Exploring the Mechanism of Neighboring Group Assisted Glycosylation Reactions

Tomoo Nukada,[1a] Attila Berces,[1b] Marek Z. Zgierski,[1b] and Dennis M. Whitfield*,[1c]

Contribution from The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama 351, Japan, and National Research Council, Ottawa, Ontario, K1A 0R6, Canada

Received March 27, 1998

Abstract: Glycosyl donors based on the 2,6-di-*O*-acyl-3,4-*O*-isopropylidene-D-galactopyranosyl-(leaving group) structure have been shown experimentally to have a high propensity for giving acyl transfer to the alcohol nucleophile as major side products in the glycosylation reaction. The corresponding cations of these relatively rigid glycosyl donors were investigated by density functional methods. The precursor cations resulting from neighboring group assistance from the 2-*O*-acyl group were found to be the most stable. The nucleophile methanol most favorably approaches the LUMO of such cations on the former carbonyl carbon. The resulting stable intermediate has a long C−O bond of 2.79 Å. It is suggested that such intermediates can lead to both acyl transfer and β-glycoside after passing through at least one further transition state.

Introduction

As part of our program to prepare and characterize vaccines based on the capsular polysaccharides of Group B Streptococcus we are synthesizing oligosaccharide fragments of these polysaccharides by polymer-supported methodologies.[2] One of our targets (serotype 1A) has a 3,4 branch at a β-linked-D-galactopyranoside.[3] For this purpose we have prepared and tested a number of donors based on the 2,6-di-*O*-acyl-3,4-*O*-isopropylidene-D-galactopyranosyl-(leaving group) structure. Such donors have acyl groups at O-2 to ensure β-selectivity in the glycosylation reaction by neighboring group participation[4] and the cleavable 3,4-isopropylidene protecting group to allow for chain extensions (Scheme 1). Unfortunately, under most glycosylation conditions these donors led to extensive transfer of acyl groups from O-2 to the nucleophilic alcohol[5] to form the acylated alcohol as the major side product.[6] Even the highly sterically hindered pivaloyl group was transferred under some conditions.[7] Such side reactions have been reported many times before and have been attributed to rearrangements of ortho ester

Scheme 1

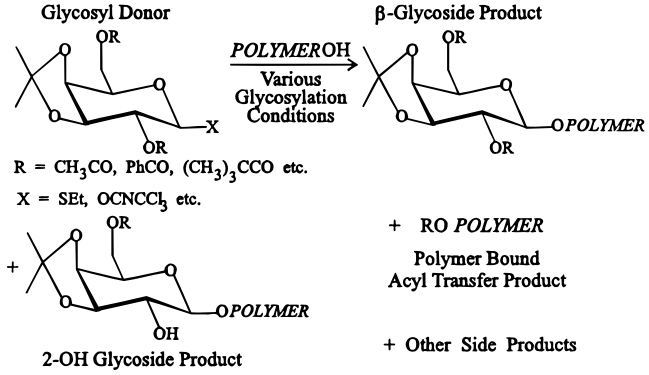
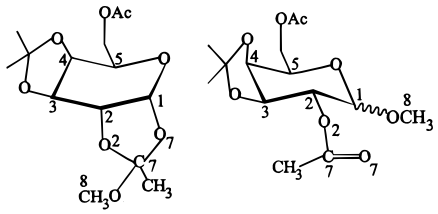


Chart 1



(Chart 1) like intermediates (cf. **D** in Scheme 2).[8] In the case of polymer-bound nucleophiles such reactions are major impediments to successful oligosaccharide synthesis.[9]

The fused 3,4-dioxolone ring of the isopropylidene protecting group rigidifies the donor and this phenomenon has been termed "torsional deactivation".[10] This rigidification is likely related to these side reactions for these donors. It occurred to us that this rigidification could be put to good use because it would

(1) (a) RIKEN. (b) Steacie Institute for Molecular Sciences (NRC). (c) Institute for Biological Sciences (NRC).

(2) Eichler, E.; Jennings, H. J.; Whitfield, D. M. *J. Carbohydr. Chem.* **1997**, *16*, 385.

(3) Zhou, W.; Jennings, H. J. *J. Carbohydr. Chem.* **1997**, *15*, 925.

(4) (a) Hünig, S. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 548. (b) Fife, T. H.; Bembi, R.; Natarajan, R. *J. Am. Chem. Soc.* **1996**, *118*, 12956.

(5) (a) Whitfield, D. M.; 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. (b) Ziegler, T.; Kováč, P.; Glaudemans, C. P. J. *Ann. Chem.* **1990**, 613.

