ELSEVIER

Carbohydrate Research 337 (2002) 765–774

CARBOHYDRATE RESEARCH

www.elsevier.com/locate/carres

Note

Can the stereochemical outcome of glycosylation reactions be controlled by the conformational preferences of the glycosyl donor?

Tomoo Nukada,[a] Attila Bérces,[b] Dennis M. Whitfield[c,*]

[a]*The Institute for Physical and Chemical Research (RIKEN), Wako-shi, 351-01 Saitama, Japan*
[b]*Novartis Forschungsinstitut GmbH, Brunner Strasse 59, A-1235 Vienna, Austria*
[c]*Institute for Biological Sciences, National Research Council Canada, 100 Sussex Drive, Ottawa, Ont., Canada K1A 0R6*

Received 12 October 2001; accepted 6 February 2002

Abstract

Previous static and dynamical density functional theory studies of the 2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-D-galactopyranosyl cations and their methanol adducts has led to an hypothesis that these cations exist in two families of conformers characterized as $^{2}S_{O}$ and $B_{2,5}$, respectively. These families differ by ring inversion, each with its own reactivity. New calculations on the 2,6-di-*O*-acetyl-3,4-di-*O*-methyl-D-galactopyranosyl cation confirmed these trends. Removing the isopropylidene group allows more flexibility, but two families of conformers can be discerned with the monocyclic oxocarbenium ions in the E_3 conformation and the bicyclic dioxolenium ions in the $^{4}H_5$ conformation. Attack on the β-face of these monocyclic cations is favored by hydrogen bonding and the anomeric effect. The experimentally observed high β-stereoselectivity of mannopyranosyl donors and high α-stereoselectivity of glucopyranosyl donors with the 4,6-*O*-benzylidene protecting groups can be rationalized assuming that the trans-fused 1,3-dioxane ring allows population of only one family of conformers. The combination of hydrogen bonding and conformational changes of the pyranose ring in response to the C-5–O-5–C-1–C-2 torsion angle changes are identified as key factors in stereoselectivity. Based on these observations a strategy to design face discriminated glycosyl donors that exist predominantly in only one family of conformers is proposed. © 2002 Published by Elsevier Science Ltd.

Keywords: Conformational analysis; Glycosylation; Density functional theory; Stereoselectivity

1. Introduction

The formation of an acetal or a ketal linkage in a glycosylation reaction is central to the development of efficient methods for oligosaccharide synthesis. An ideal reaction will be completely regio- and stereospecific and proceed free of side reactions. Given the large number of hydroxyl and amino functions in typical oligosaccharides, it is perhaps not surprising that such efficiencies are rarely achieved. If oligosaccharide synthesis is ever to be automated[1] in the way oligonucleotides and peptides are, then these efficiencies must be achieved. This paper appraises our understanding of the class of glycosylation reactions for which neighboring group participation can be used to control the stereochemistry at the reactive anomeric carbon.[2] For the sake of discussion, we will discuss only hexoses where the anomeric center is C-1 and the neighboring acyl group is attached to C-2. These results can be interpreted in ways that lead to new directions of research to control the stereochemistry of glycosylation reactions.

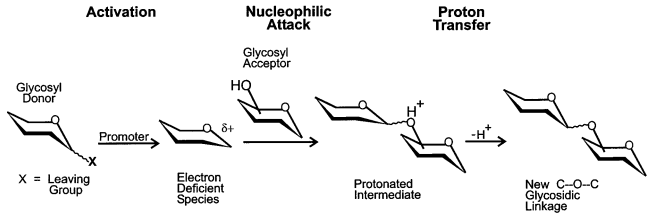
The global mechanism of glycosylation reactions has been known for a long time and falls in the borderline between S_N1 and S_N2 nucleophilic substitution reactions.[3] Typical glycosylation reactions are between a sugar acceptor with sterically hindered sugar hydroxyl groups of low nucleophilicity and the anomeric center of a sugar donor. In order to activate the donor, very good leaving groups and powerful promotors are used to generate reactive electrophilic species. Following earlier considerations,[4] we consider three sequential steps in an S_N1 like mechanism: (1) irreversible ionization of

* Corresponding author. Tel.: +1-613-9935265; fax: +1-613-9529092.
E-mail address: dennis.whitfield@nrc.ca (D.M. Whitfield).

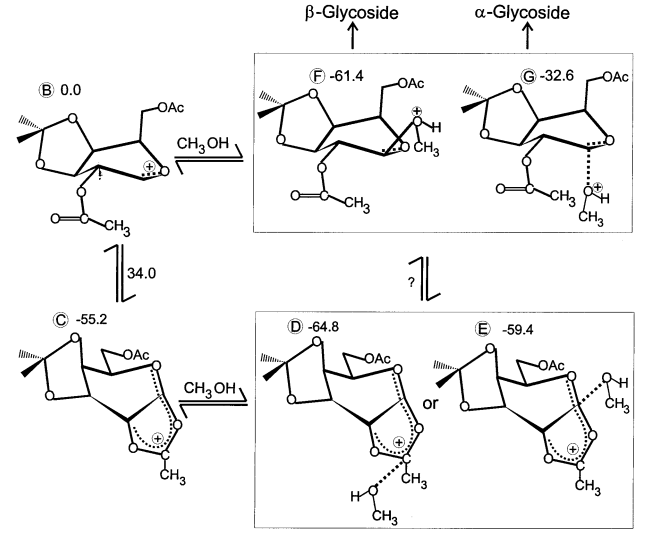
0008-6215/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0008-6215(02)00043-5

the glycosyl donor; (2) nucleophilic attack by the glycosyl acceptor; and (3) proton transfer to give the glycoside (see Scheme 1). This mechanism is analogous to ester formation between an alcohol and a source of $R–C\equiv O^+$.

Most glycosylation methods rely on making the ionization step irreversible by either precipitation of the leaving group as in heavy metal ion-promoted reactions or by rearrangements such as the trichloroacetimidate to trichloroacetamide transformation.[5] Therefore, in sharp contrast to classical S_N1 mechanistic discussions which concentrate on the kinetic barriers to ionization, it is the reactivities of the electrophilic species that we are interested in. It is well documented that the counterions such as trifluoromethanesulfonates (triflates) can in some cases form covalent intermediates[6] or that added bases such as 2-chloropyridine can also form similar covalent intermediates.[7] It is not clear if these intermediates can react directly (S_N2) to give glycosides or by prior dissociation (S_N1).[5] If the latter case occurs, then our mechanistic interpretations are still valid. We reason that nucleophilic attack precedes proton transfer for two reasons. First, the pK_a of a typical sugar



Scheme 1. Three-step (activation, nucleophilic attack, and proton transfer) model of the glycosylation reaction, adapted from Ref. 4.



