Conformational and electronic effects on the regioselectivity of the glycosylation of different anomers of *N*-dimethylmaleoyl-protected glucosamine acceptors†‡

María L. Bohn,[a] María I. Colombo,[a] Edmundo A. Rúveda[a] and Carlos A. Stortz*[b]

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In a previous paper (Bohn *et al.*, *Carbohydr. Res.*, 2007, **342**, 2522) the relative O3/O4 reactivities of both α- and β-methyl glycosides of *N*-dimethylmaleoyl (DMM) glucosamine acceptors protected at O6 with three different groups were assessed by us, using two glycosyl donors. The α-anomers showed preferential or exclusive substitution at O3, whereas the β-anomers gave preferential or exclusive substitution at O4. A DFT study of analogs of the reported acceptors indicates that whereas the β-anomers carry the DMM ring parallel to the C2–H2 bond for steric reasons, the α-anomers tilt this ring producing a strong hydrogen bond between the H(O)3 and one of the DMM carbonyl groups. In this way, the O3 group becomes more nucleophilic and thus more reactive: both charge and Fukui functions on O3 and O4 in the model compounds support the experimental results. Surprisingly, the previously mentioned hydrogen bond is not the only driving force for the slant of the DMM group: the axial methoxyl group of the α-anomers also plays a role. The ease of rotation around the C2–N2 bond for DMM-protected analogs was assessed with different models. MP2 calculations using higher basis sets yield similar relative energy and charge values to those calculated using DFT.

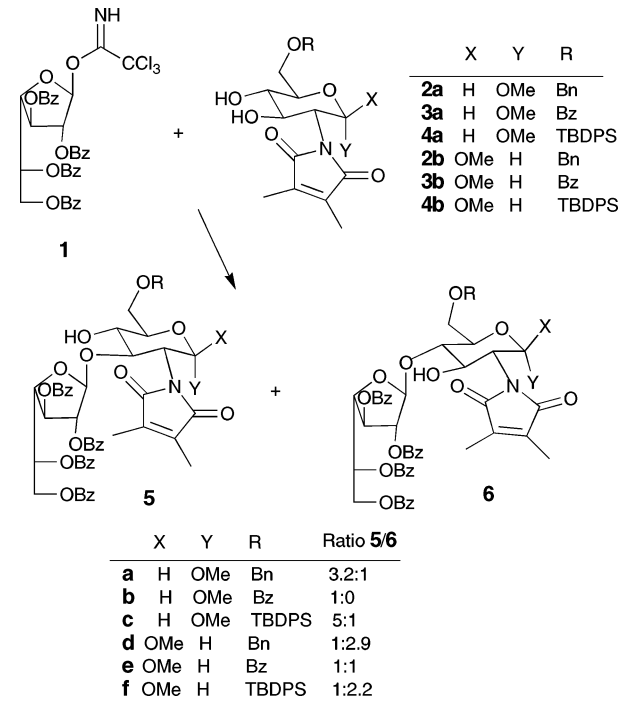
Introduction

Carbohydrate synthetic chemistry often requires the use of specific protecting groups in order to produce selective reactions at one of the secondary hydroxyl groups which often have similar reactivities. However, sometimes it is possible to pursue selective glycosylations of unprotected carbohydrates with two or three free secondary hydroxyl groups, if limiting amounts of glycosyl donors are being used. It has been generally perceived that the O4 of *N*-acetylglucosamine derivatives is a poor glycosyl acceptor.[1] However, for *N*-protected β-D-glucosamine 3,4-diols, Ellervik and Magnusson published a critical analysis[2] of previous publications where regioselective galactosylation has been attempted, showing that mixtures of 1→3 and 1→4 linked disaccharides were actually obtained in most of the reported cases. Most of the regioselectivity observed by these authors showed that the disarmed[3] (*e.g. O*-acetylated) glycosyl donors tended to give exclusively 1→4 disaccharides, whereas armed (*e.g. O*-benzylated) donors gave mixtures with predominance of 3-linked disaccharides. These observations served to develop sequential double-glycosylation procedures (first at O4 and then at O3) avoiding, at least in part, protecting group manipulations.[2,4] Anyway, further publications showed the influence of the protecting groups at N2 and O6 of the glucosamine acceptor on the regioselectivity of the reaction.[5] In a previous paper we have examined systematically the influence of the configuration of the anomeric carbon and the effect of the O6 protecting group on the relative reactivities of both free hydroxyl groups.[6] The benzoyl, benzyl and TBDPS groups, usually employed in carbohydrate chemistry, were used at O6 of *N*-dimethylmaleimido (DMM) 3,4-diols derivatives in reaction with two donors of different reactivity,[7] the furanosyl (**1**) and pyranosyl trichloroacetimidates. Scheme 1 shows that (using the furanosyl donor) both the protecting group on O6 and the anomeric configuration of the acceptor have a strong influence on the observed regioselectivity: α-methyl glycoside acceptors tend to give preferentially O3 substitution, whereas β-anomers gave mainly substitution at O4. The O3 substitution increases also with the O6 protecting group in the order benzyl < *tert*-butyldiphenysilyl < benzoyl, in agreement with their arming/disarming (benzoyl *vs.* benzyl) and steric (TBDPS *vs.* benzyl) effects.[6]

In the present work, we have modeled using the density functional theory (DFT, at the B3LYP/6-31+G** level) different conformers of analogs of the acceptors **2a**, **3a**, **2b** and **3b** where, for the sake of simplicity,[8] the benzyl group was replaced by a methyl group and the benzoyl group was replaced by a formyl group (**7a**, **8a**, **7b** and **8b**, Scheme 2). The relative O4/O3 reaction ability was measured within the framework of DFT using charge and Fukui function considerations.[9,10] In order to make further comparisons, other analogs were also analyzed (Scheme 2); in the simplest ones the rotation around the C2–N2 bond was studied using different modeling approaches. Energies and charges were also recalculated at the MP2/6-311++G**//B3LYP/6-31+G** level, and free energies were calculated in some cases at the B3LYP/6-31+G** level, in order to provide greater accuracy.

