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Beyond the two-conformer model: boat conformers provide stereoselectivity in S_N1 -type glycosylations of *manno*-type donors

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Oxocarbenium ions play a central role in shaping the stereochemical outcome of S_N1 -type glycosylation reactions. Generally, glycosylations involving 4H_3 -like glycosyl cations proceed with α -selectivity, whereas those involving 3H_4 -like cations furnish β -products, reflecting favorable chair-like transition states. While this analysis holds for many glycosyl cations, it breaks down for mannosyl donors. Although the mannosyl 3H_4 cation is significantly more stable than its 4H_3 counterpart, addition of weak carbon nucleophiles predominantly yields α -products. To elucidate the origin of this deviation from the predictive two-conformer model, we examined C-allylation reactions of nucleophiles spanning three orders of magnitude in reactivity with a series of glucosyl and mannosyl-type donors (mannose, rhamnose, and mannuronic acid). Quantum chemical calculations of the competing reaction pathways show that, for mannose, glycosylation proceeds under Curtin–Hammett control via α -attack on a $B_{2,5}$ -like (boat) oxocarbenium ion through an $^{\circ}S_2$ -type transition state that avoids the severe steric (Pauli) repulsion present along the β - 1C_4 trajectory. Activation-strain and energy-decomposition analyses quantify the steric and electronic effects and explain why rhamnose, with reduced C6 steric demand, provides slightly more β -selective glycosylation reactions and mannuronic acid, of which the 3H_4 is exceptionally favorable, shows β -selectivity. The mechanistic framework provides a quantitative basis for understanding and designing stereoselective S_N1 -type glycosylations.

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Introduction

The structure of oxocarbenium ions plays a central role in shaping the stereochemical outcome of glycosylation reactions.^{4–8} These intermediates typically arise in S_N1 -type substitution reactions, where ionization and expulsion of the leaving group is the rate-determining step, to generate a short-lived, oxocarbenium ion that subsequently undergoes nucleophilic attack. Despite the high reactivity of these intermediates, and the fact that nucleophilic addition occurs after the rate-determining step, they can display striking stereoselectivity.^{9–13}

The fleeting nature of oxocarbenium ions makes them difficult to study directly, complicating the establishment of clear structure–reactivity–stereoselectivity relationships.^{14,15}

They have been studied in super-acid media, in which their lifetime is extended to allow NMR spectroscopic structural analysis,^{16,17} and *in vacuo* using IR techniques.^{18–22} Their involvement in glycosylation reactions has also been shown using kinetic isotope effect measurements^{23–25} and cation clock experiments.²⁶ Quantum chemical calculations have been instrumental in providing insight into the stereoelectronic effects of the ring substituents on the structure, stability, and reactivity of these ions.^{27–34}

In glycosylation reactions proceeding through an oxocarbenium ion intermediate, the stereochemical outcome can be rationalized by the two-conformer model (see Fig. 1A).^{35,36} This model proposes that oxocarbenium ions typically adopt one of two half-chair conformations (3H_4 or 4H_3) each leading to a preferred product *via* a chair-like transition state.^{37,38} The model argues that 3H_4 -like ions will undergo top-face attack to give the β -anomer, while 4H_3 -like ions undergo bottom-face attack to give the α -anomer. This relationship has been validated for many systems.³⁴ Woerpel and co-workers have systematically mapped the effect of (electron withdrawing) ring substituents on the stability and reactivity of the half chair conformations and shown that the ground state conformational preference of the ions can be an all-important factor in shaping the stereochemical outcome of addition reactions on these

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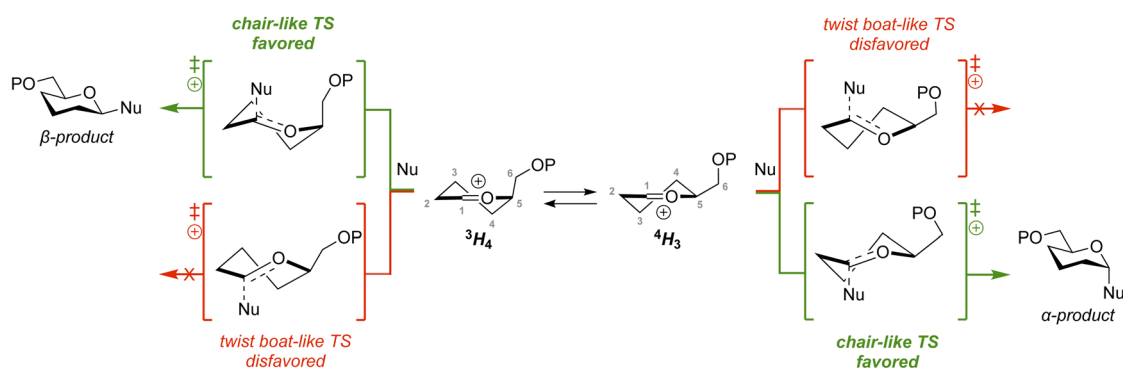
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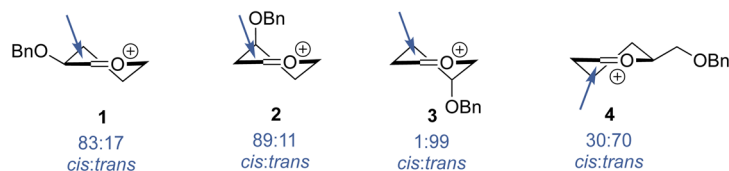
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A) The classical two-conformer model



B) Glycosylation stereoselectivities of monosubstituted pyranoses



C) Diverging stereoselectivities for glucose and mannose investigated in this work