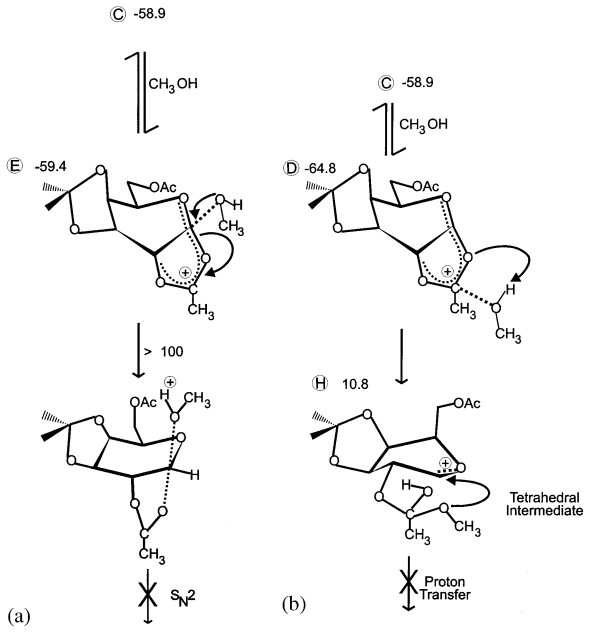
Scheme 2. Plausible (**B**–**E** for **1**) intermediates in the neighboring group-assisted glycosylation derived from donor **A**. Energies in kJ mol^{-1}, adapted from Ref. 13.

hydroxyl is about 13, which is much too high to be ionized in the presence of strong Lewis acids used in glycosylation conditions.[8] The pK_a of hydronium ions is on the order of -3, and therefore typical additives such as molecular sieves are sufficient to act as proton acceptors.[9] Two, the reverse reaction to glycosylation, namely acid-catalyzed hydrolysis, is well known to proceed by protonation followed by C–O bond cleavage.[10] Finally, we interpret proton transfer as a termination step in the mechanism as most *O*-glycosides are stereochemically inert to glycosylation conditions.

For a classical S_N2 reaction proceeding through an anti-five-coordinate transition state (TS), the α/β selectivity is determined by the relative free energies of the two possible TS's. For neighboring group-assisted glycosylations, the corresponding TS has the 2-acyl group as the leaving group (see **E** in Scheme 3(a)). Our initial goals were to find the structure of this TS, and then investigate the effects of varying the nature of the acyl group on its structure and energetics. For S_N1 reactions, the origins of α/β selectivity is much less clear. We reason that there is at least one TS past the formation of the reactive electrophilic species and that stereoselectvity arises because of different free energies for α- versus β-attack on this species. By definition, these TS must have lower energy barriers than the TS for ionization. Finding the structures of these TS is the second goal of our work.

The classical analysis of plausible electrophilic intermediates in glycosylation reactions have considered $^4H_3$ and $^3H_4$ half-chair (C-5–O-5–C-1–C-2 torsion = 0°) conformations.[11] These conformations were proposed based on the necessity to accommodate the sp^2 carbon at the anomeric centre, C-1. Since the electrophilic species are difficult to study experimentally, several attempts have been made to calculate model compounds in order to gain insight into these types of intermediates.[12] One such calculation on model compounds found ^4E as the lowest energy conformation of a tetrahydropyranyl oxocarbenium ion.[12a] However, either due to limitations in the computational methods or the inherent flexibility of the chosen models, clear answers were elusive. Our results show that pyranosyl oxocarbenium ions can exist in a variety of conformations other than ^4E, $^4H_3$, and $^3H_4$.

In order to circumvent the flexibility problem, we studied plausible intermediates in the neighboring group-assisted glycosylation reaction derived from relatively rigid glycosyl donors **A** (2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-D-galactopyranosyl-leaving group (**1**)) (see Scheme 2).[13] These computational studies were based on extensive experimental studies with this system.[14] Our approach is to optimize the geometries of plausible intermediates by quantum mechanical methods. In particular using static density functional theory (DFT) calculations as implemented in the Amsterdam



Scheme 3. Previous proposals for β-glycoside formation after nucleophilic attack on the dioxolenium ion **C**. (a) A S_N2 pathway through pentacoordinate TS. (b) A proton-transfer pathway which proceeds through tetrahedral intermediate **H**.

density functional package including continuum dielectric solvation contributions.[15] Low-energy pathways that connect these intermediates were initially searched for by using 'chemical intuition' based on numerous suggestions in the literature as guides.[16] Subsequently we have developed strategies based on dynamical DFT methods and intrinsic reaction coordinates (IRC) methods to find transition states (TS's).[17] Intermediate **B** is the monocyclic oxocarbenium ion derived by ionization of donors like **A**. Intermediate **C** is the bicyclic oxocarbenium ion resulting from neighboring-group participation. Intermediates **D**–**G** are ion–dipole complexes resulting from initial nucleophilic attack by the nucleophile methanol on **B** or **C**.[18]

Experimentally it is well established that such dioxolenium ions as **C** are formed in the absence of nucleophiles under glycosylation reaction conditions.[19] The marked energetic stability of **C** over **B** supports this observation. Since the original precursor is **A**, our results suggest that **B** is formed first. We calculated that for **B** to equilibrate to **C** the pyranose ring in **B** must invert and then the O-2 acyl group rotates to close the dioxolenium ring. The barrier is 34 kJ mol^{-1} and mostly originates from the ring-inversion step. Note that O-2 is equatorial in **A** and **B**, whereas it is pseudoaxial in **C**. It is also well established that such ions as **C** can be formed directly from **A** by anchimeric assistance if the leaving group is in the β position, plausibly by a similar mechanism.

Two mechanisms are proposed in the literature that lead from such intermediates as **C** to β-glycosides. The first is an anti S_N2 attack proceeding through a pentacoordinated TS from an intermediate of type **E** (see Scheme 3(a)).[3] The second mechanism involves a stepwise proton-transfer mechanism from intermediates of type **D** resulting from nucleophilic attack at the former carbonyl carbon (C-7) (see Scheme 3(b)).[16] We examined both mechanisms by the procedures described above and could not find low-energy pathways to β-glycosides. For example, the barrier to the five-coordinate S_N2 TS was >100 kJ mol^{-1}. The arrows in Scheme 3(b) indicate a proton transfer from the nucleophile to the anomeric oxygen with concomitant migration of the nucleophile and opening of the dioxolenium ring. Optimized intermediate, **H**, in this pathway was too high in energy to be realistic.[13] Other proton-transfer pathways and intermediates involving other tetrahedral intermediates at the carbonyl carbon were tested, but none appeared realistic. Our failures led us to hypothesize that nucleophilic attack on **B** via **F** and **G** could be the pathway to glycosides (see Scheme 2).

