nearly identical, but can be distinguished by ¹H NMR spectroscopy, and therefore any isolated sample of the reaction products can be used to reliably determine the α/β product ratio. As can be seen in Table 1, all furanosyl acetates are substituted in a stereoselective manner to provide the 1,2-*cis* products and only **3** delivers a minor amount of the *trans* product. Perhaps most striking is the result obtained with **4**, which features all ring substituents on one side of the ring. Here, the nucleophile attacks the β-face of the molecule with complete stereoselectivity to lead to the counterintuitive all-*cis* product.

The stereoselectivities in the reactions indicate that direct S_N2-type substitution on the (mixtures of) anomeric acetates can be excluded as a major reaction pathway.^[7] We also exclude selective substitution reactions on anomeric triflates^[8] as a major contributing pathway because the relative stability of the anomeric triflates cannot be readily reconciled with the experimental results (see Supporting Information for full details).^[9] To probe whether the intermediate oxocarbenium ions can be at the basis of the observed selectivities, we investigated the relative energies of the oxocarbenium ions of the different furanosyl epimers. To this end we calculated the

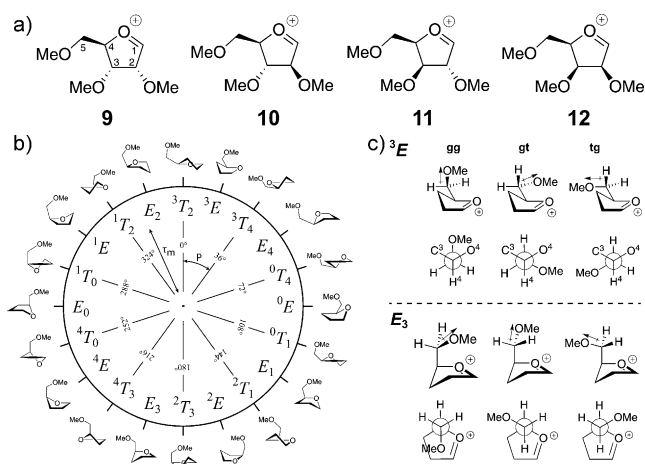


Figure 1. a) The investigated furanosyl oxocarbenium ions. b) The pseudorotational circle describing the conformational space a five-membered ring can occupy. The pseudorotational phase angle (*P*) in combination with the puckering amplitude (*τ_m*) defines the ring conformation. c) Possible rotamers around the C4–C5 bond in the ³E (top) and E₃ (bottom) envelope conformers, in which the dipoles of the C5-OMe moieties are indicated.

energy associated with the complete conformational space of the permethylated furanosyl oxocarbenium ions **9–12** (Figure 1a) using a slightly adapted version of the potential energy surface (PES) scanning method recently introduced by Rhoad, Cagg, and Carver.^[10] The conformation of a furanose ring can be defined by a phase angle (*P*) and puckering amplitude (*τ_m*) and the complete conformational space of such a ring can be displayed using the pseudorotation circle, which was introduced by Altona and Sundaralingam^[2,11] (Figure 1b). The phase angle defines the conformation of the ring, and the puckering amplitude indicates how far out of the median plane the outlying atoms (denoted with super- or subscripts) are positioned. We calculated the energies associated with 81 fixed-ring conformers with Gaussian 03,^[12] by employing the B3LYP density functional and the 6-311G** basis set, and corrected these for the solvent (CH₂Cl₂) using the polarizable continuum model (PCM) function and mapped them in the pseudorotational circle to give free-energy surface (FES) maps.^[13] Because rotation of the C4–C5 bond significantly influences the stability^[14] of furanosyl rings, we scanned the FES of the oxocarbenium ions for the three individual *gg*, *gt*, and *tg* C4–C5 rotamers (Figure 1c). Thus for each furanosyl oxocarbenium ion 243 (3 × 81) conformers were optimized and the associated energies determined.