(6) (a) Garegg, P. J.; Konradsson, P.; Kvarnström, I.; Norberg, T.; Svensson, S. C. T.; Wigilius, B. *Acta Chem. Scand. B* **1985**, *39*, 569.(b) Uvarova, N. I.; Oshitok, G. I.; Elyakov, G. B. *Carbohydr. Res.* **1973**, *27*, 79. (c) Khorlin, A. Ya.; Nesmeyanov, V. A.; Zurabyan, S. E. *Carbohydr. Res.* **1975**, *43*, 69. (d) Křen, V.; Fišerová, A.; Augé, C.; Sedmera, P.; Havlíček, V. *Bioorg. Med. Chem.* **1996**, *4*, 869. (e) Spijker, N. M.; Basten J. E. M.; van Boeckel, C. A. A. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 611. (f) Nilsson, U.; Ray, A. K.; Magnusson, G. *Carbohydr. Res.* **1994**, *252*, 117. (g) Liu, M. Z.; Fan, H. N.; Guo, Z. W.; Hui, Y. Z. *Carbohydr. Res.* **1996**, *290*, 233. (h) Lee, R. T.; Lee Y. C. *Carbohydr. Res.* **1995**, *271*, 131. (I) Hronowski, L. J. J.; Szarek, W. A.; Hay, G. W.; Ison, E. R.; Krebs, A.; Depew, W. T. *Carbohydr. Res.* **1991**, *219*, 51.

(7) Whitfield, D. M. Unpublished results.

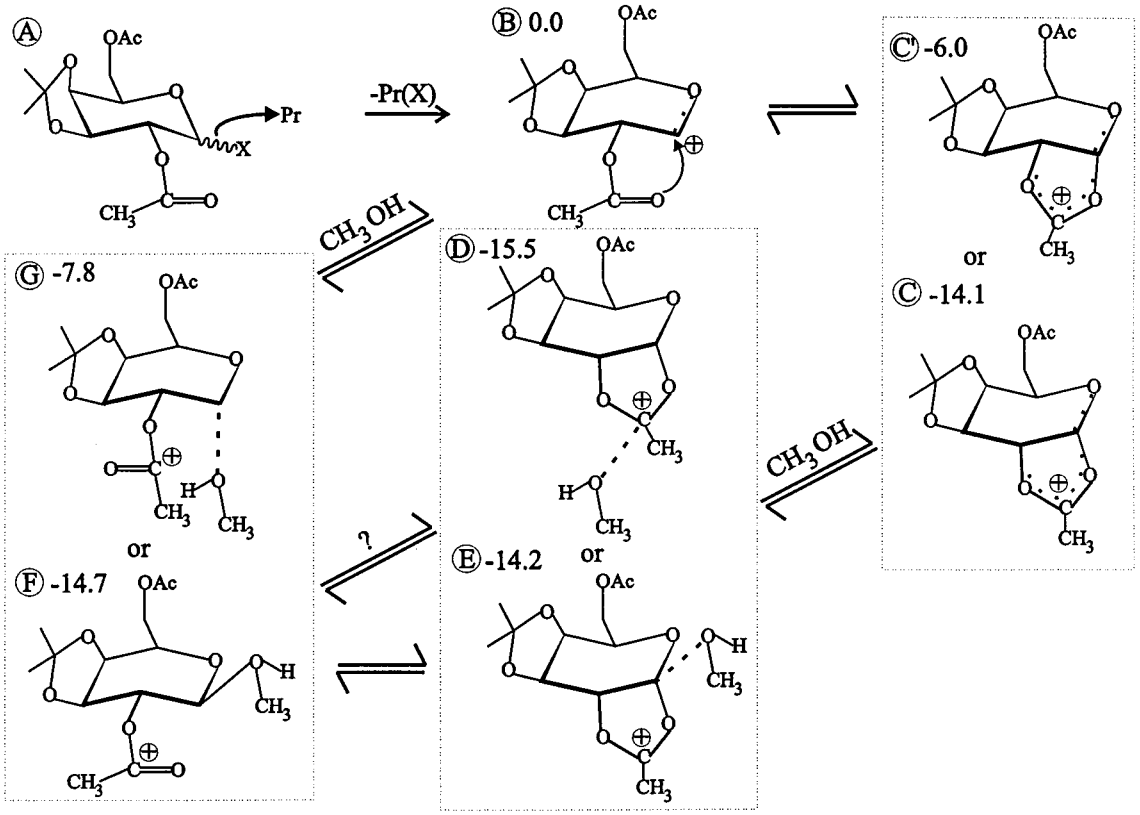
(8) (a) Banoub, J.; Bundle D. R. *Can. J. Chem.* **1979**, *57*, 2091. (b) Magnus, V.; Vikić-Topić, D.; Iskrić, S.; Kveder, S. *Carbohydr. Res.* **1983**, *114*, 209.