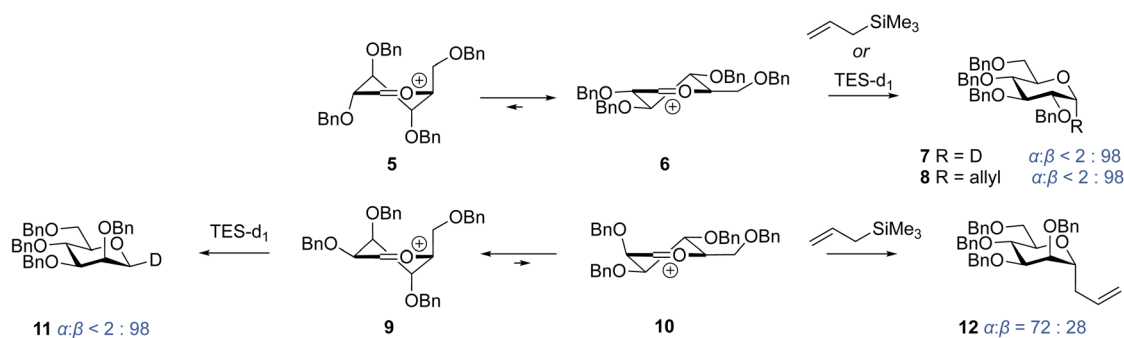


Fig. 1 (A) The two-conformer model for understanding and predicting the stereoselectivity of glycosyl cations. P = protecting group. (B) Stereoselectivities of S_E2' glycosylation reactions with monosubstituted pyranosyl donors performed by Woerpel and co-workers. (C) The diverging stereoselectivities of the glycosylation reactions of the glucosyl and mannosyl cations with TES- d_1 and allyltrimethylsilane investigated in this work.

ions.^{39–43} They showed that alkoxy substituents at C3 and C4 are most stabilizing/least destabilizing when positioned in a pseudo-axial orientation, while alkoxy groups at C2 are placed preferentially in a pseudo-equatorial position to allow hyperconjugative stabilization of the oxocarbenium ion by the axial C2–H2 bond.⁴⁴ On steric grounds, the C5 substituent prefers a pseudo-equatorial orientation.⁴⁵ These orientational preferences can translate to highly stereoselective addition reactions (Fig. 1B), with the 3-O-benzyl substituted pyranosyl ion 2 stereoselectively delivering 1,3-*cis* addition products, while the 4-O-benzyl regioisomer 3 can give exclusively 1,4-*trans* products and a 2-O-benzyl substituent (as in 1) steers the addition reactions to favor the 1,2-*cis* products. In contrast to its conformational preference, the presence of a single C-5 alkoxyethyl group (as in 4) provides only modest selectivity towards the

formation of the 1,5-*trans* product, highlighting the subtleties involved even in simple systems.³⁹

When multiple substituents are present their effects can be mutually supportive, or they can counteract one another. To gauge the overall effect of the complete substitution pattern, we have previously developed computational methods to study the structure and stability of fully substituted glycosyl oxocarbenium ions and mapped how the ring substituents affect the overall shape of the ions,^{34,46} and methodologies to compare the addition reactions.⁴⁷ The striking *cis*-selectivity in addition reactions to many pyranosyl oxocarbenium ions could be explained from the ground state preference of the involved ions. For example, for the glucosyl ion the 4H_3 ion 6 was found to be the most favorable oxocarbenium ion conformer, and addition reaction of triethylsilane- d (TES- d_1) provided the 1,2-*cis* (α) product 7 with exclusive stereoselectivity (Fig. 1C). The addition

reaction of TES-*d*₁ to the mannosyl cation, which preferentially takes up a ³H₄ conformation (**9**), also proceeds with exclusive 1,2-*cis*-stereoselectivity to deliver the β-product **11** (Fig. 1C).³⁴

However, the nature and reactivity of the nucleophile can have a strong effect on the stereochemical course of the addition reactions. When weaker and/or more sterically demanding nucleophiles are used, the stereoselectivity of the addition reactions can change because interactions between the incoming nucleophile and oxocarbenium ion become important. The mannosyl oxocarbenium ion presents a prominent example: where the addition of TES-*d*₁ stereoselectively provides the β-product, the corresponding *C*-allyl mannoside **12** is formed with (moderate) α-selectivity when allyltrimethylsilane is used as a nucleophile.⁴⁵

Woerpel and co-workers have proposed that the erosion of stereoselectivity in this case is caused by the steric interactions of the incoming nucleophile and the most stable ³H₄ mannosyl oxocarbenium ion **9**. By invoking a Curtin–Hammett kinetic scenario, they reasoned that the major α-product is formed from the least populated ⁴H₃ conformer **10**, which is in rapid equilibrium with its more stable ³H₄ counterpart. This change in stereoselectivity is not observed for the glucosyl ion, because the incoming nucleophile does not encounter prohibitively large steric interactions on the α-face of the ³H₄ ion **6**.