In Figure 2a–c, the FES maps for the three C4–C5 rotamers of the ribofuranosyl oxocarbenium ion **9** are displayed. The combination of the absolute lowest energies of these three conformers in a single picture leads to the global FES map depicted in Figure 2d. From the four graphs it becomes apparent that **9** preferentially adopts an E₃-like structure and that the orientation of the C5-OMe group has a great impact on the stability of the oxocarbenium ion. The *gg* rotamer is significantly more stable than the *gt* structure, which in turn is more favorable than the *tg* conformer. The E₃ *gg* rotamer positions the C5-OMe group above the furanosyl

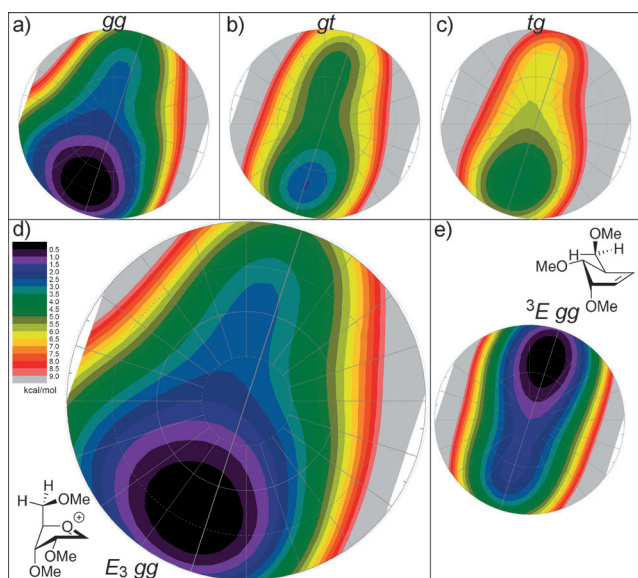


Figure 2. The FES maps of the ribofuranosyl oxocarbenium ion **9**. a) FES of the *gg* conformer. b) FES of the *gt* conformer. c) FES of the *tg* conformer. d) Global minimal FES of **9** showing the lowest-energy E_3 conformer. e) FES of ribose configured 2,3-dimethoxy-4-methylene-methoxy cyclopentene.

ring to allow through-space stabilization of the oxocarbenium ion. The enhanced stability of the *gt* conformer over its *tg* counterpart can be rationalized by the interaction of the C5–O5 dipole with the positive charge in the oxocarbenium ion ring. As pointed out by Bols and co-workers the interaction of the C5–OMe dipole with the positive charge of the oxocarbenium ion is least favorable in the *tg* conformer (Figure 2c).^[15] In the most stable E_3 conformation, the C3 and C2 methoxy groups take up a pseudoaxial and pseudo-equatorial orientation, respectively, thus lending support to the model devised by Woerpel and co-workers. Notably the E_3 envelope places two out of the three substituents in a pseudoaxial position, which is sterically rather unfavorable.^[5d] To investigate the steric preference of the system we also calculated the FES of a ribose-configured 2,3-dimethoxy-

4-methylenemethoxy cyclopentene, thus representing a structural mimic of **9**, a mimic which is lacking the positive charge. This FES is depicted in Figure 2e, and it shows a preference of the noncharged ribo-cyclopentene for the 3E envelope. Thus in the case of the ribofuranosyl oxocarbenium ion the electronic stabilization in the E_3 conformation outweighs the steric preference of the system.

With the FES map of **9**, the stereoselectivity in the substitution reaction of [D]TES with **1** can be readily explained. Attack of the nucleophile on the most favorable oxocarbenium ion, that is, the E_3 conformer, on the inside of the envelope leads to the selective formation of the 1,2-*cis* product.