For this hypothesis to be valid, at least three factors need to be true: (1) intermediate **B** must have a sufficient lifetime to equilibrate to **F** or **G**; (2) the relative stabilities of **F** and **G** must account for the observed stereoselectivities; and (3) the barriers from **F** and **G** to the respective β- and α-glycosides must be very comparable in energy.

Factor 1 has been addressed by other groups in other contexts, for example the discrete existence of glucosyl oxocarbenium ions in water has been questioned by Jencks.[20] Evidence for the existence of oxocarbenium ions in water has been presented for the more stabilized keto acid, neuraminic acid.[21] Similarly, a considerable body of evidence supports the existence of oxocarbenium ion intermediates or TS's in glycosidase catalyzed reactions.[22] Therefore, it seems likely, in the presence of powerful Lewis acids in non-nucleophilic solvents, that oxocarbenium ions are formed. However, such free oxocarbenium ions as **B** are unlikely to exist in the absence of stabilizing anions and solvent.[23] Typically such anions are present in glycosylation reactions and in some cases may even participate in the reaction as nucleophiles.[8,9,24] In other words, a continuum of species from covalent intermediates, through tight ion-pairs and loose ion-pairs are likely to exist. The equilibrium proportions will be highly dependent on the reaction conditions. Furthermore, each will have its own reactivity. However, if the ultimate precursors to glycosides are indeed such ion–dipole complexes as **F** and **G**, then the relative stabilities of these species will determine stereoselectivity. Complexes of type **F** and **G** will also exist as solvated ion-pairs and multiple species of differing stabilities may exist.

Also of relevance to factor 1 is the intrinsic barrier to nucleophilic attack on **B**. From calculations in the gas phase, we could find no calculated barrier to nucle-

ophilic attack by methoxide on **B**. Richard et al. have determined the benchmark barrier for a nucleophilic addition to the acetophenone oxocarbenium ion in water as 27.2 kJ mol^{-1}.[25] This barrier was suggested to arise from a combination of solvent reorientation and electron–electron repulsion between the nucleophile and the π-character electrons of the electrophile.[26] In the medium-polarity solvents used in glycosylation reactions, this barrier is probably lower than the 27.2 kJ mol^{-1}. Thus, the finding of a 34 kJ mol^{-1} barrier for the **B** to **C** transition suggests that nucleophilic attack should compete with ring inversion and cyclization to **C**. Since bicyclic **C** is more stable than **B** in the absence of nucleophilic reaction, **C** will accumulate. Therefore, for our mechanism a pathway from **C** to **B** should exist. Such reversions to **B** could follow one of two mechanisms. The six-membered ring may invert first or the five-membered ring may break followed by inversion. The first mechanism was studied by first-principle molecular dynamics and shown to proceed to a high-energy intermediate **C′** which does not lead to **B**. Therefore breaking of the five-membered ring and then ring inversion is the probable mechanism. Hybrid mechanisms that include the nucleophile to assist such breaking are attractive namely S_N1 alternatives to the S_N2 pathway from **E**. Note that this would lead to adducts similar to **F** and **G** but with inverted pyranosyl ring conformations.

The origin of our hypothesis is the marked stability of **F** over **G** (see Scheme 2). Obviously it is necessary to examine many more examples to test if this is general. This work studies this issue and examines the factors that lead to this stability difference. It is anticipated that such analysis will lead to hypotheses that can be tested experimentally.

Implicit in our hypothesis is the assumption that the energy barrier(s) from **F** to the β-glycoside are nearly identical to those going from **G** to the α-glycoside. This progression is complex involving at least three major changes. First, the C-1–O-8 bond length (O-8 from CH_3OH) must shorten. Second, C-1 must go from sp^2 hybridization to sp^3 and this change is accompanied by a pyranosyl ring change to a stable chair conformation (in most cases). Finally, the hydroxylic proton must be transferred. Neither the order nor the possible coupling of these steps is known. We have extensively studied these questions by computations on model compounds and will report on this in a separate communication.

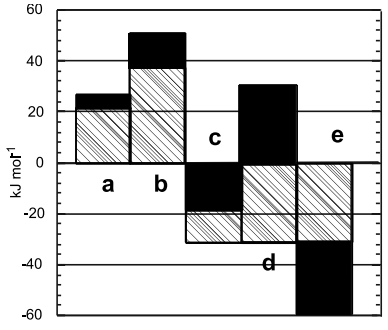
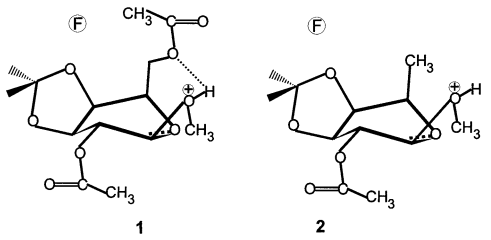


Fig. 1. Cumulative step function of the factors contributing to the difference between α-face and β-face attack for **F** and **G** for **1** and **2**. Note that contributions (d) and (e) are 0.0 kJ mol^{-1} for **F** and **G** from **2** and for **G** from **1**. Solid black for **F** and hatched for **G**. (a) Solvation. (b) Conformational distortion for glycoside formation. (c) Partial glycosidic bond formation. (d) Conformational distortion required for hydrogen bond formation. (e) Hydrogen bonding.

2. Results and discussion

3,4-O-Isopropylidenegalactose systems.—The marked energetic stability of β-complex **F** over α-complex **G** leads to the question of what factors contribute to this difference. Plausible factors include: (1) non-specific solvation; (2) bonding interactions between the nucleophile and the electrophile; (3) induced ring strain in the electrophile; (4) induced strain to accommodate hydrogen bonding; (5) hydrogen bonding; (6) differential specific solvation; and (7) differential ion pairing. The last two effects are beyond the capabilities of the computational models and resources we used, and for this reason we could not calculate them. Nevertheless we keep these limitations in mind in the interpretation of the results and when comparing with experiments for any species in this work. For the purposes of this discussion the possibilities of differential specific solvation or ion pairing are neglected, that is, the relative energetics of implicit solvent and counter ions are set to zero. This neglect probably leads to an overestimate of the strength of hydrogen bonds, since in the absence of intramolecular hydrogen bonds the proton of the nucleophile is likely hydrogen bonded to the counterion or solvent, especially once it has developed appreciable hydronium ion character. To address the remaining questions we decomposed the interaction into five components, 1–5 from above. The anomeric effect cannot be directly separated, but its effect is discussed below.