To unravel the origin behind the diverging reaction outcomes and understand why and when different Curtin–Hammett scenarios come into play in addition reactions of the mannosyl oxocarbenium ion – and by extension other glycosyl cations – we have investigated a systematic set of *C*-allylation reactions in which we have paired different allyl nucleophiles of gradually changing reactivity with gluco- and *manno*-configured

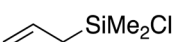
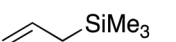
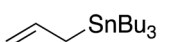
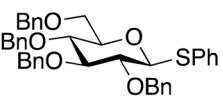
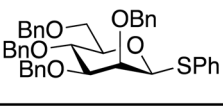
donors. To understand the stereoelectronic effects that shape the Curtin–Hammett kinetic scenario in the addition reactions to the mannose oxocarbenium ion, we have probed mannosyl, rhamnosyl and mannuronic acid systems. These have revealed clear reactivity-stereoselectivity trends. We have employed quantum chemical calculations, including potential energy surface (PES) mapping and activation strain model (ASM) analyses, to investigate the different reaction paths. These studies have identified an unexpected low-energy pathway for the addition reactions to the mannosyl cation. The steric interactions in the transition state of the addition reaction taking place on the β-face of the ³H₄ mannosyl cation and relatively high energy of the ⁴H₃ intermediate make that an alternative pathway, involving α-attack on a boat-like (*B*_{2,5}) intermediate, becomes most favorable. Our ASM analyses have quantified the steric and electronic effects in the different transition states, providing quantitative insight into how they steer the reaction outcome.

Results and discussion

Model glycosylation reactions

To investigate the different addition pathways on glycosyl oxocarbenium ions, we examined glucosyl and mannosyl donors **13** and **14** (Table 1). Each of these was reacted with a series of allyl nucleophiles of similar size but spanning three orders of magnitude in nucleophilicity: allyl (chloro)dimethylsilane (*N* = −0.57), allyltrimethylsilane (*N* = 1.68), and allyltributylstannane (*N* = 5.45).^{48–50} The results of these *C*-allylation reactions are summarized in Table 1. The glucosyl donor **13** predominantly delivered the α-products with all nucleophiles

Table 1 Model C-glycosylation reaction results from glucosyl donor, **13**, and mannosyl donor, **14**. The stereoselectivity of the reaction is expressed as α : β and based on ¹H-NMR of purified α/β-product mixtures. Pre-activation-based glycosylation conditions were used: donor **13** or **14** (1.0 eq.), Tf₂O (1.3 eq.), Ph₂SO (1.3 eq.), TTBP (2.5 eq.), DCM (0.05 M), −80 to −60 °C, then add nucleophile (2.0 eq.) at −80 °C and allow to warm to −60 °C¹

				
		A	B	C
N		−0.45	1.79	4.41
Donor		α:β (yield)	α:β (yield)	α:β (yield)
13		13A >98:2 (32%)	13B >98:2 (41%)	13D 69:31 (70%)
		14A >98:2 (23%)	14B 72:28 (66%)	14D 28:72 (69%)
		>90:10	>75:25	>60:40
		50:50	<40:60	<25:75
				<10:90

tested. The erosion of α -selectivity observed with allyltributylstannane may be accounted for by the higher reactivity of this nucleophile, making direct substitution of the intermediate α -triflate through a more associative S_N2 -like transition state possible. The stereoselectivity of the reactions of the mannosyl donor **18** exhibited a much larger dependence on nucleophile reactivity. The reaction with the weakest allyl nucleophile, showed complete α -selectivity ($\alpha : \beta > 98 : 2$), which shifted to a moderate α -selectivity ($\alpha : \beta = 72 : 28$) for allyltrimethylsilane (in line with reports by Crich⁵¹), to a moderately β -selective reaction (28 : 72) for the strongest nucleophile (in line with reports by McGarvey⁵²). The results for the weaker nucleophiles, allyl (chloro)dimethylsilane and allyltrimethylsilane, may be accounted for by Woepel's hypothesis that the α -products are formed from the minor 4H_3 -like oxocarbenium ion (**10**), that is in equilibrium with its more stable 3H_4 -counterpart (**9**). In the chair-like transition state originating from the 3H_4 -oxocarbenium ion, steric interactions will develop with the pseudo-axial substituents at C3 and C5. With weaker nucleophiles, that react through a later transition state these interactions will be more severe, making this transition state less favorable. The higher α -selectivity for the weakest nucleophile (allyl (chloro)dimethylsilane) in comparison with allyltrimethylsilane is in line with this hypothesis. An earlier transition state for allyltributylstannane, (partially) restores the β -selectivity, predicted by the two-conformer model. A more associative pathway, in which the anomeric α -triflate (or contact ion pair) is substituted by the nucleophile can also contribute to the 1,2-*cis* selectivity.

Computational analysis

To better rationalize these experimental observations, we computed potential energy surfaces for these addition reactions in DCM solution at the PCM(CH₂Cl₂)-B3LYP/6-311G (d,p) level of theory. Benzyl groups were replaced with methyl ethers to reduce computational cost. In several cases, the electronic potential energy surface for reactions with these cationic species appeared barrierless. However, entropic contributions often introduced an overall reaction barrier. To identify the corresponding barriers, we performed constrained scans along the reaction coordinate and evaluated partition functions at each computed point to obtain Gibbs free energies. This approach was benchmarked against systems for which both constrained and unconstrained reaction barrier were available (see SI for all computational details) and was found to reproduce consistent trends.