A similar calculation approach was taken to investigate the FESs of the remaining three furanosyl oxocarbenium ions. The results of these calculations are graphically summarized in Figure 3 (see the Supporting Information for the FES maps of the individual *gg*, *gt*, and *tg* maps, and the corresponding cyclopentene rings). As can be seen in Figure 3a the arabinofuranosyl oxocarbenium ion **10** is most stable when taking up the 3E envelope conformation. Also in this case the relative stability of the three C5–O5 rotamers decreases going from the *gg* to the *gt* to the *tg* rotamer (see the Supporting Information for details). Because the C5–OMe group cannot be positioned above the ring in the arabinosyl 3E envelope, this stability trend arises from the different interactions between the C5–OMe dipole with the positive charge of the oxocarbenium ion. This interaction is most favorable for the *gg* C5–OMe, and least favorable for the *tg* conformer, as discussed above (Figure 1c).^[15a] In addition to the unfavorable dipole–charge interaction of the C5–OMe *tg* conformer, this orientation also suffers from unfavorable steric and electronic interactions of the C5–OMe with the C3 substituent in the 3E envelope. Comparison of the FESs of the ribofuranosyl and arabinofuranosyl oxocarbenium ions shows not only that the two oxocarbenium ions prefer opposite envelope conformers, but also that the FES of the arabinosyl oxocarbenium ion is more shallow. This outcome indicates that the preference for the arabino 3E envelope is not as strong as the preference for the ribo 3E envelope, and can be explained by the fact that ribo 3E envelope positions all substituents in an

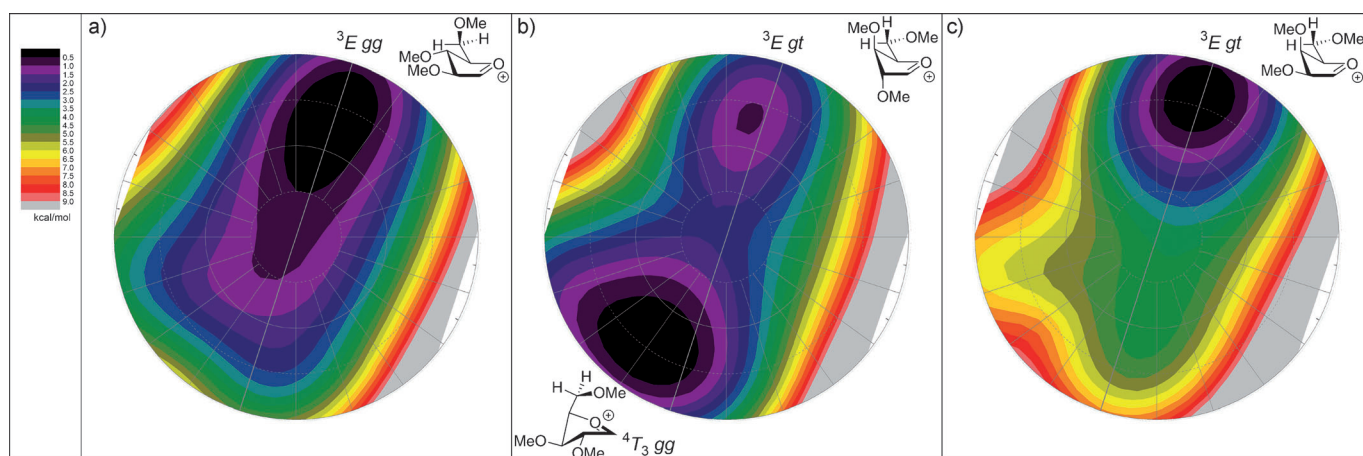


Figure 3. The global minimal FES maps of the arabinofuranosyl (**10**; a), xylofuranosyl (**11**; b), and lyxofuranosyl (**12**; c) oxocarbenium ions.

ideal orientation to maximize the stability of the oxocarbenium ion, and this is not the case for the arabino 3E envelope. Nonetheless, the preference for the arabino 3E conformer is strong enough to allow a selective substitution reaction as shown by the [D]TES reaction (Table 1, entry 2). Only the β -deuterium epimer was isolated in this experiment, the formation of which can be accounted for by inside attack of [D]TES on the 3E oxocarbenium ion.