The energetic terms of this decomposition are illustrated in Fig. 1 as a step function. This was done by first calculating the isolated electrophile (that is **B** from **1**) and methanol. Then reoptimizing the geometry (that is **F** or **G** from **1**), a process that leads to steps 2 and 3. To separate the effect of hydrogen bonding from the binding energy of the forming glycosidic bond, we removed the C-6 side chain of **B**, **F**, and **G** of **1** and carried out calculations on **B**, **F**, and **G** of 2-*O*-acetyl-6-deoxy-3,4-*O*-isopropylidene-D-galactopyranosyl (**2**, see Scheme 4). From this, steps 4 and 5 can be calculated. Finally non-specific solvation was calculated for all six species to give step 1.



Scheme 4. Models of **F** from **1** and **2** used to calculate the energies in Fig. 1.

The C-5–O-5–C-1–C-2 dihedral angle which is almost planar in **B** (7.7°) as expected to accommodate the sp^2 carbon, determines the anomeric preference. Our calculations show that it is easier to distort **B** to accommodate positive values of this dihedral angle consistent with the $+23$ and $-7°$ distortions for the β and α anomer (that is, **F** and **G** of **1**) respectively. In addition to electrostatic stabilization, hydrogen bonding contributes to the stabilization of the glycosidic bond. The forming C-1–O-8 glycosidic bond reduces from 1.99 to 1.54 Å once hydrogen bonding is enabled in **F** of **1**. Considering the **2**–methanol adducts, the α anomer **G** is marginally more stable than the β anomer precursor **F** (compare hatched versus black for (c) and (d) of Fig. 1). In spite of the stronger anomeric interaction of the β anomer indicated by the shorter glycosidic bond and the larger C-5–O-5–C-1–C-2 dihedral angle, the higher-energy penalty for ring distortion and higher repulsion-energy leads to a marginally lower stability of **F** than that of **G** of **2**. This finding supports the conclusion of Sinnott, who found no evidence for a decisive kinetic anomeric effect in reactions of acetal derivatives in conformationally flexible compounds.[27]

For complexes **F** and **G** and the like to proceed to glycosides, the O-8–C-1 bond must shorten and the H–O-8 proton must be transferred.[4] The most energetically favorable complex **F** of **1** has the shortest O-8–C-1 bond and the longest O-8–H-8 bond, 1.059° in **1** versus 0.987° in **2**. Thus, the most stable complex is also the most product-like, suggesting that this is indeed a realistic reaction pathway.

Both the hydrogen bonding and the anomeric effect are specific to the ^2S_O ring conformation common to **F** and **G** of **1** and **2**. Hydrogen bonding with O-6 becomes impossible if C-6 is in the equatorial disposition. The inversion of the ring conformation reverses the stereoselectivity of the nucleophilic attack due to the reversal of the anomeric effect and the removal of the hydrogen bonding of the β intermediate. These intermediates (**C**, **D**, and **E**) have a $B_{2,5}$ ring conformation which supports α selectivity, but they all have the O-2 acyl protecting group in the axial position and the five-membered ring is closed. These observations suggest an alternative explanation for the stereospecificity of neighboring group-assisted glycosylation reactions. The basis of our theory is the existence of two families of conformations of electrophilic glycosyl donors. One family allows face discriminated S_N1 glycosylations and the other favors dioxolenium ion formation. Proton transfer from any of the intermediates leads to stable products.

*3,4-Di-*O*-methylgalactose systems.*—Our initial studies have focused on the 3,4-*O*-isopropylidene derivatives derived from **1**. This choice of a relatively rigid-ring system was deliberate because it reduces the multiple minima problem and it is directly related to glycosyl donors that led to acyl-transfer side-reactions.[14] Since our original hypothesis was based on this system, we decided to consider the more flexible analogue of **1**, namely 2,6-di-*O*-acetyl-3,4-di-*O*-methyl-D-galactopyranosyl (**3**). For this purpose, intermediates corresponding to **B** to **G** were optimized at the same level of DFT calculations. Computational details are identical to the ones described in our previous publications.[13] The results are compared in Table 1. It is readily apparent that the trends observed for **1** are followed closely for **3**. Two families of conformers are found, one conformer family which supports the oxocarbenium ion found in **B** and in methanol complexes **F** and **G**, and another family which exhibits the closure of the five-membered dioxolenium ion **C**, **D**, and **E**. For **C** and **D**, conformers with the opposite ring conformation were found, **C′** and **D′**, but these are much higher in energy. Also, a complex resulting from endo attack on **C** was considered, but it was very much higher in energy **D″**.

Three different complexes with the nucleophile on the β-face and with hydrogen bonds from OH-8 to the C=O group attached to O-6, to the C=O attached to O-2, and to O-6 were found, **F-1**, **F-2**, and **F-3**. All of these are much more stable than the α-face complex **G**. Thus the more flexible **3** also exists in at least two different families of conformations.

The conformations in Table 1 are characterized by their projections on the 38 idealized conformations of six-membered rings.[28] The first three columns describe the three leading conformers of the chair, boat, and skew types. The fourth column includes the intermediate half-chair and envelope conformations. For example, monocyclic **B** has as leading projections 0.506 $^4C_1$ and 0.566 $B_{O,3}$ with only residual contributions from the $^1S_5$ (0.030). The first two values show that its conformation is approximately half a chair and half a boat namely the E_3 envelope. Likewise **F-1** has as leading projections 0.638 $^4C_1$ and 0.519 skew $^1S_3$ with residual contributions from $^{2,5}B$ (0.106), i.e., approximately half a chair and half a skew so therefore a $^4H_3$ half-chair. This classification follows the IUPAC nomenclature and has been described in detail by us.[29] The more familiar Cremer–Pople classification is also shown in Table 1.[30] The close similarities of the ring

conformations of the family **B**, **F-1**, **F-2**, **F-3**, and **G** of **3** can be ascertained from the Cremer–Pople parameters where the values are $\theta = 120 \pm 20°$ and $\phi = 200 \pm 20°$. Whereas for the second family **C**, **D**, and **E** these values are $\theta = 140 \pm 10°$ and $\phi = 10 \pm 10°$. Ion–dipole complexes **F1–3** all exhibit distortions from the E_3 conformation of **B** to adjacent conformations on the spherical representation to accommodate the hydrogen bonding (see Fig. 2). For example, **F-3** moves to the ^2S_O, which puts C-6 in the axial disposition and allows O-6 to act as hydrogen bond acceptor as in **F** from **1** above. Ball and stick representations of structures **B**, **C**, **D**, **E**, **F-1**, **F-2**, **F-3**, and **G** are shown in Fig. 2.