(9) Whitfield, D. M.; Douglas, S. P. *Glycoconjugate J.* **1996**, *13*, 5.

(10) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1434.

10.1021/ja981041m CCC: $15.00
Published on Web 12/04/1998

Scheme 2. The Numbers Beside the Labels Are Relative Energies Including Solvation (in kcal mol^{-1})[a]



[a] The corresponding gas phase energies are (B) 0.0, (C) −13.2, (C′) −4.8, (D) −22.9, (E) −20.6, (F) −21.3, (G) −13.4, and (H) −3.7 (Chart 2). Plus charges are assigned to the atom with the highest calculated positive charge density.

make these molecules more amenable to study by theoretical methods since the multiple minima problem is greatly reduced. In this study we report density functional theory, DFT, calculations augmented with solvation free energy calculations based on continuum dielectric theory of several of the proposed intermediates in the neighboring group assisted glycosylation reaction. To the best of our knowledge, this is the first theoretical study of a glycosylation reaction actually used in an oligosaccharide synthesis.

Methods

The reported DFT calculations were carried out with the Amsterdam Density Functional (ADF) program system version 2.3 derived from the work of Baerends et al.[11] and developed at the Free University of Amsterdam[12] and at the University of Calgary.[13] All optimized geometries calculated in this study are based on the local density approximation[14] (LDA) augmented with gradient corrections to the exchange[14b] and correlation[14c] potentials. The atomic orbitals were described by an uncontracted double-ζ Slater function basis set[15] with a single-ζ polarization function on all atoms. The 1s configurations on carbon and oxygen were assigned to the core and treated by the frozen-core approximation.[11] A set of s, p, d, f, g, and h Slater functions, centered on all nuclei, was used to fit the electron density and to evaluate the Coulomb and exchange potentials accurately in each SCF cycle.[16]

The numerical integration accuracy parameter which approximately represents the number of significant digits for the scalar matrix elements was gradually increased to 4.5 until convergence with respect to integration accuracy was reached. This numerical accuracy is sufficient to determine energies within a fraction of a kcal mol^{-1}, and bond distances within 0.001 Å (which is more accurate than predicted by the definition of the numerical integration accuracy parameter). The scalable numerical accuracy implemented in the ADF program makes

(11) Baerends, E. J.; Ellis, D. E.; Ros, P. *Chem. Phys.* **1973**, *2*, 41.
(12) (a) Ravenek, W. In *Algorithms and Applications on Vector and Parallel Computers*; te Riele, H. J. J., Dekker, Th. J.; van de Vorst, H. A., Eds.; Elsevier: Amsterdam, 1987. (b) Boerrigter, P. M.; te Velde, G.; Baerends, E. J. *Int. J. Quantum Chem.* **1988**, *33*, 87. (c) te Velde, G.; Baerends, E. J. *J. Comput. Phys.* **1992**, *99*, 84.
(13) (a) Fan, L.; Ziegler, T., *J. Chem. Phys*. **1991**, *94*, 6057. (b) Fan, L.; Ziegler, T. *J . Chem. Phys*. **1991**, *95*, 7401. (c) Fan, L.; Versluis, L.; Ziegler, T.; Baerends, E. J.; Ravenek, W. *Int. J. Quantum Chem*. **1988**, *S22*, 173. (d) Fan, L.; Ziegler, T. *J. Chem. Phys*. **1992**, *96*, 9005. (e) Fan, L.; Ziegler, T. *J. Phys. Chem*. **1992**, *96*, 6937.
(14) (a) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys*. **1980**, *58*, 1200. (b) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 2398.(c) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822. (d) Perdew, J. P. *Phys. Rev. B* **1986**, *34*, 7046.
(15) (a) Snijders, G. J.; Baerends, E. J.; Vernooijs, P. *At. Nucl. Data. Tables* **1982** *26*, 483. (b) Vernooijs, P.; Snijders, G. J.; Baerends, E. J. *Slater Type Basis Functions for the whole Periodic System*, Internal Report; Free University of Amsterdam, The Netherlands, 1981.
(16) Krijn, J.; Baerends, E. J. *Fit Functions in the HFS-method*, Internal Report (in Dutch); Free University of Amsterdam, The Netherlands, 1984.
(17) Ziegler, T. *Chem. Rev.* **1991**, *91*, 651.
(18) Paulsen, H.; Dammeyer, R. *Chem. Ber.* **1973**, *106*, 2324−32.
(19) Breneman, C. M.; Wiberg, K. B. J. *Comput. Chem*. **1990**, *11*, 361.
(20) (a) Bashford, D. *Curr. Op. Struct. Biol*. **1991**, *1*, 175. (b) Bashford, D.; Gerwert, K. J. *Mol. Biol*. **1992**, *224*, 473. (c) Lim, C.; Bashford, D.; Karplus, M. J. *Phys. Chem*. **1991**, *95*, 5610. (d) Bashford, D.; Case, D. A.; Dalvit, C.; Tennant, L.; Wright, P. E. *Biochemistry* **1993**, *32*, 8045.
(21) (a) Toshima, K.; Tatsuta, K. *Chem. Rev*. **1993**, *93*, 1503. (b) Sinaÿ, P. *Pure Appl. Chem.* **1991**, *63*, 519. (c) Schmidt, R. R. *Pure Appl. Chem.* **1989**, *61*, 1257. (d) Paulsen, H. *Chem. Soc. Rev.* **1984**, *13*, 15. (e) Ogawa, T. *Chem. Soc. Rev.* **1994**, *23*, 397.
(22) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.
(23) (a) Lemieux, R. U. *Chem. Can*. **1964**, *16*, 14. (b) Wulff, G.; Röhle, G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 157.
(24) Kondo, H. K.; Aoki, S.; Ichikawa, Y.; Halcomb, R. L.; Ritzen, H.; Wong, C. H. *J. Org. Chem.* **1994**, *59*, 864.
(25) (a) Perst, H. *Oxonium Ions in Organic Chemistry;* Verlag Chemie Academic Press: Weinheim, **1971**. (b) Kochetkov, N. K.; Zhulin, V. M.; Klimov, E. M.; Malysheva, N. N.; Makarova, Z. G.; Ott, A. Y. *Carbohydr. Res.* **1987**, *164*, 241.
(26) Chiappe, C.; Moro G. L.; Munforte, P. *Tetrahedron* **1997**, *53*, 10471.
(27) (a) Banait, N. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 7951. (b) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888.