[a]*Instituto de Química Orgánica y de Síntesis (CONICET-UNR), Facultad de Ciencias Bioquímicas y Farmacéuticas, Suipacha 531, 2000, Rosario, Argentina*
[b]*Departamento de Química Orgánica-CIHIDECAR, Facultad de Ciencias Exactas y Naturales, UBA, Ciudad Universitaria, Pab. 2, 1428, Buenos Aires, Argentina. E-mail: stortz@qo.fcen.uba.ar; Fax: (5411) 4576 3346; Tel: (5411) 4576 3346*

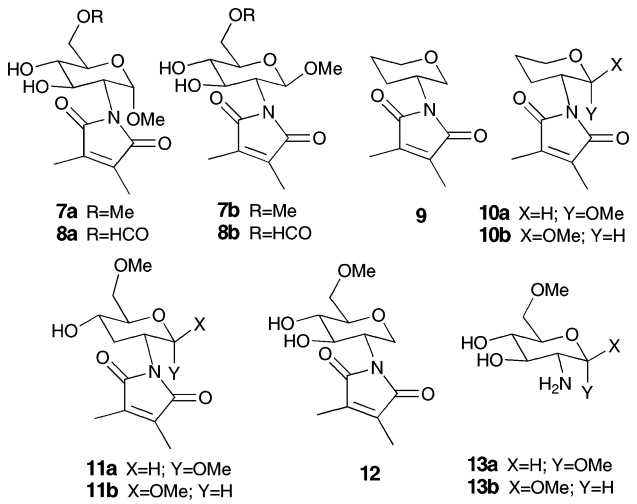
† The HTML version of this article has been enhanced with colour images.
‡ Electronic supplementary information (ESI) available: Six Tables (see text) and the DFT-calculated Cartesian coordinates of all the conformers under study. See DOI: 10.1039/b715847e



	X	Y	R
2a	H	OMe	Bn
3a	H	OMe	Bz
4a	H	OMe	TBDPS
2b	OMe	H	Bn
3b	OMe	H	Bz
4b	OMe	H	TBDPS

	X	Y	R	Ratio **5**/**6**
a	H	OMe	Bn	3.2:1
b	H	OMe	Bz	1:0
c	H	OMe	TBDPS	5:1
d	OMe	H	Bn	1:2.9
e	OMe	H	Bz	1:1
f	OMe	H	TBDPS	1:2.2

Scheme 1



Scheme 2

Results and discussion

Compounds **7a**, **7b**, **8a** and **8b** were submitted to optimization with DFT at the B3LYP/6-31+G** level. Several different orientations of the exocyclic groups were used as starting points, taking also into account the results of a full search with molecular mechanics, further calculations with AM1, and previous experiences with similar compounds.[8] Results showed that up to six conformations are possible for each compound: the remaining starting points converge to one of those, or give high-energy points. One of the conformers has the methoxymethyl group in an *anti* arrangement with O5 (TG, according to the usual nomenclature), thus allowing to establish a hydrogen bond between H(O)4 and O6; the other conformations (up to five) have a positive ω dihedral (GT), and differ by their arrangements of the exocyclic groups at C3, C4 and C6. The first two conformers usually arrange in such a way as to produce a hydrogen bond (H(O)4 to O3 or H(O)3 to O4). The relative energies, geometries and hydrogen bond data are shown in Table 1. There have been controversies about the accuracy of B3LYP/6-31+G** for modeling carbohydrates. Csonka[11] considered it as a reliable method and basis set. However, it was reported that better evaluation of hydrogen bonding[12] or charge[13] can be achieved using higher basis sets (6-311++G**). There were also reported errors in the energy calculations made by B3LYP (and other DFT methods)[14] for alkanes, suggesting that the use of Møller–Plesset perturbation theory gives better results. However, for a study made on carbohydrates, the differences between the B3LYP and MP2 relative energies were indeed small.[15] In this work, we attempted to gain more accuracy by doing single point energy calculations on the previous 17 conformers at the MP2/6-311++G** level. These data are also included in Table 1.

Regarding the geometrical features, the most significant one encountered is the slant observed for the DMM group with respect to the C2–H2 bond for the α-anomers **7a** and **8a** ($\chi_2 = 131$–$135°$, see definition in Fig. 1), not occurring for the β-anomers **7b** and **8b** (χ_2 around 180°). This obliquity allows to produce a strong hydrogen bond between H(O)3 and one of the O=C groups of the maleimido moiety (Fig. 2). This slant has already been observed in preliminary studies using molecular mechanics calculations with compounds containing the *N*-dimethylmaleimido group (like **2a** and **2b**, regardless of the substituent on O6): the value for α-anomers was $\chi_2 = 126°$.

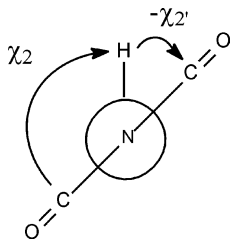


Fig. 1 Newman projection of the N2 (front)–C2 (back) bond, showing the definition of angles χ_2 and $\chi_{2'}$. C1 and C3 are omitted for clarity. The negative sign before $\chi_{2'}$ is used to keep IUPAC sign conventions.