Although many more systems need to be studied, the analysis of cations related to **1** and **3** supports a two family of conformers model, each with its own reactivity. The structures of **B**, **C**, **F** or **F-2** and **G** of **1** and **3** are directly compared in Scheme 5. In both cases **F** or **F-2** are the lowest energy intermediates. These calculations agree with the experimental observation of high β-selectivity. In cases where neighboring-group participation is possible, one family of conformers allows for ring closure to bicyclic dioxolenium ions, thus preventing α-glycosides. Is there any experimental evidence for this hypothesis? Several 2,6-dibenzoyl donors with various alkyl or acyl substituents at O-3 and O-4 all cleanly give β-glycosides.[31] This is the expected result with neighboring-group participation and does not directly test our hypothesis. In one case, the 2-deoxy-2-acetamido-3,4,6-tri-*O*-acetyl-D-glucopyranosyl cation has been unequivocally shown to react to give predominantly β-glycosides without reacting through the neighboring-group like oxazolinium ion.[32]

4,6-O-Benzylidenemannose and -glucose systems.— What about other systems? In recent years a number of examples of dramatic control of reactivity by using very bulky silicon protecting groups have been reported.[33] In all cases the ground-state conformation has been shown to be a reversal of the pyranose ring conformation, typically $^1C_4$ instead of $^4C_1$. In a more relevant system, a wide variety of 4,6-*O*-aryl- or alkylidene-substituted mannose donors have been shown to exhibit a high preference for the formation of β-glycosides.[34] Preliminary analysis of a prototype of this system (4,6-*O*-benzylidene-2,3-di-*O*-methyl-D-mannopyranosyl cation (**4**)) shows that only one family of conformers can be populated in this system (see Table 2). Ring inversion of the cation is inhibited by the trans-fused 1,3-dioxane ring. Intermediates **B**, **F**, and **G** have been calculated for this system, and in agreement with the hypothesis the observed β-stereoselectivity is rationalized by the relative energetics of **F** over **G**. As expected, all three cations show similar pyranose ring conformations ($B_{2,5}$ or $^1S_5$) and all of the 1,3-dioxane rings are chairs (see Table 2 and Fig. 3). As for **F** from **1** the C-5–O-5–C-1–C-2 torsion angle increases for **F** from **4** (15.4°)

Table 1
Conformational descriptions, Cremer–Pople (CP) parameters, and relative energies of cation **3** and its methanol adducts

Cation	Chair	Boat	Skew	Half-chair/envelope	CP-Q	CP-θ	CP-ϕ	Energy (kJ mol^{-1})
B	$^4C_1$ (0.506)	$B_{O,3}$ (0.566)	$^1S_5$ (0.030)	E_3 (1.012)	0.603	123.6	303	0.0 [a]
C	$^4C_1$ (0.729)	$B_{O,3}$ (0.040)	$^1S_5$ (0.392)	$^4H_5$ (0.785)	0.54	144.2	17	−100.3
C′	$^4C_1$ (0.046)	$^{2,5}B$ (0.174)	$^1S_3$ (1.115)		0.805	95.3	320	−74.4
D	$^4C_1$ (0.711)	$^{1,4}B$ (0.346)	^2S_O (0.080)		0.542	142.6	7.3	−136.6
D′	$^4C_1$ (0.136)	$^{2,5}B$ (0.043)	$^1S_3$ (1.082)		0.78	99.1	328	−104.0
D″	$^1C_4$ (0.629)	$^{2,5}B$ (0.338)	$^3S_1$ (0.063)	^5E (0.676)	0.466	38.4	225	−91.1
E	$^4C_1$ (0.710)	$B_{O,3}$ (0.047)	$^1S_5$ (0.379)	$^4H_5$ (0.758)	0.524	144.2	15.6	−143.5
F-1	$^4C_1$ (0.638)	$^{2,5}B$ (0.106)	$^1S_3$ (0.519)	$^4H_3$ (1.037)	0.578	133.9	317	−127.5
F-2	$^4C_1$ (0.166)	$B_{O,3}$ (0.840)	$^1S_5$ (0.122)		0.692	101.6	307	−150.8
F-3	$^4C_1$ (0.138)	$^{1,4}B$ (0.169)	^2S_O (0.970)		0.725	99.2	280	−121.7
G	$^4C_1$ (0.593)	$B_{O,3}$ (0.468)	$^1S_5$ (0.002)	E_3 (0.935)	0.568	131.2	302	−52.6

[a] The energy of solvated methanol is added to that of solvated **B** and then set to 0.0 kJ mol^{-1}.