it possible to reduce the computational cost at the initial stages of geometry optimization when the gradient is still large. These calculations were carried out on a multi-processor Silicon Graphics Origin 2000 workstation.

We do not take into account some effects such as finite temperature, zero-point energy corrections, and basis set superposition error. Most of the error in the final results should be related to these neglected effects and not to error in the DFT energies. Gradient corrected DFT calculations were repeatedly shown to provide exceptionally good energetics for organic and organometallic systems.[17] As a positive control, the structure of the 2,4,4,5,5-pentamethyl-1,3-dioxolan-2-ylium cation was calculated by using the ADF-DFT method. The ring was found to be almost planar and the methyls eclipsed as found experimentally.[18]

Initial structures were generated by using the semiempirical method Parametric-Method-3, PM3, as implemented in the Hyperchem program package. Structures for the acetyl, benzoyl, and pivaloyl groups for ions **B** to **I** were calculated. The ring geometries and relative energies were nearly independent of the acyl group. The optimized structures for the acetyl compounds were used as input for the ADF-DFT calculations. The geometries of the DFT optimized structures were not wildly different from the input structures except for the $C_{1\ or\ 7}-O_8$ bond lengths and related bond angles in **D** to **G**. The ADF-DFT geometry of **F** could not be obtained with PM3 since it optimized to a ring geometry resembling **E** despite starting from several different initial structures. The relative energies from the semiempirical and density functional calculations were different. For example, **C** is 11 kcal mol^{-1} more stable than **B** with PM3. Similarly **D** and **E** were nearly isoenergetic and **F** is 7 and **G** 9 kcal mol^{-1} less stable (cf. Scheme 2).

To calculate solvation energies, we fitted a set of point charges to reproduce the electrostatic potential from the density functional calculations using the total net charge and the dipole moment as constraints by a modified version of the CHELPG program.[19] The fitted points lay on a cubic grid between the van der Waals radius and the outer atomic radius with a spacing of 0.2 Å. The outer radii for all atoms are 5 Å while the van der Waals radii for carbon, oxygen, and hydrogen are 1.7, 1.4, and 1.2 Å, respectively. The solvent reaction field potential due to the fitted ESP charges was calculated by solving the Poisson−Boltzmann equation with the MEAD (Macroscopic Electrostatics with Atomic Detail) program.[20] In the solvation energy calculations, the solute molecule within the interior region was assigned a dielectric constant of $\epsilon = 1$, while that in the outside was assigned the experimental dielectric constant of the solvent. The solute interior was defined as the region inaccessible to any part of a probe sphere with a radius $r = 2.4$ Å, rolling on the molecular surface of the atomic spheres. The probe radius and the dielectric constant of $\epsilon = 9.0$ correspond to CH_2Cl_2, which is a typical solvent for the glycosylation reactions.