For the most nucleophilic allylic reagents, such as allyltributylstannane, we were unable to locate transition states on the electronic potential energy surface. As discussed above, the high reactivity of these nucleophiles leads to barrierless additions. Because the strongest deviation from the stereoselectivity predicted by the two-conformer model was found in the additions of allyl (chloro)dimethylsilane, and this nucleophile also allowed for the location of most transition states, these will be used in the following analyses and discussion. For each donor-nucleophile pair, multiple plausible trajectories were identified: α -attack *via* a chair-like 4C_1 from a 4H_3 , a 3S_1 from a 3H_4 , or an

0S_2 from a boat-like $B_{2,5}$; and β -attack *via* a 1C_4 from a 3H_4 , a 1S_3 from a 4H_3 , or a 1S_5 from a $B_{2,5}$ (Fig. 2A). Fig. 2B compares the barrier heights for the addition reactions of allyl (chloro)dimethylsilane on the glucosyl and mannosyl cations. The $\Delta\Delta G^\ddagger$ values of $-1.6 \text{ kcal mol}^{-1}$ (glucose) and $-2.2 \text{ kcal mol}^{-1}$ (mannose) between the lowest α - and β -forming transition states are fully consistent with the experimentally observed $>98 : 2$ α -selectivities for allyl (chloro)dimethylsilane: application of the Eyring equation at -60°C (213 K) gives predicted $\alpha : \beta$ ratios of *ca.* 98 : 2 and 99.5 : 0.5, respectively.

For the glucosyl cation, the lowest transition state (the 4C_1 -like TS, $\Delta G = 11.2 \text{ kcal mol}^{-1}$) originated from the lowest energy oxocarbenium ion half chair (the 4H_3 -ion **6**), in keeping with the two-conformer model. As previously established, the latter half chair is more stable than its counterpart on the other side of the Cremer-Pople conformational sphere, which adopts a the $E_4/2S_0$ -like structure. This conformer deviates from the canonical 3H_4 conformation (**5**, shown in Fig. 1) to diminish the steric interactions between all the pseudo-axial substituents in this half chair conformation. These steric interactions also make the transition states departing from this conformer unfavorable. As a result, attack of the nucleophile on the β -face of the lowest energy 4H_3 ion, which deforms the glucosyl cation into a 1S_3 -like structure in the transition state, represents the lowest energy pathway to the β -products, being more favorable than the chair-like transition state originating from the $E_4/2S_0$ -like ion.

The mannosyl 3H_4 cation **9** is significantly more favorable than its 4H_3 counterpart **10** (by $2.4 \text{ kcal mol}^{-1}$). However, the trajectory of the incoming nucleophile on the β -face of the former ion (see Fig. 2C, mannosyl-TS- β - 1C_4), is met with significant steric interactions, which makes this pathway rather unfavorable ($13.0 \text{ kcal mol}^{-1}$). The chair-like transition state originating from the alternative, higher energy 4H_3 half-chair oxocarbenium ion **10** was found to be more favorable ($12.5 \text{ kcal mol}^{-1}$). Notably the most favorable approach we located, involved attack of allyl (chloro)dimethylsilane on the α -face of the $B_{2,5}$ conformer of mannosyl. In this mode of attack the mannosyl ring adopts a 0S_2 -like conformation, thereby avoiding severe steric interactions between the nucleophile and pseudo-axial C3 and C5 substituents, which destabilize the β - 1C_4 approach (see Fig. 2C, mannosyl-TS- α - 0S_2). Notably, Crich and co-workers have previously described a similar transition state conformation for the intramolecular attack of an C2-trimethylsilyl (methallyl) ether in a benzyldene mannosyl system.²² We could also find a transition state for the attack of the nucleophile on the β -face of the $B_{2,5}$ mannosyl ion, but this was found to be significantly less favorable ($13.4 \text{ kcal mol}^{-1}$).

While the potential energy surfaces and transition state barriers discussed above are reported as Gibbs free energies (ΔG), we verified that the relative reactivity trends are identical when considering the corresponding electronic energies (ΔE). Accordingly, the selectivity trends observed in the PES analysis can be rationalized using the activation strain model (ASM) of reactivity and energy decomposition analysis (EDA), which describe the reaction profile in terms of electronic energies.^{53–56} In this fragment-based approach, the potential energy surface can be described with respect to, and understood in terms of,

A) Trajectories considered in this work

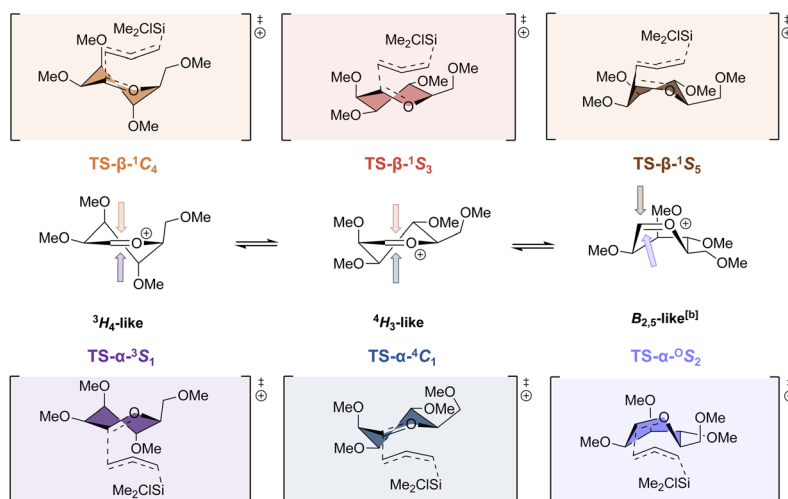
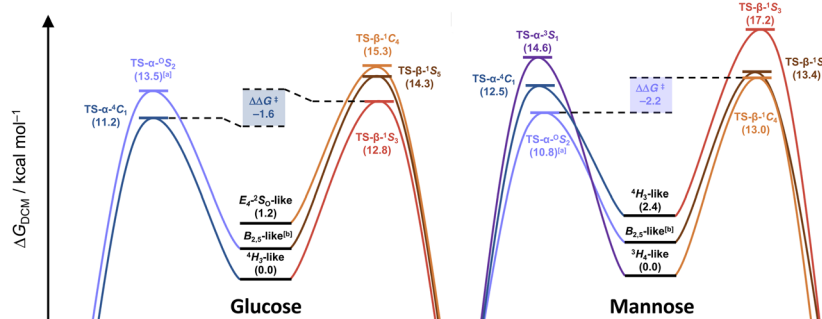
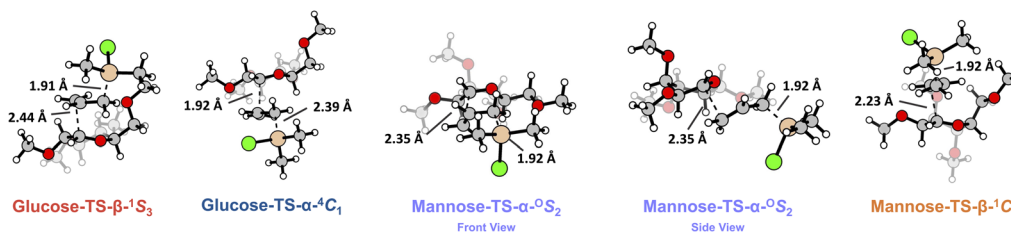
B) Potential energy surface (PES) for the S_E2' glycosylation reactions with Allyl-SiMe₂ClC) Transition state geometries for the lowest energy α and β forming pathways