The xylofuranosyl oxocarbenium ion **11** FES map (Figure 3b) shows two energy minima, one on the side of the 3E envelope and one on the opposite side, around $P=216^\circ$, thus indicating that a 4T_3 conformer is energetically most favorable on the southern hemisphere. The two minima have different C4–C5 rotamers which contribute most favorably to the overall oxocarbenium ion energy. The stability of the 4T_3 -*gg* rotamer originates from the stabilizing interaction of the C5-OMe with the underlying oxocarbenium ion. In the 3E envelope, in contrast, the *gg* rotamer suffers from destabilizing steric and dipole interactions with the pseudoaxial C3-OMe. The most stable orientation for the C5-OMe group in the 3E envelope is achieved in the *gt* rotamer, because the *tg* conformer puts the C5-OMe group in an unfavorable antiparallel orientation with respect to the C4–O4 bond (Figure 1c). The two energy minima found for the xylose furanosyl oxocarbenium ion explain the mixture of products obtained in the [D]TES substitution reaction (Table 1, Entry 3), and the 85:15 α/β -ratio fits well with the difference in energy between the two envelope oxocarbenium ions, a difference which the calculations show to be about 1 kcal mol $^{-1}$.

Finally, when **4**, featuring an all-*cis* substituent decoration, is reacted with [D]TES/TMSOTf, the β -deuterium lyxofuranoside **8** is isolated as the sole product (Table 1, entry 4). Also in this case the stereoselectivity can be adequately explained by considering the FES of the intermediate oxocarbenium ion **12**, which shows a single, rather deep energy minimum for the 3E conformation (Figure 3c). In this structure both the C2 and the C3 substituent adopt positions allowing maximum stabilization of the oxocarbenium ion. The C4 group has a pseudoequatorial orientation thereby avoiding steric interactions. Inside attack on the 3E -envelope oxocarbenium ion leads to the all-*cis* product.

Overall, the calculated FES maps provide a detailed picture of the substituent effects on the stability of furanosyl oxocarbenium ions. Individual stabilizing or destabilizing influences and the interplay between the substituents have become apparent. There is a very good agreement between the calculated lowest-energy furanosyl oxocarbenium ion conformers and the experimental results obtained in the substitution reactions. In a Curtin–Hammett scenario^[16] the product stereoselectivity solely depends on the relative ground-state energies of the oxocarbenium ions depicted in Scheme 1, if both conformers react at the same rate. If the more stable conformer reacts more quickly, the product distribution will be even more outspoken, whereas the stereoselectivity erodes (or even inverts) in the case where the more stable conformer reacts slower. During the attack of the nucleophile on the furanosyl ring, interactions will develop between the incoming nucleophile and the furanosyl

ring substituents. Rehybridization of the furanosyl ring will alter the mutual interactions of the ring substituents. In the ribose case, a prominent 1,3-diaxial-like interaction will emerge upon inside attack (Scheme 1) of the nucleophile on the ribosyl E_3 oxocarbenium ion between the nucleophile and the substituent at C3. Where this will be unfavorable from a steric point of view, the lone pairs of the O atom at C-3 can help stabilize the development of positive charge on the incoming nucleophile. A similar situation unfolds in the 3E xylo and lyxo case, while inside attack of the nucleophile on the 3E arabino and 4T_3 xylo oxocarbenium ions can occur relatively unhindered. In all, it appears that none of these interactions prevail here as judged from the agreement between the calculated FES maps and the experimental results.^[17]

The set of substitution experiments, supported by the in-depth quantum mechanical calculations, show that all furanosyl oxocarbenium ions intrinsically react in a 1,2-*cis*-selective manner. These results in turn imply that stereoselective *cis*-glycosylation reactions can be effected if they are persuaded to proceed via the furanosyl oxocarbenium ion as the product-forming intermediate. In combination with glycosylation methodology relying on anchimeric assistance by a suitable neighboring group at the C2 hydroxy, which allows for the reliable installation of 1,2-*trans*-furanosidic linkages, the stereoselective construction of all furanosidic linkages is in theory feasible. We do note that given the differences between the nucleophile used in this study and O nucleophiles, such as typical glycosyl acceptors, transposition of the reaction pathway described here to an O-glycosylation event will not be trivial.^[15b] The detailed furanosyl oxocarbenium ion energy maps presented here will also be useful for gaining insight into the reaction mechanisms by which furanose-processing enzymes, such as glycosyl hydrolases and transferases, operate and the FES maps will be valuable in the analysis of conformational itineraries used by furanosyl-processing enzymes.^[18] This analysis in turn can guide inhibitor design and understanding of inhibitor structure–activity relationships.^[19]

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