Results and Discussion

To synthesize 1,2-*trans*-glycosides neighboring group participation by 2-*O*-acyl protecting groups is widely used.[21] For activation of such donors, leaving groups such as halide, alkylthio, and *O*-trichloroacetimidate are used. These leaving groups are typically activated by electrophilic Lewis acid promoters. Such promoters often react irreversibly with the leaving group to generate an electrophilic sugar species. Most glycosylation reactions employ nonnucleophilic anions such as trifluoromethanesulfonate or perchlorate, which allows the weakly nucleophilic hydroxyl of the alcohol to successfully compete with the anion, so that the new glycosidic linkage is formed. Compelling evidence that such anions can form covalent intermediates has been presented.[22] However, in the presence of participating 2-*O*-acyl groups such covalent intermediates react to form ortho esters and glycosides (Chart 1), suggesting that other intermediates lie on the reaction pathway. Similarly, solvent molecules can also specifically stabilize the charged species and in some cases can explicitly be involved in the reaction. Solvation was considered in our study by a continuum dielectric method, but the multibody problem associated with explicit solvent and counterions is still beyond present theoretical capabilities. There are many types of glycosylation reactions and not all will conform to the above criteria, but most share some of these features.

The mechanism that we have assumed follows from several proposals in the literature (Scheme 2).[23] It starts by activation of the glycosyl donor, **A**, by a promoter leading to irreversible formation of a precursor glycosyl oxocarbenium ion, **B**.[24] Neighboring group participation leads to ions such as **C**. There is definitive experimental evidence for such cations in other systems.[18,25] This intramolecular participation distinguishes this mechanism from nonparticipatory mechanisms where nucleophilic assistance to formation of the oxocarbenium ion by the alcohol is probable.[26] In our case two conformers **C** and **C′** were found by optimization (see methods for details) to be 14.1 and 6.0 kcal mol^{-1} more stable than **B**, in CH_2Cl_2 solvent. Intramolecular neighboring group participation is also expected to be kinetically favored over intermolecular nucleophilic attack so that precursor ion **B** is unlikely to have a long lifetime.[27] In the standard mechanism formation of the unwanted α-glycoside is generally attributed to attack on **B** via **G**, i.e., an S_N1 mechanism.[28] Analogous β attack on **B** leads to **F**, which could result from other pathways too, see below.

Precursor ion **C** can react with nucleophiles at, at least two positions: the anomeric carbon, C_1, to give **E** or at what was the carbonyl carbon, C_7, to give **D**. For both sites two directions are possible, namely α or β for approach to C_1 and exo or endo to C_7. But, α and endo attacks are usually excluded for steric reasons especially for the relatively large carbohydrate alcohols, and are not considered here. We have chosen to use methanol as the nucleophile to keep the computational problem tractable. These calculations give **D** as the most stable complex cation, approximately 1.3 and 0.8 kcal mol^{-1} more stable than **E** and **F**, respectively. It is also calculated to be 1.4 kcal mol^{-1} more stable than **C** + CH_3OH. Note that solvation energies and the energies of methanol have been included to allow comparison of **B** through **G**. Proposed intermediates **D** to **G** can be compared to the nucleophile:carbonium ion, ion:dipole complexes of S_N1 mechanisms. Therefore, like S_N1 reactions there could be at least one transition state, TS, further along the reaction pathway. The acidities of **D** to **H** were calculated by optimizing the corresponding neutral species and are 0 (D), −5.4 (E),[29] −6.9 (F), −11.8 (G), and −16.2 (H) kcal mol^{-1}. Since all species are more acidic than **D**, this suggests that proton transfer may be important for conversion of **D** to **F**. As expected, the protonated α-glycoside **G** is more acidic than the corresponding β-glycoside **F**.[30]

The six-membered-ring dihedral angles are given in Table 1, and the corresponding Cremer−Pople parameters are given in Table 2.[31] Ions **C**, **D**, **E**, and **H** have one six-membered-ring conformation whereas **B**, **C′**, **F**, **G**, and **I** have a second conformation as characterized by Cremer−Pople parameter $\phi 2$ values of about 60° and 270°, respectively. The ring dihedrals for **C′** and **F** are close to each other and have differences up to 30° from the rest of group 2, **B**, **G**, and **I**. A perfect boat or twist-boat conformation should have a θ value of 90° and perfect

(28) Kochetkov, N. E. in *Studies in Natural Products Chemistry*; Rahman, A., Ed.; 1994; Vol. 14, p 201.

(29) The neutral species was not stable and so acidity is calculated relative to the neutral β-glycoside, i.e., the neutral corresponding to **F**.

(30) Jebber, K. A.; Zhang, K.; Cassady, C. J.; Chung-Phillips, A. *J. Am. Chem. Soc.* **1996**, *118*, 10515.