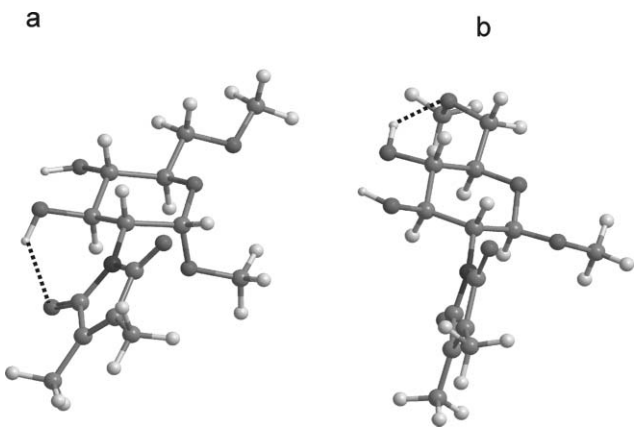


Fig. 2 Molecular representations of the most stable conformers of compounds **7a** (a) and **7b** (b), calculated at the B3LYP/6-31+G** level. The stronger hydrogen bond in each case is indicated by a dotted line.

Table 1 Relative energies (kJ mol^{-1}), torsion angles (°) and hydrogen bonds observed for the main conformers of DMM-protected glucosamine derivatives **7a**, **7b**, **8a** and **8b** calculated at the B3LYP/6-31+G** level. Electronic energies were also recalculated at the MP2/6-311++G** level

									Hydrogen bonds					
Conformer	ΔE^a	ΔG	χ_1	χ_2	χ_3	χ_4	ω	χ_6		d(H·O)/Å	θ/°		d(H·O)/Å	θ/°
7a														
G1	0.0 (0.0)	0.0	−51	132	37	−73	73	−179	HO3···O=C	2.02	136	HO4···O3	2.30	110
G2	4.3 (2.5)	—	−50	131	37	−73	70	−93	HO3···O=C	2.02	136	HO4···O3	2.30	110
G3	6.0 (4.9)	—	−50	132	37	−73	74	86	HO3···O=C	2.02	136	HO4···O3	2.31	110
T1	15.5 (13.7)	13.2	−47	135	22	67	178	−86	HO4···O6	2.05	137	HO3···O=C	2.25	125
8a														
G1	0.0 (0.0)	0.0	−49	131	37	−72	72	−175	HO3···O=C	2.02	136	HO4···O3	2.32	110
G3	5.3 (2.8)	—	−48	131	37	−73	63	92	HO3···O=C	2.02	136	HO4···O3	2.30	110
T1	21.6 (19.3)	19.2	−48	135	23	58	177	−93	HO4···O6	2.21	127	HO3···O=C	2.21	126
7b														
T1	0.0 (0.0)	0.0	49	−179	−67	69	−178	−88	HO4···O6	2.04	136	HO3···O4	2.40	106
G1	4.6 (4.3)	1.2	52	−173	52	−69	73	−179	HO4···O3	2.37	107			
G2	9.0 (6.6)	—	49	−173	51	−69	71	−92	HO4···O3	2.38	107			
G3	10.0 (8.3)	—	52	−172	53	−68	72	85	HO4···O3	2.39	107			
G4	10.2 (11.3)	—	50	180	−62	35	74	−177	HO3···O4	2.42	105			
G5	13.8 (13.7)	—	47	180	−62	34	72	−91	HO3···O4	2.42	105			
8b														
G1	0.0 (0.0)	0.0	51	−173	51	−68	72	−176	HO4···O3	2.40	106			
T1	3.3 (3.1)	5.7	48	−179	−65	61	−179	−97	HO4···O6	2.20	127	HO3···O4	2.40	106
G3	4.4 (1.2)	—	51	−173	51	−69	62	88	HO4···O3	2.38	107			
G4	5.7 (7.0)	—	49	180	−60	27	71	179	HO3···O4	2.45	104			

[a] In parentheses, energy calculated at the MP2/6-311++G**//B3LYP/6-31+G** level.

However, it was also found that in molecular mechanics calculations this obliquity diminishes as the dielectric constant is raised (around 134° for $\varepsilon = 3$ and 166° for $\varepsilon = 80$). For the DFT calculations (Table 1), only two strong hydrogen bonds were encountered, as can be judged by the hydrogen-acceptor distances and the angles: (a) those between H(O)4 and O6, only occurring for the **T** conformations, and (b) those between H(O)3 and the O=C, occurring for the α-anomers, but by far stronger for **G** conformations than for **T** conformations (Table 1). As expected, in the β-anomers, where the only strong hydrogen bond which can be established is that between H(O)4 and O6, more stable **T** conformations are produced, whereas these conformations are less important in α-anomers (Table 1). Besides, the TG conformation (**T1**) appears to be more important in 6-*O*-methyl derivatives than in 6-*O*-formyl derivatives (Table 1), as expected considering that the higher electron-withdrawing effect of the formyl moiety leaves O6 less prone to produce a strong hydrogen bond. The **T1** conformation is thus the most stable for compound **7b**. There are also less important hydrogen bonds between the hydrogens on O4 and O3. Although controversial, a series of recent papers by Klein[16] indicated that such interactions on vicinal oxygen atoms should not be called "hydrogen bonds" neither from the topological point of view nor according to some experimental data. The longer distances and smaller angles observed (Table 1) agree with the lower importance of those interactions. The application of modeling in the presence of a solvent (chloroform) by the polarizable continuum method (PCM)[17] gave a similar picture: for α-linked compounds (**7a** and **8a**) **T1** conformations appeared better solvated than **G1** conformations, but just by 0.7–2.4 kJ mol^{-1}, keeping still **T1** as a high-energy conformation. For the β-linked compounds (**7b** and **8b**), the **T1** conformations (which showed stronger hydrogen bonds) appeared *less* solvated than the **G1** conformations, by 1.3–2.2 kJ mol^{-1}, a difference not enough as to change their order of stabilities. The energies determined by DFT or by using MP2 at a higher basis set level gave very similar results (Table 1), although slight differences were encountered: the **G1** conformations appear less stabilized than the remaining ones for compounds **7a** and **8a** (by 1.1–2.5 kJ mol^{-1}), whereas **G2** and **G3** appear better stabilized than the remaining ones (by 1.4–3.5 kJ mol^{-1}) for compound **8a** and **G3** for compound **8b** (by 3.0–4.5 kJ mol^{-1}). For the latter compound, it was found the only change in order of stabilities of different conformers, working with B3LYP and MP2 (Table 1).