Fig. 2 (A) An overview of the possible S_E2' reaction trajectories considered in this work, and (B) the corresponding reaction profiles of the addition of allyl (chloro)dimethylsilane to the glucosyl and mannosyl cations via the following transition states: TS- β -1 C_4 (orange), TS- β -1 S_5 (brown), TS- β -1 S_3 (red), TS- α - 0S_2 (light violet), TS- α - 4C_1 (blue), and TS- α - 3S_1 (purple). Energies are depicted as Gibbs free energies ($T = 213.15$ K) and were computed at PCM(CH₂Cl₂)-B3LYP/6-311G (d,p). The TS- α - 3S_1 on glucose is unfavourable and could not be located. ^[a]A representative structure for the transition state geometry was used. ^[b]The itinerary leading up to TS- α - 0S_2 and TS- β -1 S_5 start from a boat-like non-stationary point. (C) Structures of the lowest energy transition states of the S_E2' reactions of allyl (chloro)dimethylsilane with the glucosyl or mannosyl cations leading to the α and β products. The mannose-TS- α - 0S_2 is depicted from two distinct angles to show the 'sideways' approach of the nucleophile, avoiding most steric interaction.

the characteristics of the reactants, here the allylic nucleophile and the glycosyl oxocarbenium ion substrate. The energy (ΔE) along the potential energy surface is expressed as the sum of the strain energy (ΔE_{strain}) required to deform the individual reactants from their equilibrium geometries and the interaction energy (ΔE_{int}) between the deformed fragments: $\Delta E = \Delta E_{\text{strain}} + \Delta E_{\text{int}}$. These are then plotted along the potential energy surfaces in activation strain diagrams (ASDs). Here, the glycosyl oxocarbenium ion and the allylic C-nucleophile served as the two

fragments. The intrinsic reaction coordinate (IRC) was projected onto the carbon-leaving group ($C \cdots Si$) distance of the nucleophile, which changes in a well-defined manner during the S_E2' attack, and this coordinate has been validated as a suitable reaction coordinate for this type of bimolecular processes.⁴⁷

Energy decomposition analysis (EDA) was applied to the ΔE_{int} term to dissect it into the electrostatic interactions (ΔV_{elstat}), Pauli repulsion (ΔE_{Pauli}), and orbital interaction

energy (ΔE_{oi}). EDA values are reported as gas-phase electronic energies (ΔE_{gas}).⁵⁷ For consistent comparison, ASM and EDA profiles for different pathways were analyzed at points with identical C...Si distances. Because the EDA terms are highly dependent on the distance between the fragments,^{55,56,58,59} we additionally verified the results using double-consistent geometries (DCGs) in which both the C...Si and C1...C-allyl distances were matched (see SI for computational details). This eliminates geometric artefacts that can distort interaction terms, especially the Pauli repulsion term. All DCG-verified data, including geometries and numerical values, are provided in SI Fig. S5 and S6.

Our activation strain analyses revealed that, for mannose, the β - 1C_4 pathway accumulates strain more steeply along the C...Si coordinate than the competing α - 0S_2 pathway (Fig. 3A, orange). This reflects the deformation required for the 3H_4 conformer to accommodate the nucleophilic approach on the β -face, which brings the incoming nucleophile into close proximity with pseudo-axial C3 and C5 substituents. Steric congestion initially manifests as Pauli repulsion (as evident from the corresponding EDA term), part of which is converted into strain upon deformation. Although this strain remains destabilizing, it is less unfavorable than the scenario without deformation, in which Pauli repulsion would increase even more strongly. In