(31) (a) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354. (b) Ragazzi, M.; Ferro, D. R.; Provasoli, A. *J. Comput. Chem.* **1986**, *7*, 105.

Table 1. Ring Dihedrals (deg) for Proposed Intermediates **B** to **I**

intermediate	$O_5C_1C_2C_3$	$C_1C_2C_3C_4$	$C_2C_3C_4C_5$	$C_3C_4C_5O_5$	$C_4C_5O_5C_1$	$C_5O_5C_1C_2$
B	40.7	−59.6	35.4	7.6	−33.4	7.7
C′	15.7	−51.6	33.1	17.5	−58.3	40.9
C	−22.3	22.1	17.6	−58.3	62.4	−21.4
D	−23.8	24.9	15.2	−57.5	63.0	−23.8
E	−9.9	6.6	27.8	−60.1	59.5	−24.3
F	29.7	−62.1	38.6	14.9	−52.7	29.7
G	43.8	−57.6	33.4	5.8	−25.6	0.0
H	−43.6	29.9	19.6	−60.3	51.8	0.4
I	45.5	−62.4	36.4	7.2	−31.2	2.8

Table 2. Cremer−Pople Parameters for Proposed Intermediates **B** to **I**

intermediate	Q	θ (deg)	$\phi 2$ (deg)[a]
B	0.7	83.2	274.9
C′	0.6	89.9	280.2
C	0.6	72.6	60.2
D	0.6	74.0	61.7
E	0.5	62.8	54.5
F	0.7	83.2	274.9
G	0.5	71.1	264.9
H	0.7	81.4	50.0
I	0.6	72.7	266.0

[a] The ^{1,4}B conformation is referenced as 0. This definition follows from the original derivation[31] but differs from some others used in the literature.[43]

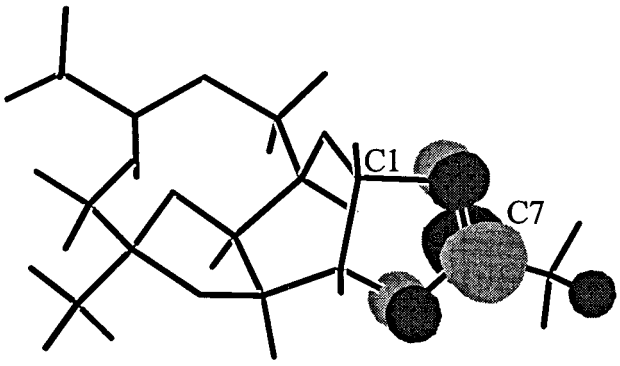


Figure 1. Graphical representation of the LUMO of proposed intermediate **C**. Gray and black lobes are of opposite sign and clearly indicate the antibonding character of the orbital.

twist-boats have $\phi 2$ values of 30°, 90°, 150°, etc. Thus, these two conformers can be described as flattened $B_{2,5}$ and ^2S_O conformers, respectively. The five-membered dioxolenium rings in cations **C**, **C′**, **D**, and **E** are nearly planar as expected (see Methods).[32]

Together these results suggest that the preferred glycosylation pathway is from **A** to **C** to **D**. Additional evidence for the proposition that the site of nucleophilic attack is C_7 comes from frontier molecular orbital analysis of the LUMO of **C**, see Figure 1. The LUMO is generally thought to be the site of nucleophilic attack and in this case is clearly an antibonding orbital centered predominantly on C_7.

Further insight into the reaction mechanism can be gleaned from the structures of cations **D** and **E**, see Figure 2. In both cases the oxygen, O_8, of the methanol is found at approximately 90° from the O−C−O plane it is attacking, i.e., approaching a vacant p-like orbital, $O_7C_7O_8$ (**D**) is 95.3° and $O_5C_1O_8$ is 79.8° (**E**). Another important feature is the length of the C_7-O_8 2.79 Å (**D**) and C_1-O_8 2.87 Å (**E**) bonds, see Table 3. In both cases this is much longer than the 1.42 ± 0.3 Å of a carbohydrate C−O bond. These geometric results are consistent with the antiperiplanar lone pair hypothesis[33] developed to describe glycoside hydrolysis and the experimental structures observed with some glycosidases.[34]

The long C−O bond is a particularly important characteristic of **D** because the literature describes such intermediates as ortho ester like (Chart 1). To convert **D** to the ortho ester not only must the proton be lost but the C_7-O_8 bond must shorten. Therefore at least one TS should separate these species. The converse is also true, and during the rearrangement of neutral ortho esters to β-glycosides by Lewis acid[35] or protic catalysis[36] this bond must lengthen and protonate. Also, the higher acidity of **H** (Chart 2) suggests that ortho esters should protonate on the anomeric oxygen and therefore rearrangements to the glycoside may be difficult for this reason. The yields of such rearrangements are often low[37] and acyl transfer is known to be a side reaction.[38] Our results suggest that both glycosylation reactions and ortho ester rearrangements proceed through a common intermediate that can lead to acyl transfer. Further support for this hypothesis is the observation that 1,2-*O*-cyanoethylidene sugar derivatives which must ionize to first form intermediates such as **D** also exhibit acyl transfer as a side reaction.[39]