Free energies were also calculated (at the B3LYP/6-31+G** level) for conformers **G1** and **T1** of the four compounds (Table 1). It was pointed out that although hydrogen bonding causes a decrease in strain energies, an opposite trend might be shown for the other free energy terms (zero-point energy, change in vibrational enthalpy from 0 to 298 K, and the entropic term).[18] This is probably caused by the expected loss of entropy upon the formation of the hydrogen bond, and by an increase in enthalpy by the zero-point energy correction.[18,19] The present results follow the expected relationships: in α-anomers **G1** and **T1** (both with strong hydrogen bonds) show small effects for calculating free energies (Table 1). By disclosing each term (see ESI,‡ Supplementary Table 1) it is shown that vibrational enthalpic effects are similar, whereas the entropic factor favors the **T1** compound, suggesting that the H(O)3···O=C hydrogen bond (stronger in **G1**) appears to be more important than the H(O)4···O6 hydrogen bond. For β-anomers, on the other hand, the **T1** conformers, strongly hydrogen-bonded, appear to be relatively less favored than **G1** when free energy determinations are made (Table 1). Both zero-point energy and vibrational entropy (see ESI,‡ Supplementary Table 1) contribute to this effect, as expected.[18,19]

The relative reactivity of O3 and O4 of compounds **2a**, **2b**, **3a** and **3b** was studied in reactions with furanosyl and pyranosyl donors.[6] It has been shown that compound **3a** reacts exclusively through its O3 with the galactofuranosyl donor **1**, whereas **2a** gives a predominance of O3 over O4 (3.2 : 1). On the other hand, in **3b** O3 and O4 react at a similar rate (final ratio 1 : 1), and in **2b** a higher reactivity of O4 is observed (2.9 : 1).[6] Qualitatively, the higher reactivity of O3 with respect to O4 in α-anomers might be explained in terms of the hydrogen bond between H(O)3 and the carbonyl oxygen of the tilted DMM ring observed for the analogs **7a** and **8a**, which does not appear for the β-anomeric acceptors. On the other hand, the relatively higher reactivity of O3 in benzoylated compounds with respect to the benzylated ones when keeping the remaining conditions identical (*i.e.* **3b** *vs.* **2b** and **3a** *vs.* **2a**) can be explained in terms of the higher electron-withdrawing capacity of the former substituent, thus decreasing the stability of the conformers leading to a strong hydrogen bond between H(O)4 and O6. The calculations (Table 1) showed exactly this trend, by making the **T** conformation less stable for the 6-*O*-formylated **8b** analogs than for the 6-*O*-methylated ones **7b**.

In order to produce a more quantitative description, the net charges of atoms O3 and O4 were determined for each of the conformers shown on Table 1. The most usual description of charge is that made by Mulliken, but other fits to the electrostatic potential were made as those originated in the Merz–Singh–Kollman scheme (MK),[20] the CHelp scheme,[21] and the CHelpG scheme.[22] In several systems it was shown that the electron density distribution can be useful to describe reactivity: the site with maximum net charge will be the one preferably attacked by a hard electrophile.[23] However, when in the application of the hard and soft acid and base principle (HSAB), the interaction between nucleophile and electrophile corresponds to a soft–soft interaction,[9,23] another numerical descriptor is needed. One of the more common descriptors for soft–soft interactions, is the Fukui function, related to the electron density in the frontier molecular orbitals HOMO (for electrophilic attack) and LUMO (for nucleophilic attack).[9,10] In this work, the condensed-to-atom Fukui functions for electrophilic attack on O3 and O4 were calculated considering the difference in charge distribution of the ground molecule and that of the radical cation,[10] using the different charge assignments mentioned above. Results for the different conformers are shown as ESI‡ (Supplementary Tables 2 and 3). After Boltzmann-averaging, the results corresponding to each compound were generated (ESI‡ Supplementary Table 4). The plot of the experimental rate on O4/O3 *vs.* the charge and Fukui function relationships is shown on Fig. 3. It can be appreciated that the experimental rate relationships parallel quite well the theoretical charge relationships. By using B3LYP charges (Fig. 3(a)), the CHelp scheme gives the best results, whereas using MP2 charges, the Mulliken population calculations yielded the best results (Fig. 3(b)). Other schemes also worked, but less sharply. On the other hand, the Fukui functions show a more erratic behavior, especially for compound **2a**/**7a** which gives a