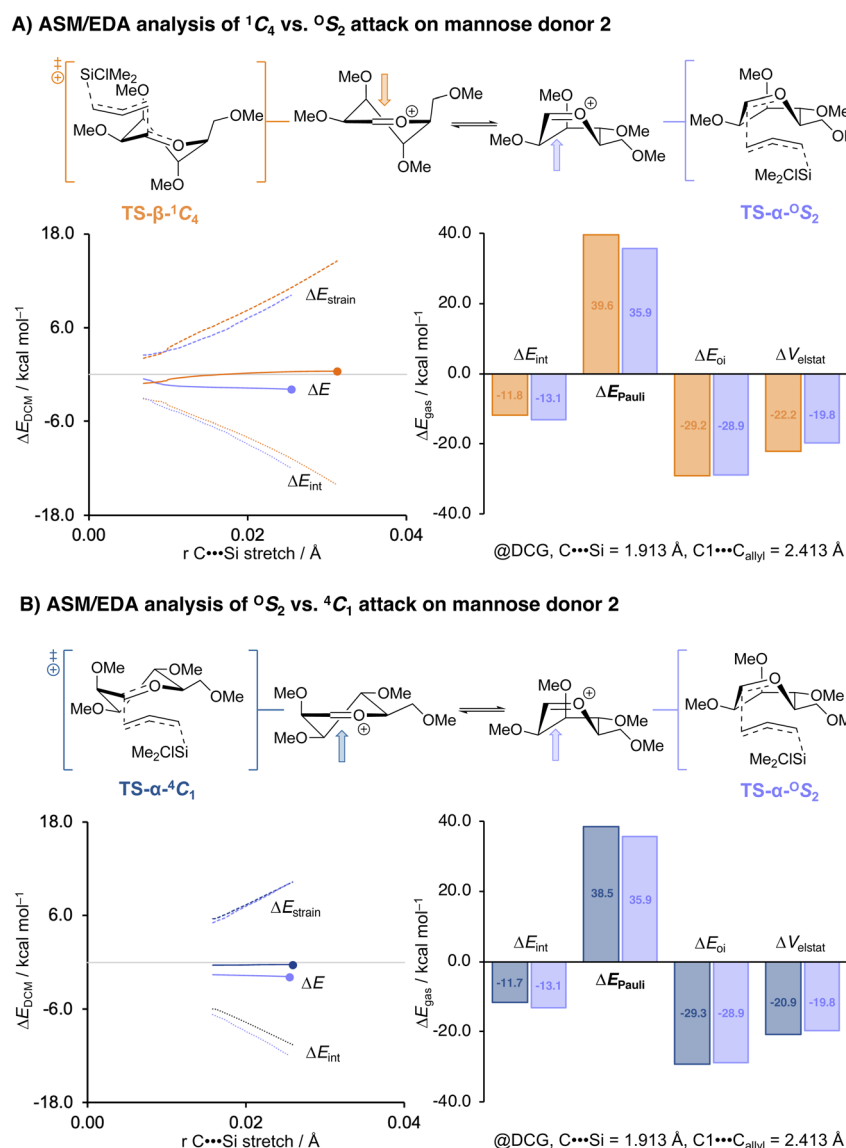


Fig. 3 Activation strain and energy decomposition analyses for the S_E2' reactions of allyl (chloro)dimethylsilane and the mannosyl cation (A) via the β -product-forming TS- β - 1C_4 (orange) and the α -product-forming TS- α - 0S_2 (light violet) and (B) via both α -product-forming TS- α - 4C_1 (blue) and TS- α - 0S_2 (light violet). ASM energy values are plotted to the transition state (indicated by a dot), along the IRC projected on the C...Si bond stretch. EDA results are numerical experiments at double consistent TS-like geometries (ΔE^*) obtained from the IRC at a C...Si bond stretch of 1.913 Å. The C1...C_{allyl} were set to 2.413 Å (C...Si and C1...C_{allyl} distances in the consistent TS-like geometry for TS- α - 4C_1). Energies are depicted as electronic energies and were computed at PCM(CH₂Cl₂)-B3LYP/6-311G (d,p) for ΔE_{DCM} or ZORA-B3LYP/TZ2P//PCM(CH₂Cl₂)-B3LYP/6-311G (d,p) for ΔE_{gas} .³

contrast, while the α - $^{\circ}S_2$ pathway (light violet in Fig. 3A) starts from a higher-energy $B_{2,5}$ conformer it avoids the most severe steric interactions, which results both in less strain build-up along the reaction trajectory, and less Pauli repulsion from the start of the nucleophilic approach.

Crucially, this mechanistic option is viable because the 3H_4 and $B_{2,5}$ conformers of the mannosyl cation are relatively close in energy. The small energy gap between these means that the additional strain required to reach the $B_{2,5}$ geometry is not prohibitive under Curtin–Hammett control. Were the 3H_4 – $B_{2,5}$ gap appreciably larger, the cost of conformer interconversion would outweigh the gain in interaction energy in the $^{\circ}S_2$ transition state and the canonical β - 1C_4 pathway would be expected to be dominant. Thus, the combination of strong Pauli repulsion for β -attack on the 3H_4 conformer and a narrow 3H_4 / $B_{2,5}$ energy gap enables the boat-like itinerary to prevail over the classical two-conformer model.

Finally, it was examined why the bottom-face attack on a boat-like conformation leading to TS- α - $^{\circ}S_2$ is more favorable than the canonical bottom-face attack on a half chair-like conformation (TS- α - 4C_1). The ASM analyses are depicted in Fig. 3B, which show the ASDs for these TS- α - 4C_1 (blue) versus the TS- α - $^{\circ}S_2$ (light violet) pathways. From the C...Si bond stretch diagram, it can be seen that both bottom face pathways incur similar strain, while the approach leading to TS- α - 4C_1 is paired with less stabilizing interaction energy. The increased destabilizing Pauli repulsion for the TS- α - 4C_1 pathway is the main

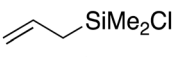
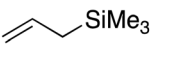
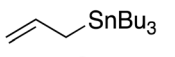
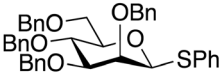
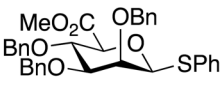
contributor to the observed difference in interaction energy. While this might seem counterintuitive, this indicates that at the same C₁...C_{allyl} bond distance, the nucleophile is positioned more favorably in the TS- α - $^{\circ}S_2$ pathway, than in the TS- α - 4C_1 . Inspection of the structures in Fig. 2, reveals that the terminal allyl methylene group is positioned under the mannose ring in the TS- α - 4C_1 while it approaches the cation parallel to the C=O⁺ moiety in the TS- α - $^{\circ}S_2$ avoiding steric interactions with the electrophile.