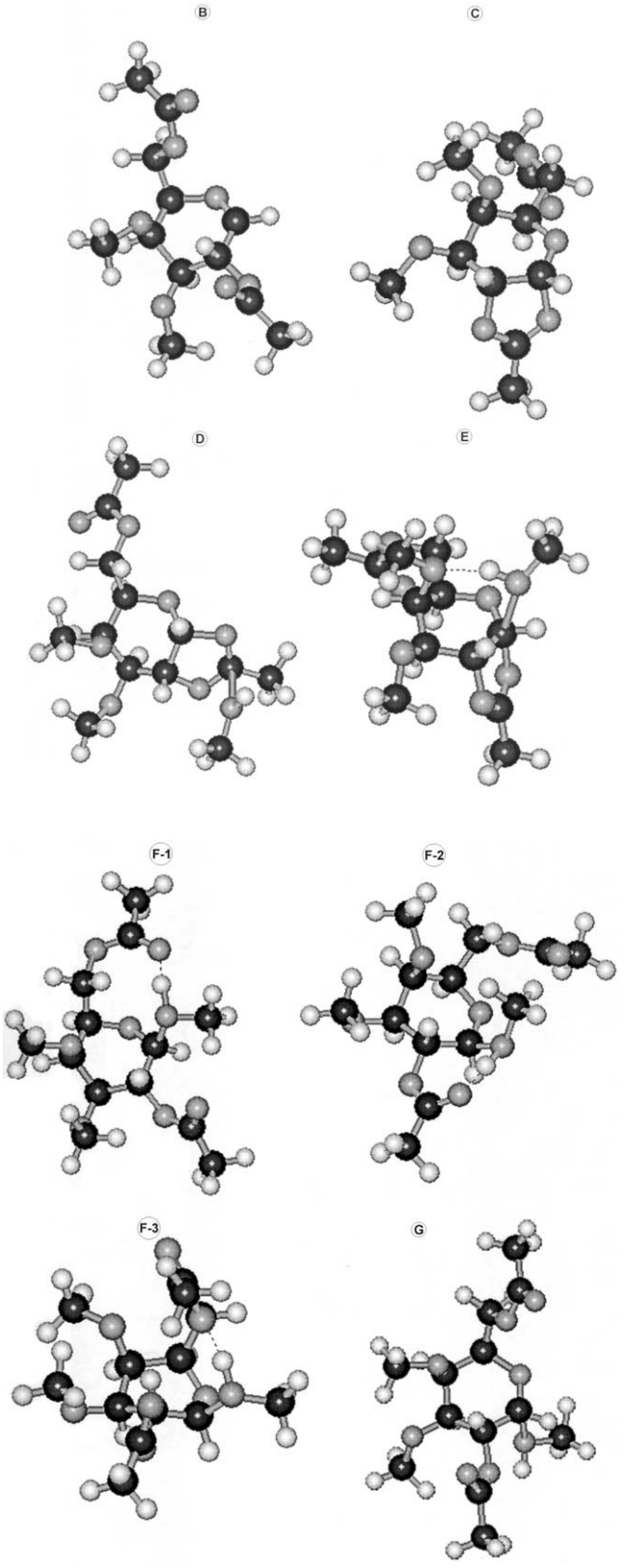
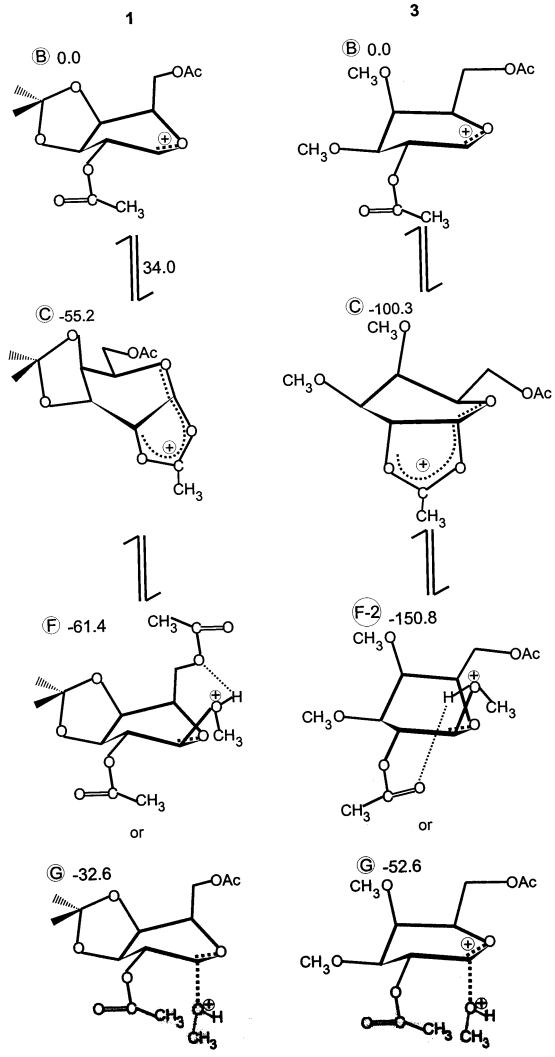


Fig. 2. Ball and stick representations of proposed intermediates **B**, **C**, **D**, **E**, **F-1**, **F-2**, **F-3**, and **G** of 2,6-di-*O*-acetyl-3,4-di-*O*-methyl-D-galactopyranosyl cation (**3**) and its methanol adducts.

versus **B** (2.2°) whereas this angle decreases for **G** from **4** ($-7.7°$). For this **G**, this maintains the unfavorable $B_{2,5}$ ring conformation whereas for this **F**, the ring shifts to the more favorable adjacent $^{1}S_{5}$ conformation. Along with the hydrogen bonding to O-3 from OH-8 enabled in **F**, the ring conformational change leads to the β-selectivity. The longer C-1–O-8 bond length (2.298 Å in **G** versus 1.632 Å in **F**) suggests caution in interpreting these results (see Table 2).

Recently it has been shown experimentally that 4,6-*O*-benzylidene substituted glucose donors exhibit a marked stereoselectivity for α-glycosides.[35] The calculated stabilities of cations related to this system, namely the prototype 4,6-*O*-benzylidene-2,3-di-*O*-methyl-D-glucopyranosyl (**5**), cation show a marked preference for α-glycosides (see Table 2 and Fig. 4). The conformational analyses of the corresponding pyranose rings reveal an interesting trend. The parent **B** from **5** is



Scheme 5. Comparison of the structure and energetics of **B**, **C**, **F** or **F-2**, and **G** of **1** and **3**.

Table 2
Conformational descriptions, selected geometric parameters, and relative energies of cations (**B**) **4**, and **5** and their methanol adducts (**F** and **G**)

Cation	Chair	Boat	Skew	Half-chair/envelope	C-1–O-8 (Å)	O-5–C-1–O-8 angle (°)	C-5–O-5–C-1–C-2 angle (°)	Energy (kJ mol^{-1})
4-B	$^4C_1$ (0.052)	$B_{2,5}$ (0.834)	$^1S_3$ (0.090)				2.2	0.0 [a]
4-F	$^1C_4$ (0.024)	$^{O,3}B$ (0.251)	$^1S_5$ (0.970)		1.632	107.4	15.4	−51.5
4-G	$^4C_1$ (0.111)	$B_{2,5}$ (0.825)	$^3S_1$ (0.018)		2.298	96.3	−7.7	−13.5
5-B	$^4C_1$ (0.483)	$^{1,4}B$ (0.495)	$^OS_2$ (0.046)	^4E (0.967)			−0.4	0.0 [a]
5-F	$^4C_1$ (0.344)	$^{1,4}B$ (0.629)	$^OS_2$ (0.046)	^4E (0.688)	2.222	97.9	16.1	−18.9
5-G	$^4C_1$ (0.780)	$^{O,3}B$ (0.018)	$^1S_5$ (0.266)		1.645	108.1	−39.8	−67.2

[a] The energy of solvated methanol is added to that of solvated **B** and then set to 0.0 kJ mol^{-1}.

calculated to have an almost exactly ^4E conformation.[12a] In **F** the C-5–O-5–C-1–C-2 torsion angle is distorted towards positive values, as calculated for **1**–**4**. This change distorts the ring towards the unfavorable $^{1,4}B$ conformation. For **G** this angle is distorted to more negative values, which pushes the ring towards the favorable $^4C_1$ conformation. Apparently the pyranose ring conformation is a major factor in controlling the stereoselectivity in this system. Since most preparative glycosylations use ethers larger than methyl as protecting groups, each glycosylation reaction mixture will have different relative stabilities of **F** versus **G**.