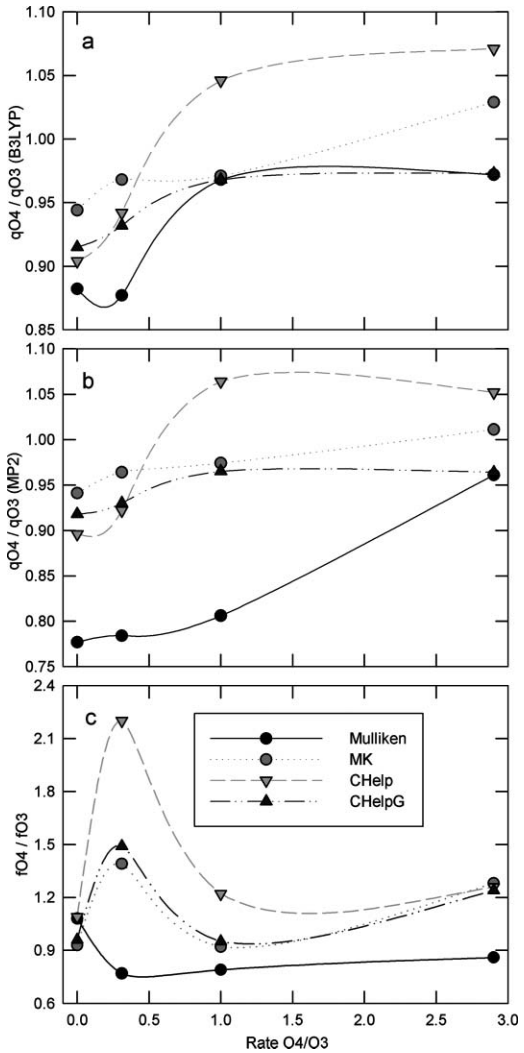


Fig. 3 Plots of charge and Fukui functions relationships calculated on O3 and O4 for **7a**, **7b**, **8a** and **8b** against the experimental rates on these oxygen atoms for the analogs **2a**, **2b**, **3a** and **3b**: (a) using DFT charges; (b) using MP2 charges; (c) using DFT Fukui functions.

maximum value of Fukui function using the CHelp, CHelpG and Merz–Singh–Kollmann charge schemes, and a minimum value using Mulliken analysis. In any case, the behavior of the other three compounds may be an indication that the reaction is proceeding through a hard–hard interaction, as we had already shown,[8] thus suggesting that in these systems the determination of the net charges at the reaction sites is useful to predict their reactivity.

The higher O4 reactivity of β-anomers has been already reported for acceptors with D-*galacto* configuration,[24] and explained in terms of the higher basicity of O5 in these anomers (produced by an *endo*-anomeric effect) generating a strong hydrogen bond with H(O)4. However, for equivalent D-*gluco* acceptors with no possibility of such hydrogen bond arrangement, the β-anomers also showed higher O4 reactivity (though less pronounced than that for the *galacto* counterparts). The explanation given for the reported example indicated that the above mentioned higher electron density on O5 of β-anomers was generating a higher electron density on C4 by delocalization of the n electrons of O5 by the σ* orbital of the C4–C5 bond.[24] Although the discussion of the charges of the ring atoms is made later, it seems to be originated by the conformational differences between the DMM group in the α- and β-anomers and not by the anomeric configuration itself (see below).

Which is the driving force for tilting the DMM group in α-anomers? Why can not the β-anomers tilt the DMM group in the same manner? We have first tried to understand how the rotation of the DMM group affects the energy in a simpler molecule, like the tetrahydropyran analog **9** (Scheme 2). By DFT calculations, the minimum energy corresponds to a χ_2 of 179.3° ($\chi_{2'} = 0.9°$, see Fig. 1), *i.e.* the DMM group parallel to the C2–H2 bond. The complete energy surface was scanned not only using the DFT method, but also molecular mechanics (MM3) and a semiempirical method. Results are shown on Fig. 4(a). The plot indicates clearly that the parallel arrangement ($\chi_2 = 0$ or 180°) gives rise to the minimum energy whereas, as expected, the maximum energy is achieved when the DMM ring appears perpendicular to the C2–H2 bond ($\chi_2 = \pm 90°$), reaching to a difference in energy of almost 24 kJ when calculated by the DFT method and less than 12 kJ by AM1. Furthermore, the close-to-planar DMM ring becomes highly deformed when deviations from the parallel arrangement appear, as indicated by the lower plot of Fig. 4(b), for which deviations of almost ±30° occur from the expected value of the addition of the absolute values of χ_2 and $\chi_{2'}$ (180°, Fig. 1). The deviation of $\chi_{2'}$ is also greater when using DFT, as by molecular mechanics the degree of deviation was lower

