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DFT/MM modeling of the five-membered ring in 3,6-anhydrogalactose derivatives and its influence on disaccharide adiabatic maps

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ABSTRACT

Different conformations of methyl 3,6-anhydro-4-*O*-methyl-α-D-galactoside (**1**) and 3,6-anhydro-4-*O*-methylgalactitol (**2**) were studied by molecular mechanics (using the program MM3) and by quantum mechanical (QM) methods at the B3LYP/6-31+G** and MP2/6-311++G** levels, with and without solvent emulation. In **2**, where the five-membered ring is free to move, two main stable conformations of this ring were found, identified as North (N) and South (S). The latter appears to be more stable, by either calculation, though the energy difference is reduced when emulating solution behavior. In order to find out the possible influence of a glycosidic bond over its shape, and to explain the marked NMR chemical shift displacements observed by opening of the ring, the adiabatic maps of two disaccharides carrying an analog of β-galactoside linked to O-4 of **1** and **2** were generated. It was shown that the characteristics of the 3,6-AnGal terminal influence the characteristics of the map, especially at lower dielectric constants. On the other hand, different glycosidic angles also promote distinct stable conformations of the five-membered ring, changing from N to S, or even variants. Comparison with experimental results leads to the idea of highly flexible disaccharides, with variable values for both the five-membered ring and the glycosidic angles.

1. Introduction

Conformational analysis of mono- and oligosaccharides can be carried out by either experimental or modeling techniques.[1] When rings are present, their shape is a key factor. Most of the hexoses and pentoses occur naturally as pyranosyl rings,[2] with chair forms dominating their conformer populations. The occurrence of sugars as five-membered rings is less common, although many furanosyl forms of sugars have biological importance.[3] However, the conformational features of five-membered rings are not as simple as those of their six-membered counterparts: cyclopentane is not flat,[4] but puckered, and it experiences a facile and rapid interconversion of conformers with similar energies (pseudorotation).[5] Substituted five-membered rings show different degrees of puckering and altered rotational barriers, leading to some puckered conformations more stable than others. Computer-aided calculations showed only the presence of a few conformational minima in those substituted rings, but keeping a low-energy barrier of pseudorotational pathway.[6] In many cases, these theoretical calculations were confirmed by experimental determinations, especially three-bond NMR coupling constants.[6] Each of those stable envelopes or twist conformations can be identified by their Cremer–Pople puckering parameters Q and Φ.[7,8]

A rather rigid sugar as 3,6-anhydrogalactose (3,6-AnGal) is a key constituent of some seaweed polysaccharides.[9] It is a bridged bicyclic system carrying at the same time a six- and a five-membered ring. Only a few theoretical calculations have been carried out for methyl 3,6-anhydro-α-galactopyranoside.[10,11] Both rings appear to be constrained given their lack of mobility. However, for the six-membered ring it has been shown that the $^{1}C_{4}$-system observed in crystal structures, sometimes (as in 3,6-An-β-D-Gal derivatives) a boat-like conformation ($B_{1,4}$) is obtained in nonpolar solvents,[12] as occurs with other bicyclo[3.2.1]octane systems.[13] In our laboratory, the puckering of different 3,6-anhydroglycosides was studied by HF, DFT, and MM methods.[11] In such systems, the five-membered ring remains constrained to a conformation close to ^{4}E. However, when a 3,6-anhydrogalactoside is hydrolyzed, the six-membered ring is opened to alleviate the strain: in water, the hydrated aldehyde is more stable than the pyranose form.[14] The resulting products and their derivatives after reduction or other reactions show only a five-membered ring which is free to find its most stable conformation.

Herein, the geometries and energies of the main conformers of 3,6-An-4-*O*-Me-D-Galol (**2**, Fig. 1) studied by MM (MM3 at different dielectric constants) and QM (at B3LYP/6-31+G** and MP2/6-311++G** levels) methods, with and without solvent emulation