Based on these ideas we propose that one way to control the stereochemistry of glycosylation reactions is to create face-discriminated cations that can only access one ring conformation. That is, to synthesize donors that can only populate one of the two normal families of cations and in the populated family has the approach to one face greatly favored over the other. One plausible approach to such compounds is to prepare bridged compounds where the bridge both prevents ring inversion and provides the basis for facial selectivity. We are currently attempting to synthesize such a derivative to test this hypothesis.

3. Conclusions

The wide diversity of calculated conformations for oxocarbenium ions strongly suggests that conformations in addition to the $^4H_3$ and $^3H_4$ half-chairs need to be considered. Such considerations lead us to give a tentative yes to the answer posed by the title of this communication, that is, can the stereochemical out-

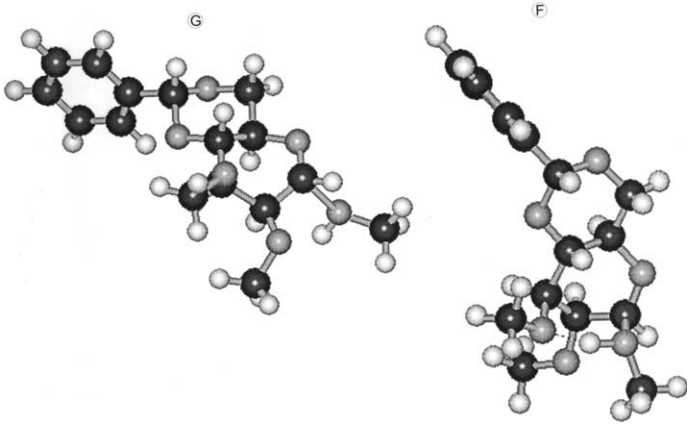


Fig. 3. Ball and stick representations of proposed intermediate **F** and **G** for 2,3-di-*O*-methyl-4,6-*O*-benzylidene-D-mannopyranosyl cation (**4**) methanol adducts.

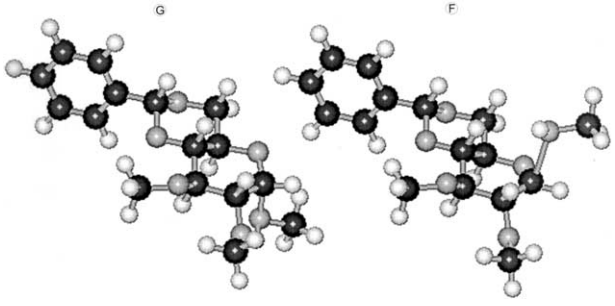


Fig. 4. Ball and stick representations of proposed intermediate **F** and **G** for 2,3-di-*O*-methyl-4,6-*O*-benzylidene-D-glucopyranosyl cation (**5**) methanol adducts.

come of glycosylation reactions be controlled by the conformational preferences of the glycosyl donor? Although it would be appealing to think that calculating the relative stabilities of intermediates **F** and **G** for any glycosyl donor–acceptor pair would lead to the prediction of the experimental stereoselectivity, this is unlikely due to the relative simplicity of our current models. Implicit in our theory is that stereoselectivity is under thermodynamic control, based on the relative stabilities of intermediates **F** and **G**. This key point is not known and it may be that stereoselectivity is under kinetic control. The apparent success of our calculations may be that they partially mimic the key features of the relevant TS's. Indeed arguments have been presented that, when possible, glycosyl triflates or functionally similar derivatives are formed and therefore such glycosylation reactions proceed by an apparent S_N2 mechanism.[35] In this case our intermediates could well resemble the S_N2 TS, noting that symmetrical five-coordinate S_N2 TS's are unfavorable and therefore the S_N2 TS may have little bonding to the leaving group. The inclusion of counterions in our calculations may help resolve this important question.

Our main motivation is to find experimental methods to control the stereoselectivity of glycosylation reactions. From the present communication, four important factors have been presented: (1) the five-coordinate S_N2 pathway is high energy for glycosylation reactions; (2) ion–dipole complexes can exist in two families of conformations which differ by ring inversion; (3) ion–dipole complexes are stabilized by intramolecular hydrogen bonding; (4) the anomeric effect increases the C-5–O-5–C-1–C-2 torsion angle for β-attack and decreases if for α-attack. The resulting pyranose distortions can be favorable or unfavorable depending on the uncomplexed conformation. These factors form the basis for the design of experiments to control the stereoselectivity of glycosylation reactions.

4. Computational details

The ADF calculations use the methods described in Ref. 13 and include a continuum dielectric solvent term. The basis set used was a double zeta basis set with a single polarization function. The conformational description based on the IUPAC nomenclature is described in detail in Ref. 29. A fully working version of the program is available at http://www.sao.nrc.ca/ibs/6ring.html.

Acknowledgements

The authors gratefully acknowledge the use of the VPP770 Fujitsu parallel computer situated in the RIKEN Computer Center. This is NRC paper no. 42452.