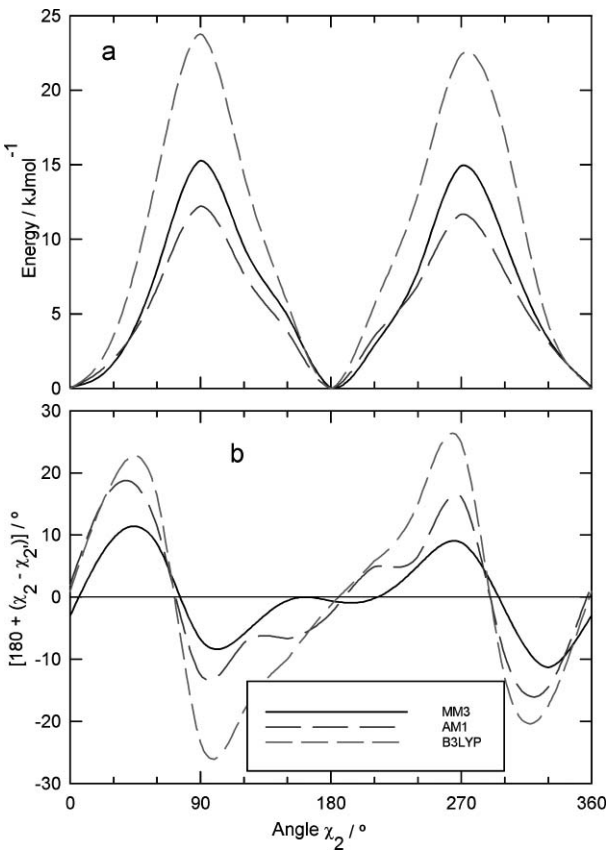


Fig. 4 (a) Rotational profiles around the C2–N2 torsion (carbohydrate nomenclature, expressed as χ_2) for compound **9**, calculated at different levels; (b) variation of the $\chi_{2'}$ angle with the expected value ($180° - \chi_2$) around the profile.

than 10°. These results showed that the preferred conformation of the DMM group, just based on steric grounds should be that close to $\chi_2 = 180°$ when no substituent appears on C1. When the same calculations were carried out with **10a** and **10b** (1-methoxy derivatives of **9**), for the β-substituted compound **10b**, χ_2 is close to parallel (−171°), whereas for the α-substituted compound **10a**, the DMM group appears tilted ($\chi_2 = 158°$) even if no hydroxyl group is present in C3. The tilting in β-anomers is highly unfavorable: a simple inspection of molecular models shows that the equatorial O1 of β-anomers gets too close to one of the oxygens of the carbonyl groups when the DMM group is rotated well out of its parallel arrangement. Scanning of the energy surface of **10a** and **10b** against the χ_2 angle reflect these assertions (Fig. 5(a)): **10b** shows a curve similar to that of **9**, but of higher amplitude, suggesting that the equatorial methoxyl group not only allows the parallel conformation of DMM, but also that it discourages any tilting. The rotation profile for **10a** shows the minimum shifted from $\chi_2 = 180°$, as expected. The dihedral angle appears to be more "flexible" (the amplitude is smaller), and the curve becomes more complicated, as a secondary minimum with higher energy appears. Furthermore, in order to produce some tilting in **10b**, a severe deformation of the $\chi_{2'}$ angle is produced (Fig. 5(b)).

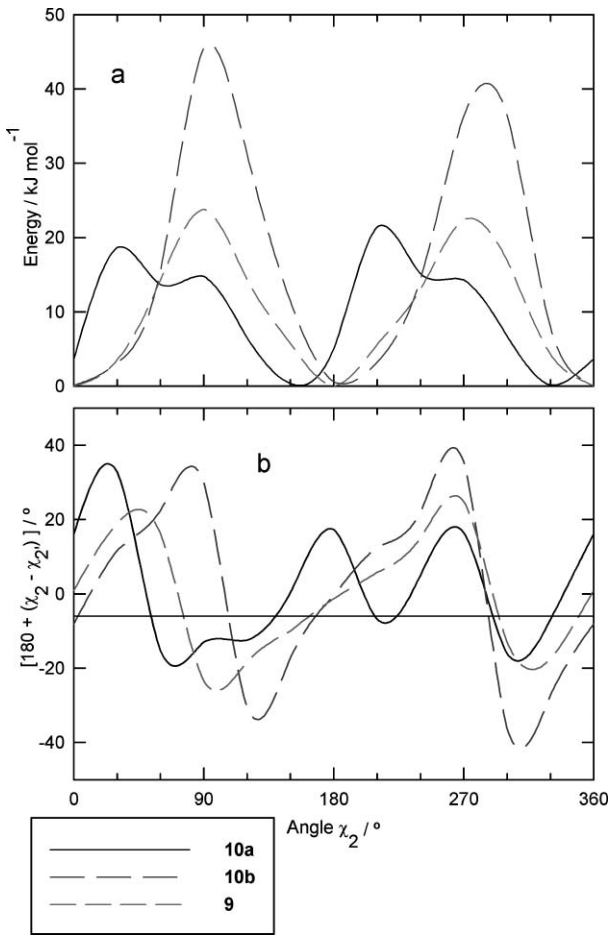


Fig. 5 (a) Rotational profiles around the C2–N2 torsion (carbohydrate nomenclature, expressed as χ_2) for compounds **9**, **10a** and **10b** calculated with DFT; (b) variation of the $\chi_{2'}$ angle with the expected value ($180° - \chi_2$) around the profile.