C6-modified donors

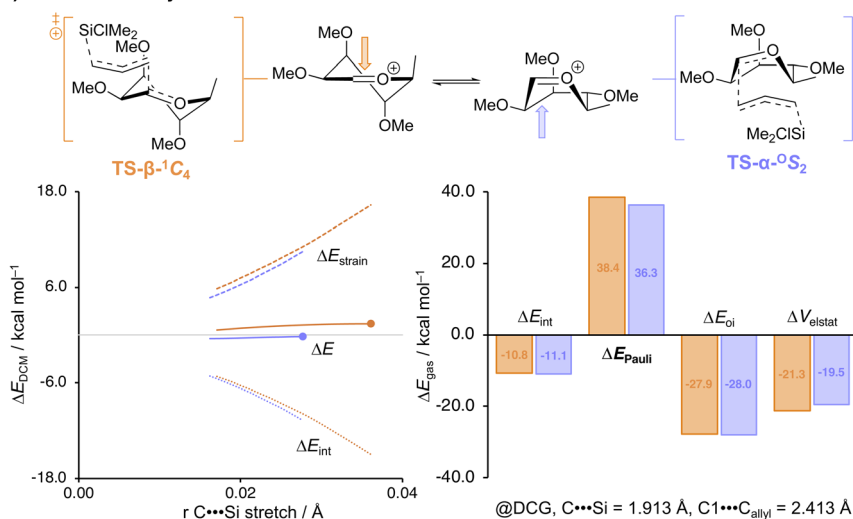
To further test the relative importance of the Pauli repulsion on the β -face and the energy gap between the competing 3H_4 and $B_{2,5}$ conformers we next explored different mannosyl-configured donors, carrying different C6-modifications. We turned to rhamnose and mannuronic acid donors, in which the C6-CH₂OBn group of mannose is replaced by the slightly smaller and electronically different CH₃ or CO₂Me group, respectively. Mannuronic acid donors have been shown to provide 1,2-*cis* products with a wide variety of acceptors in a very reliable manner, and it has been reported that in the C-glycosylation reaction with allyltrimethylsilane solely the β -allyl products are obtained,⁶⁰ in contrast to their mannose counterparts.

Thus, we subjected the rhamnosyl and mannuronosyl donors, **15** and **16**, respectively, to the same set of model C-nucleophiles, as described above, to reveal the stereoselectivity trends shown in Table 2. We also performed the ASM/EDA

Table 2 Model C-glycosylation reaction results from mannosyl donor, **14**, rhamnosyl donor, **15**, and mannuronosyl donor, **16**. The stereoselectivity of the reaction is expressed as α : β and based on 1H -NMR of purified α / β -product mixtures. Pre-activation-based glycosylation conditions were used: donor **14**–**16** (1.0 eq.), Tf₂O (1.3 eq.), Ph₂SO (1.3 eq.), TTBP (2.5 eq.), DCM (0.05 M), –80 to –60 °C, then add nucleophile (2.0 eq.) at –80 °C and allow to warm to –60 °C[†]

		 A	 B	 C
N		–0.45	1.79	4.41
Donor		α : β (yield)	α : β (yield)	α : β (yield)
14		14A >98:2 (23%)	14B 72:28 (66%)	14D 28:72 (69%)
		15A 89:11 (43%)	15B 50:50 (72%)	15D 25:75 (77%)
16		16A <2:98 (39%)	16B <2:98 (73%)	16D <2:98 (64%)
		>90:10	>75:25	>60:40
		50:50	<40:60	<25:75
				<10:90