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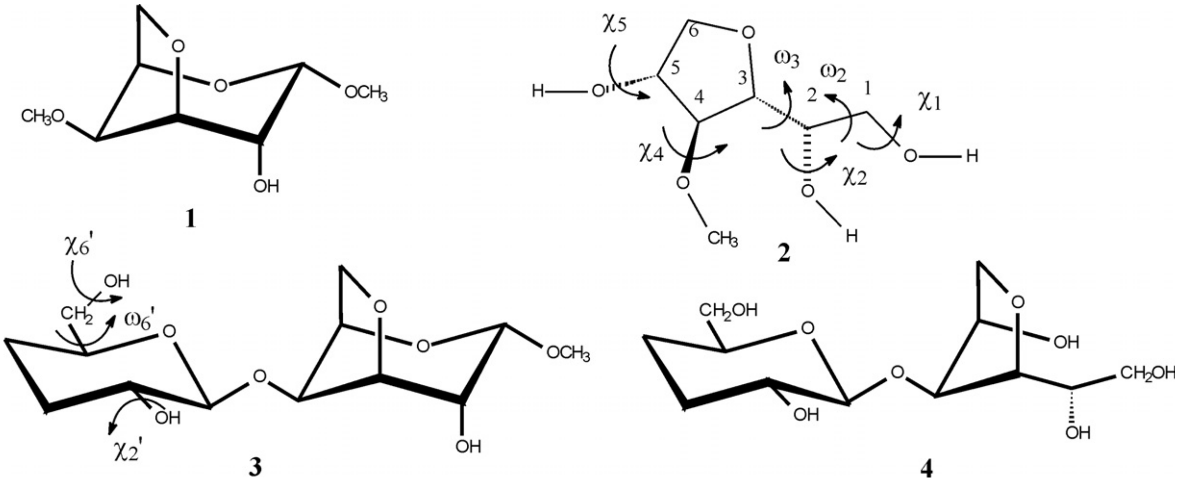

Figure 1. The compounds studied in this work.

are presented. Besides, the adiabatic maps of two disaccharides with variants of 3,6-AnGal at their reducing ends were also studied by MM3: 3′,4′-dideoxy derivatives of the α-methyl glycoside of carrabiose and carrabiitol (**3** and **4**, Fig. 1). Comparisons with experimental data and calculated NMR tensors are also provided. The present results show how the combination of experimental data and accurate calculations can help to understand the conformational features of flexible systems like those occurring after reduction of a 3,6-AnGal moiety.

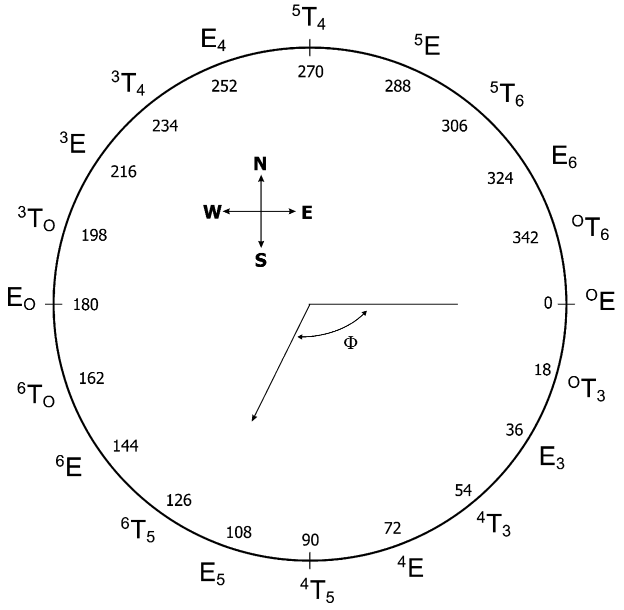

Figure 2. Perfect envelopes and twists for the five-membered ring in 3,6-anhydrogalactitol and derivatives, with their Cremer–Pople puckering parameter Φ.

2. Methods

2.1. Computational details and nomenclature

MM calculations were carried out using the program MM3(92) (QCPE, Indiana University, USA) developed by Allinger et al.,[15] with some parameters modified as the MM3(2000) version.[16] The dielectric constant was held as indicated in Section 3. The termination conditions were tightened 250 times from the default ones. QM calculations were performed using GAUSSIAN 98W (version 5.2, revision A-7) with standard basis sets.[17] When indicated, the free energy of solvation was estimated by the polarizable continuum solvation model (PCM, with water as solvent) of Tomasi and coworkers,[18] after optimization of the gas-phase geometries.