Table 2 Relative energies (kJ mol^{-1}) and torsion angles (°) observed for the main conformers of DMM-protected glucosamine derivatives **11a**, **11b** and **12** calculated at the B3LYP/6-31+G** level. Electronic energies were recalculated at the MP2/6-311++G** level (in parentheses)

Conf.	ΔE	ΔG	χ_1	χ_2	χ_3	χ_4	ω	χ_6
11a								
T1	0.0 (0.0)	—	−48	158	—	70	180	−87
G1	6.2 (6.3)	—	−52	158	—	−71	73	−179
11b								
T1	0.0 (0.0)	—	50	−171	—	68	−179	−87
G1	7.9 (8.3)	—	52	−171	—	−64	73	−179
12								
T1	0.0 (0.0)	0.0	—	172	57	70	−179	−88
G1	5.4 (8.7)	5.1	—	128	37	−72	74	−178
G1′	8.7 (10.3)	3.3	—	176	45	−70	74	−178

In order to confirm the answers to the questions which started the previous paragraph, we have modeled some analogs of **7a/7b** missing the O3 (**11a/11b**), or the O1 substituents (**12**, Scheme 2), trying to focus in the two most important arrangements, equivalent to the **G1** and **T1** conformations. Results are shown in Table 2. As expected, on **11b** the lack of O3 does not change much the pattern, with the **T1** conformation as preferential, and the **G1** conformation less important. On the other hand, with **11a**, where the strong hydrogen bond between H(O)3 and the carbonyl group is not feasible, the **T1** conformation becomes preferential, but there is still an important **G1** conformation. Both of them carry a partly tilted DMM group (Table 2). The slant (158°), as occurs with **10a** is intermediate between that observed for **7a** (132°) and **7b** (∼180°). In any case, these facts indicate that the tilting of the DMM group in α-anomers is not driven only by the hydrogen bond with H(O)3, but that other steric factors occur. The calculations made for compound **12** (lacking the C1 substituent, Table 2) confirm that the presence of the α-methoxyl group on C1 is not just allowing the DMM group to tilt, but it is also favoring it: the most stable conformer for **12** is **T1**, with an almost parallel DMM. However, two **G1** conformations of slightly higher energy are found: one with a tilted DMM group (hydrogen bond minimum) and another (**G1′**) with a parallel DMM group (steric minimum). If the α-methoxyl group would not have any influence in tilting the DMM group, the **G1** conformation should have been a global minimum, and **G1′** should have not existed, as occurs with **7a**. However, some influence of the remaining exocyclic groups exist: attempts to minimize a "**T1′**" conformation, with a tilted DMM group finally gets to the current **T1** conformation. Free energy calculations (Table 2) also support this conclusions: the **G1′** minimum (steric) becomes relatively favored with respect to **T1** and **G1** (with hydrogen bonds). Both zero-point energy and entropic effects (see ESI,‡ Supplementary Table 1) contribute to the 5 kJ difference between electronic and free energy calculations.

The Mulliken population analysis of the different conformers of compounds **7a/8a** and **7b/8b** were calculated (see ESI,‡ Supplementary Tables 5 and 6). Fig. 6 shows graphically the difference in charge for each ring atom. An odd/even alternating feature was observed: the electron density is higher for the β-anomers on C2, C4 and O5, whereas it is higher for the

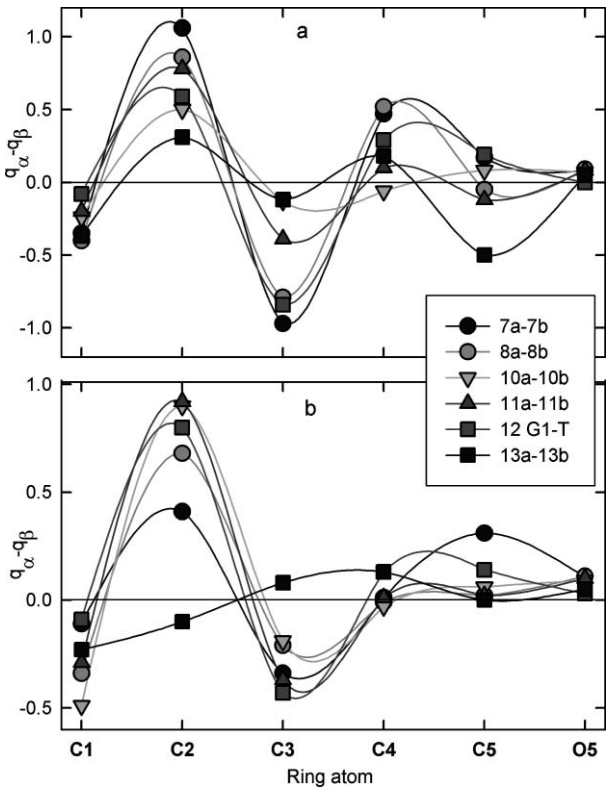


Fig. 6 Plots showing the difference in charge (Mulliken) between the α- and β-anomers (or **G1** and **T** conformers for **12**) for each of the ring atoms of the compounds indicated. The upper plot was calculated by B3LYP/6-31+G**, the lower plot by MP2/6-311++G**//B3LYP/6-31+G**.

α-anomers on C1 and C3. The electron density on C5 is absolutely dependent upon the conformation of the C5 substituent (**G** or **T**). The dependence of the charge on the anomeric character is much higher on the ring carbon atoms than those observed on O1, O3 or O4, but still can be helpful in understanding why α-anomers show higher O3 reactivity and β-anomers show higher O4 reactivity, by the way of the carbons to which they are attached to. The comparison with the electron density calculated for the different conformers of **12** or those of **13** (not having the DMM group) indicate that whereas the difference in charge on C1 and O5 is generated just by the anomeric character, those on C2, C3 and C4 are motivated (at least in part) by the tilting of the DMM group. By the DFT calculation, C2 shows a much higher electron density on β-anomers than on α-anomers with a tilted DMM group (difference 0.9–1.1). The difference in electron density between the compounds with a free amino group **13a** and **13b** are much lower (0.3, Fig. 6), whereas for the compound with no anomeric substituent (**12**), the conformer with non-tilted DMM has a higher electron density than those for a tilted DMM (difference 0.3–0.6), suggesting that the tilting motivates (at least in part) the decrease in electron density. A similar pattern occurs for C3 and C4: the values for the **G1** conformer of **12** (with a tilted DMM group) appear closer to those of the α-anomers with a tilted DMM group **7a** and **8a**, whereas those for the **G1′** and **T1** conformers of **12** (with a parallel DMM group) are within the range expected for the β-anomers **7b** and **8b**. The difference observed between the electron density on C3 and C4 for the α- and β-anomers of the glucosamine derivative **13** are almost negligible (Fig. 6). The charge distribution on compounds **10** and **11** agrees with the previous discussion. Calculations made with MP2 gave different numerical values but led to the same conclusions.