A) ASM/EDA analysis of the addition on rhamnose donor 15



B) ASM/EDA analysis of the addition on mannanosyl donor 16

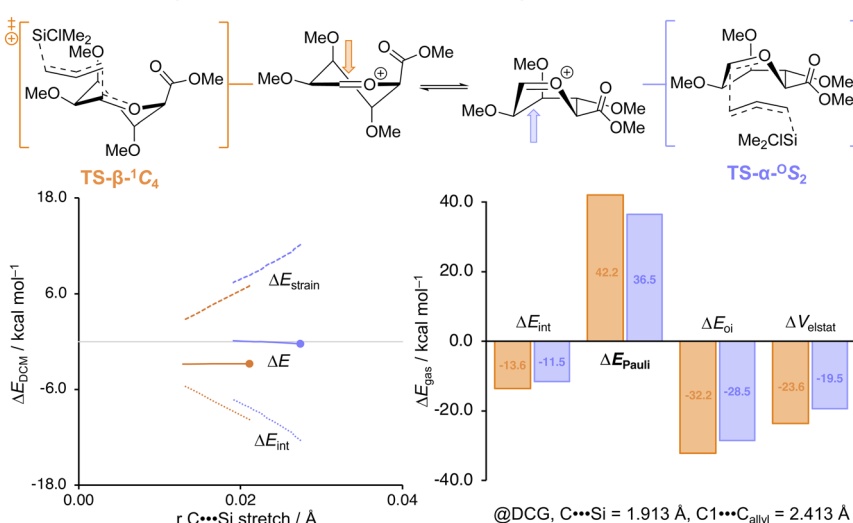


Fig. 4 Activation strain and energy decomposition analyses for the S_E2' reactions of allyl (chloro)dimethylsilane and the (A) rhamnosyl cation and (B) the mannanosyl cation via the β-product-forming TS-β¹C₄ (orange) and the α-product-forming TS-α-^OS₂ (light violet). Energy values are plotted to the transition state (indicated by a dot), along the IRC projected on the C...Si bond stretch. Energies are depicted as electronic energies and were computed at PCM(CH₂Cl₂)-B3LYP/6-311G (d,p) for ΔE_{DCM} or ZORA-B3LYP/TZ2P//PCM(CH₂Cl₂)-B3LYP/6-311G (d,p) for ΔE_{gas}.

analyses for the addition reactions for these donor systems. The profiles generated by these computational approaches are depicted in Fig. 4. Full potential energy profiles for the addition reactions to the rhamnosyl and mannanosyl cations are provided in the SI (SI Fig. S3 and S4).

The rhamnose donor 15 displayed a reactivity-stereoselectivity trend that closely paralleled that of the mannosyl donor: across the series of allyl nucleophiles the product distribution shifted from the predominance of the α-product for the weakest nucleophile towards formation of more β-product with the stronger nucleophiles. The rhamnosylations were moderately but consistently more 1,2-*cis* selective than the mannosylations. The increase in the formation of the β-products can be rationalized by examining the ASM/EDA analyses.

The reduced steric demand on the β-face delays the onset of Pauli repulsion and lowers its maximum along the β¹C₄ trajectory, flattening the energy profiles and narrowing the energy difference between β- and α-attack (Fig. 4A). As a result, the kinetic advantage of the α-^OS₂ pathway is diminished, in comparison to the mannosylation reactions.

In sharp contrast to the reactions of the mannosyl and rhamnosyl donors, the mannuronic acid donor 16 furnished exclusively the β-products regardless of the reactivity of the used C-nucleophile. This behavior is consistent with an approach to the β-face of the most favorable ³H₄-like oxocarbenium ion and in line with the predictive two-conformer model. The persistence of β-selectivity with weak nucleophiles, where α-product formation could emerge through a Curtin-Hammett scenario,

can be attributed to the strong preference for the 3H_4 oxocarbenium ion conformer. This conformer is stabilized (with respect to the other conformers) by the carboxylate ester, which prefers to occupy a (pseudo)-axial orientation in an oxocarbenium ion species. When the ASM/EDA of the addition to the mannuronic acid ester ion is regarded, the effect of the carboxylic acid ester immediately becomes apparent (Fig. 4B); the β - 1C_4 pathway is associated with both significantly less strain than the α - $^{\circ}S_2$ itinerary and more stabilizing interaction energy. When the interaction energy is analyzed a trend similar to the mannosyl cation (Fig. 3A) is observed, the TS- α - $^{\circ}S_2$ pathway proceeds with significantly less Pauli repulsion and the β - 1C_4 pathway proceeds with more stabilizing electrostatic and orbital interactions. The difference in strain is already present at the start of the pathway, which can be traced back to the stability of the 3H_4 oxocarbenium ion. The high stability of this conformer raises the barrier to the formation of other conformers and prevents access to the $B_{2,5}$ - $^{\circ}S_2$ pathway that is the dominant addition trajectory to the mannosyl ion.

Conclusions

This combined experimental and computational study establishes that the classical two-conformer model, while predictive for many glycosyl donors, does not adequately describe S_N1 -type glycosylations of *manno*-configured donors. Detailed potential-energy surface mapping and activation-strain/energy-decomposition analyses reveal that attack of the mannosyl cation, leads to strong steric (Pauli) repulsion along the β - 1C_4 trajectory. The small ground-state energy difference between 3H_4 and $B_{2,5}$ conformers, allows an alternative pathway to become competitive: α -attack on a $B_{2,5}$ -like cation that passes through an $^{\circ}S_2$ transition state. This route provides a lower overall barrier than the canonical chair-like β -attack and accounts for the α -selectivity observed with weak nucleophiles.

Modifications of C6 of the mannose donor confirm and quantify the roles of steric and conformational effects. Reducing steric demand by utilizing a C6-CH₃ group (as in rhamnose) lowers steric (Pauli) repulsion and pushes selectivity towards 'two-conformer behavior'. In contrast, stabilizing the 3H_4 conformation with a C5-CO₂CH₃ moiety (as in mannuronic acid) widens the energy gap between the 3H_4 and $B_{2,5}$ conformers, enforcing exclusive β -selectivity.

Together, these findings extend the mechanistic framework for S_N1 -type glycosylations beyond the classical two-conformer model. They show that higher-energy boat-like intermediates can control stereochemistry when they offer a lower-repulsion reaction trajectory and that small, targeted changes in ring substitution can be used to bias glycosylation outcomes in a predictable way. This insight provides a quantitative foundation for designing stereoselective glycosylation reactions and highlights the need to critically (re-)examine other oxocarbenium ion conformers for different glycosyl configurations, as similarly unconventional boat-like or other high-energy intermediates may play underappreciated roles in determining selectivity.

Author contributions

JDCC, TH, FMB: conceptualisation; DH, WAR, JS: investigation; JDCC, TH, FMB: supervision; DH, WAR, JDCC: writing – original draft; DH, WAR, JS, FMB, TH, JDCC: writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d6sc02312f>.

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