References

1. (a) Plante, A. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523–1527;
(b) Sears, P.; Wong, C. H. *Science* **2001**, *291*, 2344–2350.
2. Whitfield, D. M.; Douglas, S. P. *Glycoconjugate J.* **1996**, *13*, 5–17.
3. Lemieux, R. U. *Chem. Can.* **1964**, *16*, 14–22.
4. Whitfield, DM.; Douglas, S. P.; Tang, T. H.; Csizmadia, I. G.; Pang, H. Y. S.; Moolten, F. L.; Krepinsky, J. J. *Can. J. Chem.* **1994**, *72*, 2225–2238.
5. (a) Halcomb, R. L.; Wong, C. H. *Curr. Opin. Struct. Biol.* **1993**, *3*, 694–700;
(b) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531;
(c) Sinaÿ, P. *Pure Appl. Chem.* **1991**, *63*, 519–528;
(d) Paulsen, H. *Chem. Soc. Rev.* **1984**, *13*, 15–45;
(e) Ogawa, T. *Chem. Soc. Rev.* **1994**, *23*, 397–407;
(f) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927–942;
(g) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123.
6. Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11213–11217.
7. Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269–4279.
8. Rendleman, J. A., Jr. *ACS Adv. Chem. Ser.* **1971**, *117*, 51–69.
9. Perst, H. *Oxonium Ions in Organic Chemistry*; Verlag Chemie Academic Press: New York, 1971.
10. Smith, B. J. *J. Am. Chem. Soc.* **1997**, *119*, 2699–2706.
11. (a) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859–864;
(b) Deslongchamps, P.; Dory, Y. L.; Li, S. *Can. J. Chem.* **1994**, *72*, 2021–2027;
(c) Andrews, C. W.; Fraser-Reid, B.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 8293–8298;
(d) Jones, D. K.; Liotta, D. *Adv. Mol. Model.* **1995**, *3*, 67–98.
12. (a) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E. *J. Am. Chem. Soc.* **1991**, *113*, 1434–1435;
(b) Paulsen, H. *Adv. Carbohydr. Chem. Biochem.* **1971**, *26*, 127–195.
13. Nukada, T.; Bérces, A.; Zgierski, M. Z.; Whitfield, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 13291–13295.
14. Nukada, T.; Bérces, A.; Whitfield, D. M. *J. Org. Chem.* **1999**, *64*, 9030–9045.
15. Bérces, A.; Nukada, T.; Margl, P.; Ziegler, T. *J. Phys. Chem. A* **1999**, *103*, 9693–9701.
16. (a) Garegg, P. J.; Kvarnström, I. *Acta Chem. Scand. B* **1976**, *30*, 655–658;
(b) Garegg, P. J.; Kvarnström, I. *Acta Chem. Scand. B* **1977**, *31*, 509–513;
(c) Banoub, J.; Bundle, D. R. *Can. J. Chem.* **1979**, *57*, 2091–2097;
(d) Magnus, V.; Vikić-Topić, D.; Iskrić, S.; Kveder, S. *Carbohydr. Res.* **1983**, *114*, 209–224;
(e) Garegg, P. J.; Konradsson, P.; Kvarnström, I.; Norberg, T.; Svensson, S. C. T.; Wigilius, B. *Acta Chem. Scand. B* **1985**, *39*, 569–577.
17. Bérces, A.; Nukada, T.; Whitfield, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 5460–5464.
18. Harris, J. M. *Prog. Phys. Org. Chem.* **1974**, *11*, 89–173.
19. (a) Crich, D.; Dai, Z.; Gastaldi, S. *J. Org. Chem.* **1999**, *64*, 5224–5229;

(b) Wallace, J. E.; Schroeder, L. R. *J. Chem. Soc., Perkin Trans 2* **1977**, 795–802.
20. (a) Banait, N. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 7951–7958;
(b) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888–7900;
(c) Zhu, J.; Bennet, A. J. *J. Am. Chem. Soc.* **1998**, *120*, 3887–3893.
21. Horenstein, B. A.; Bruner, M. *J. Am. Chem. Soc.* **1998**, *120*, 1357–1362.
22. Zechel, D. L.; Withers, S. G. *Acc. Chem. Res.* **2000**, *33*, 11–18.
23. Kochetkov, N. E. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1994; Vol. 14, pp. 201–266.
24. Gildersleeve, J.; Pascal, R. A., Jr.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 5961–5969.
25. Richard, J. P.; Williams, K. B.; Amyes, T. L. *J. Am. Chem. Soc.* **1999**, *121*, 8403–8404.
26. Richard, J. P. *Tetrahedron* **1995**, *51*, 1535–1573.
27. Sinnott, M. L. In *ACS Symposium Series* 539; Thatcher, G. R. J., Ed. The Anomeric Effect and Associated Stereoelectronic Effects; ACS: Washington, DC, 1993; pp. 97–113.
28. (a) Hendrickson, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 7047–7061;
(b) Schwartz, J. C. P. *J. Chem. Soc., Chem. Commun.* **1973**, 505–508.
29. Nukada, T.; Bérces, A.; Whitfield, D. M. *Tetrahedron* **2001**, *57*, 477–491.
30. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.
31. (a) Mehta, S.; Whitfield, D. M. *Tetrahedron* **2000**, *56*, 6415–6425;
(b) Eichler, E.; Yan, F.; Sealy, J.; Whitfield, D. M. *Tetrahedron* **2001**, *57*, 6679–6693.
32. Hodosi, G.; Krepinsky, J. J. *Synlett* **1996**, 159–161.
33. (a) Shuto, S.; Yahiro, Y.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2000**, *65*, 5547–5557;
(b) Crich, D.; Dudkin, V. *Tetrahedron Lett.* **2000**, *41*, 5643–5646;
(c) Moutel, S.; Prandi, J. *Tetrahedron Lett.* **1994**, *35*, 8163–8166;
(d) Hosoya, T.; Ohasi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663–666;
(e) Tius, M. A.; Busch-Petersen, J. *Tetrahedron Lett.* **1994**, *35*, 5181–5184;
(f) Yahiro, Y.; Ichikawa, S.; Shuto, S.; Matsuda, A. *Tetrahedron Lett.* **1999**, *40*, 5527–5531;
(g) Yamada, H.; Nakatani, M.; Ikeda, T.; Marumoto, Y. *Tetrahedron Lett.* **1999**, *40*, 5573–5576;
(h) Ikeda, T.; Yamada, H. *Carbohydr. Res.* **2000**, *329*, 889–893.
34. (a) Crich, D.; Li, H. *J. Org. Chem.* **2000**, *65*, 801–805;
(b) Weingart, R.; Schmidt, R. R. *Tetrahedron Lett.* **2000**, *41*, 8753–8758;
(c) Yun, M.; Shin, Y.; Chun, K. H.; Nam Shin, J. E. *Bull. Korean Chem. Soc.* **2000**, *21*, 562–566;
(d) Crich, D.; Dudkin, V. *Org. Lett.* **2000**, *2*, 3941–3943;
(e) Ito, Y.; Ohnishi, Y.; Ogawa, T.; Nakahara, Y. *Synlett* **1998**, 1102–1104.
35. (a) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926–4930;
(b) Bowden, T.; Garegg, P. J.; Maloisel, J. L.; Konradsson, P. *Israel J. Chem.* **2000**, *40*, 271–277.