Calculations also indicate that the hydrogen bonding between H(O)3 and the carbonyl group in α-anomers appears to be a stabilizing factor for these anomers: in compounds **7a/7b** and **8a/8b** the α-anomer is 4.8–9.7 kJ mol^{-1} more stable than the β-anomer. Solvent modeling (PCM) in chloroform reduces this difference to 2.6–5.9 kJ mol^{-1}. MP2 calculations stretch the difference to 7.4–11.8 kJ mol^{-1}. However, for the compounds lacking O3, like **10a/10b** and **11a/11b**, the β-anomer is 6.1–6.6 kJ mol^{-1} more stable (2.4–2.7 kJ mol^{-1} by MP2).

Computational details and nomenclature

Quantum mechanical calculations were performed using Gaussian 98 W (version 5.2, revision A-7) with standard basis sets and default minimization methods and termination conditions.[25] In order to determine the best starting points for the QM calculations, a full search of the rotamers made by changing in turn all the exocyclic groups was done with MM3(92) (QCPE, Indiana University, USA).[26] The parameters for this force-field were modified as the MM3(2000) version in the O–C–C–O and O–C–O–H torsional parameters, O–H bonding parameters and C–H electronegativity correction.[27] Some of the main conformers were also submitted to an AM1 calculation[28] in order to find out starting points for the QM calculations. The DFT calculations were made at the B3LYP/6-31+G** level, starting with several different geometries around the exocyclic moieties on C3, C4, C5 and C6. This level of basis set was considered to yield good results on carbohydrates,[11] although it has been the matter of controversies (see above). The determination of net charge attributed to each atom was made by several methods, including the regular Mulliken analysis, fits to the electrostatic potential according to the Merz–Singh–Kollman scheme,[20] the CHelp scheme,[21] and the CHelpG scheme.[22] The condensed-to-atom Fukui function for electrophilic attack was calculated considering the difference in charge distribution of the ground molecule and that of the radical cation,[10] using the different charge assignments above mentioned. The values of charges and Fukui functions obtained for each atom of all studied conformers of each compound were Boltzmann-averaged (T = 298.15 K). The free energy of solvation was estimated by the polarizable continuum method (PCM, with chloroform as solvent) of Tomasi and co-workers,[17] on the gas-phase geometries obtained by the DFT procedure, *i. e.* with no further optimization. The energies and charges were also calculated at the MP2/6-311++G** level, as single points on the optimum geometries determined by the DFT procedure. Free energies were calculated from the vibrational analysis of the minima, at 298.15 K and 1 atm of pressure, with no special treatment for low-frequency vibrations.

The orientations of the methoxyl anomeric group and hydroxyl hydrogen atoms are indicated by χ_n, defined by the atoms H*n*–C*n*–O*n*–H(O)*n* (n = 3 or 4), or replacing the last atom for the methyl carbon in χ_1. The dihedral χ_2 is defined by the atoms H2–C2–N2–C(=O), whereas $\chi_{2'}$ corresponds to the same relationship but with the other carbonylic carbon of the dimethylmaleimido group (see the Newman projection on Fig. 1). As χ_2 and $\chi_{2'}$ appear to be interchangeable, the non-primed acronym was used (with the

exception of the potential energy surface) for the angle with higher absolute value (Fig. 1). As usual, the dihedral ω is defined by the atoms O5–C5–C6–O6, and χ_6 by the atoms C5–C6–O6–C. The dihedral signs were defined according to the IUPAC conventions: for a dihedral A–B–C–D the sign is positive, when looking to a Newman projection from B towards C, A is rotated clockwise respect to D. For a hydrogen bond, the angle θ is defined as that between donor, hydrogen and acceptor.

For the construction of potential energy surfaces of sugar analogs against an exocyclic angle, this angle was kept fixed at 30° steps, while the remaining coordinates were allowed to relax fully.

Conclusions

The differential reactivities of O3 and O4 towards glycosyl donors for α- and β-anomers of 6-*O*-protected/*N*-dimethylmaleoyl (DMM)-substituted glucosamine derivatives can be explained using state-of-the-art molecular modeling of acceptor analogs. Whereas the β-anomers carry the DMM group parallel to the C2–H2 bond, the α-anomers tilt this group generating a hydrogen bond between H(O)3 and the oxygen of one of the carbonyl groups in DMM. This hydrogen bond enhances the nucleophilic character of O3 and thus its reactivity: a recent experimental work has shown that α-anomers exhibit a higher O3/O4 selectivity than β-anomers. Modeling also explains the effect of the protecting group on O6, diminishing the reactivity of O4 by the way of a higher electron-withdrawing power or by a steric effect. Localized charge computations on O3 and O4 can help to explain the observed differential reactivity trends. This is a new example of computational chemistry as a useful tool not only to determine preferential conformations or energetic relationships, but to predict reactivities and provide comparison with the experimentally determined ones.

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