Acyl transfer can be rationalized by the breaking of the C_7-O_2 bond accompanied by proton transfer to O_2 from intermediates such as **D** to give **I** and methyl acetate (Chart 2). Such a possibility is calculated to be 5.3 kcal mol^{-1} more stable than **B** + CH_3OH but 12.2 kcal mol^{-1} less stable than **D**. The experimental results show that steric bulk about C_7 and about the alcoholic carbon, C_8, minimizes acyl transfer.[7] This can be interpreted to mean that acyl transfer is a kinetic product from **D** whereas the glycoside is the thermodynamic product.

Given that **D** is probably the initially formed species, how does this lead to the observed β-glycosides? The generally assumed mechanism is that **D** is in equilibrium with **E**, which leads to **F** and hence the β-glycoside, after proton transfer. Note that analogous mechanisms can be written replacing the proton with a Lewis acid.[26] The relative energetics of such possibilities have not been investigated yet. One plausible pathway from **D** to **F** starts with proton transfer (or Lewis acid proton exchange) to the anomeric oxygen, but such an intermediate **H** is 16.8 kcal mol^{-1} higher in energy than **D** and therefore unlikely (Chart 2). In Scheme 2 an arrow with a question mark is put between

(32) Paulsen, H.; Schüttpelz, E. *Chem. Ber.* **1979**, *112*, 3214.
(33) Miljković, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597.
(34) Sulzenbacher, G.; Driguez, H.; Henrissat, B.; Schülein, M.; Davies, G. J. *Biochemistry* **1996**, *35*, 15280.
(35) Bochkov, A. F.; Betaneli, V. I.; Kochetkov, N. K. *Bioorg. Khim.* **1997**, *3*, 39.
(36) Bochkov, A. F.; Betaneli, V. I.; Kochetkov, N. K. *Bioorg. Khim.* **1976**, *2*, 927.
(37) (a) Garegg, P. J.; Kvarnstorm, I. *Acta Chem. Scand.* **1976**, *B30*, 655. (b) Garegg, P. J.; Kvarnstorm, I. *Acta Chem. Scand.* **1977**, *B31*, 509.
(38) Bochkov, A. F.; Betaneli, V. I.; Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1974**, *6*, 1379.
(39) Tsvetkov, Yu. E.; Kitov, P. I.; Bakinovskii, L. V.; Kochetkov, N. K. *Bioorg. Khim. (Engl.)* **1990**, *16*, 50.

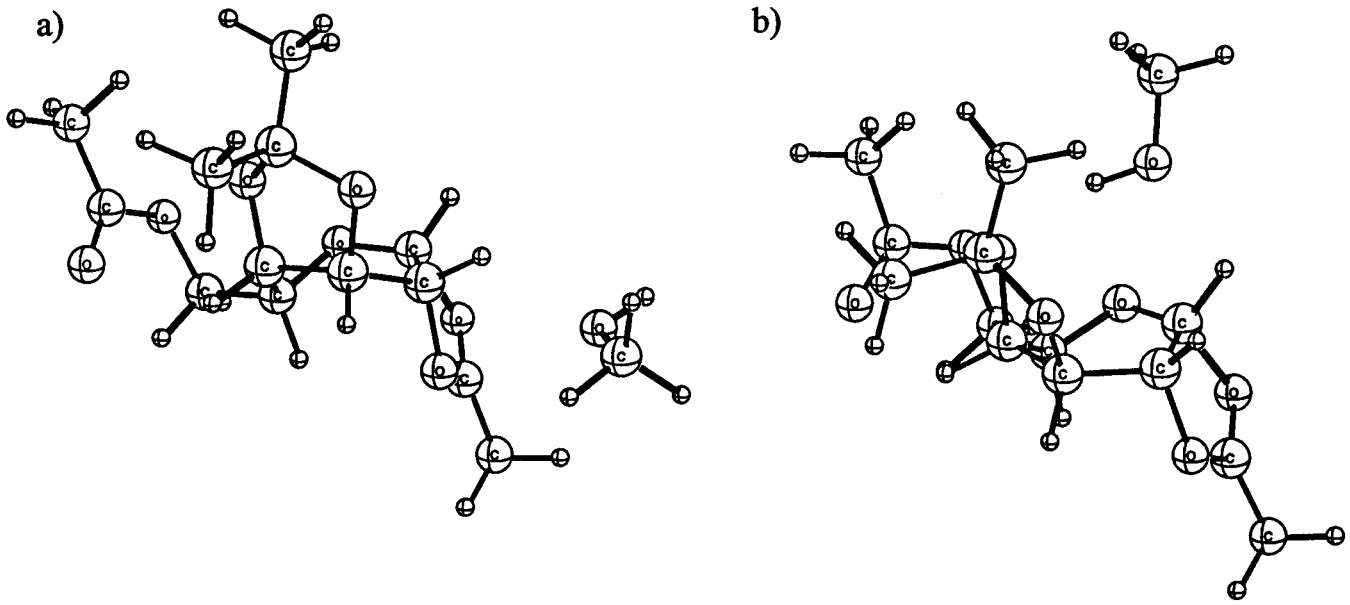
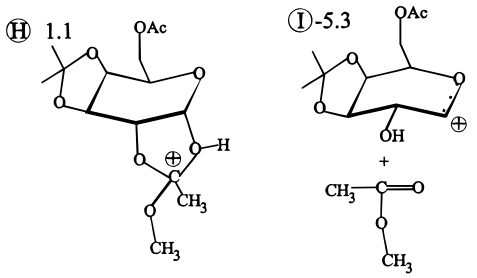


Figure 2. Ball and stick representations of the proposed intermediates (a) **D** and (b) **E**.

Table 3. Selected Calculated Bond Lengths (Å) and Bond Angles (deg) for Proposed Intermediates D to H

intermediate	$O_5C_1O_8$	$C_1C_2O_8$	$O_7C_7O_8$	C_7O_8	C_1O_8	C_1O_7	O_5C_1	C_7O_7	C_7O_2
D	165.1	97.7	95.3	2.79	3.67	1.64	1.33	1.28	1.31
E	79.8	51.6	45.8	5.16	2.87	1.66	1.33	1.27	1.30
F	109.8	58.9	75.7	3.58	1.59	3.71	1.36	1.21	1.39
G	102.0	51.7	123.0	4.25	2.15	3.72	1.28	1.21	1.41
H	138.7	96.9	100.9	1.38	3.33	2.02	1.29	1.47	1.43

Chart 2



D and **F**. Attempts to identify plausible pathways between **D** and **F** are in progress. Both **D** and **E** are shallow minima on the PE hypersurface, and it would be of interest to know the pathways of interconversion. Experimental evidence for such motions in optically active oxonium ions in the gas phase has been reported.[40]

Repeated attempts to find a S_N2 TS connecting **D** or **E** with **F** were unsuccessful by traditional TS optimization methods. Constrained ab initio molecular dynamics simulations have confirmed that the S_N2 reaction would be a high-energy reaction pathway.[41] This result is consistent with the prediction of Dewar and co-workers that S_N2 reactions do not proceed on the α carbon of oxocarbenium ions. A TS of this kind is isoconjugate with a cyclopropenium ion and is antiaromatic.[42] Our preliminary results suggest that the conformational change of the pyranose ring plays a crucial role in the mechanism (i.e., transition from **E** to **F**). We are currently developing methods for the quantitative characterization of such processes.

Conclusions

These calculations strongly support the proposition that the cations derived from the relatively rigid 2,6-di-*O*-acyl-3,4-*O*-isopropylidene-D-galactopyranosyl-(leaving group) donors form precursor ions which allow for neighboring group assistance, cf. **C**. Furthermore, initial nucleophilic attack on such ions is postulated to occur at C_7 with the incoming nucleophile at 90° to the $O_1-C_7-O_2$ plane. Such intermediates have long C_7-O_8 bonds. It is suggested that side reactions such as acyl transfer are kinetic products whereas the desired β-glycosides are the thermodynamic products.

Acknowledgment. The authors would like to thank Dr. L. O. Kononov for some of the references to the Russian literature. They would also like to thank Dr. S. Immel for providing the Fortran code for the program to convert Cartesian coordinates to Cremer−Pople parameters. Finally the authors would like to thank Profs. H. Paulsen and T. Ogawa for helpful discussions. This is NRC paper 42367.

Supporting Information Available: Tables of Cartesian coordinates of structures **B** to **I** (19 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981041M

(40) Troiani, A.; Speranza, M. *J. Org. Chem.* **1998**, *63*, 1012.
(41) Nukada, T.; Berces, A.; Whitfield, D. M. Unpublished results.
(42) Dewar, M. J. S.; Dougherty R. C. *The PMO Theory of Organic Chemistry*; New York Plenum Pub. Corp.: New York, **1975**; p 263.
(43) Smith, B. J. *J. Am. Chem. Soc.* **1997**, *119*, 2699.