The orientations of exocyclic angles in **2** and **4** are indicated by χ_n, defined by the atoms H-*n*–C-*n*–O-*n*–H(O)-*n*, for *n* = 2 and 5, and replacing the last atom for the CH_3 in χ_4. The angle χ_1 is defined by atoms C-2–C-1–O-1–H(O)-1. The angles ω_2 and ω_3 are defined by the atoms C-3–C-2–C-1–O-1 and H-3–C-3–C-2–C-1, respectively. For **3** and **4**, the orientations of hydroxyl hydrogens are also indicated by χ_n, defined by the atoms H-*n*–C-*n*–O-*n*–H(O)-*n*, $\chi_{6'}$ is defined by the atoms C-5′–C-6′–O-6′–H(O)-6′, and $\omega_{6'}$ by the atoms O-5′–C-5′–C-6′–O-6′ (see Fig. 1). Their values are described by a one-letter code:[19] *S* for angles between −30° and +30°, *g* for 30–80°, *T* for angles with absolute value larger than 150°, *G* for angles between −30° and −80°, and *E* for angles between −80° and −150°. The puckering in each structure was determined from the Cartesian coordinates using a home-made program. The relationship between the Cremer–Pople Φ parameter[7] and the actual ring conformation[1] is shown in Figure 2. In order to obtain the minimal conformations of **2** with MM3 at each dielectric constant, a preliminary study indicated that two coarse conformations of the five-membered ring were possible (N with Φ values around 270° and S with Φ values around 120°, Fig. 2), whereas attempts to start from other shapes of the ring usually converge to either N or S, as occurs with furanosic sugars.[8] Then, for each of them, a full conformational search was carried out with all the 729 possible starting structures with modified exocyclic angles. The four structures with lower energies for each ring conformation and ω_3 angle were tabulated, and the sixteen structures obtained at $\varepsilon = 1.5$ were submitted to the DFT vacuum calculations. For the DFT/PCM calculations, these 16 structures and the additional 16 obtained by MM calculations at $\varepsilon = 80$ were used as starting points. Only the four most stable conformers in each category were tabulated. For **1**, a full search of the 27 possible conformers was made with MM3. The two most stable ones were submitted to a DFT calculation. The glycosidic dihedral angles ϕ and ψ of **3** and **4** are defined by the atoms O-5′–C-1′–O-1–C-4 and C-1′–O-1–C-4–C-5, respectively. The vicinal coupling constants were calculated with the Karplus equation using the parameterization of Haasnoot et al.[20] The conformations are described as ‘perfect’ *E* or *T* when their values are no more than 4° apart from their defining values (e.g., $^5T_4$ for Φ between 266° and 274°), with two descriptions separated by a slash when intermediate between both (e.g., $^5T_4$/^5E for Φ between 278° and 280°), and with both separated by an arrow when closer to one of both (e.g., ${}^{5}T_{4}\rightarrow{}^{5}E$ for Φ between 275° and 277°).

2.2. Generation of disaccharide energy surfaces

The maps were generated following the general procedure already described,[21] using a 20° grid. Details can be found as Supplementary data.

2.3. Generation of the energy versus Φ surfaces

The general procedure for generating 441 conformers with different puckerings was followed,[8,11,22] using MM3. For compound **2**, the procedure was repeated with the sixteen most stable conformers (see later) at $\varepsilon = 1.5$ and $\varepsilon = 80$. For compound **4**, the procedure was followed separately starting from conformers with the glycosidic linkage in the **A** and **B** regions. Exocyclic combinations leading to the most stable conformer with different shapes of the five-membered ring (see Table 4) were studied, plus those close (up to 0.5 kcal/mol at $\varepsilon = 1.5$, up to four conformers at $\varepsilon = 80$) in energy. In total, six conformers were studied at $\varepsilon = 1.5$ and ten at $\varepsilon = 80$. The final output contained the energies of all the resulting conformers and their Cremer–Pople puckering parameters.[7] In order to construct the energy surface, the data were grouped approximating their Φ values to the nearest multiple of 15°. The lower energy within each Φ range was recorded regardless of the values of Q, actual Φ value, or exocyclic angle distribution.

3. Results and discussion

Methyl 3,6-anhydro-4-*O*-methyl-α-D-galactopyranoside (**1**, Fig. 1) is a highly strained molecule. An MM3 calculation at $\varepsilon = 1.5$ for the most stable structure gives a five-membered ring with puckering parameters $Q = 0.46$ Å and $\Phi = 81°$. Similar results were obtained by a B3LYP/6-31+G** calculation (0.47 Å, 81°) or by MM3 at $\varepsilon = 80°$ (0.47 Å, 79°). The Φ values are close to those of the expected ${}^{4}E$ conformation ($\Phi = 72°$), but directed toward a twist form (${}^{4}T_{5}$, see Fig. 2). Within the pseudorotational cycle, these conformations are defined as South (Fig. 2). The crystal structure of neocarrabiose[23] exhibits a five-membered ring with puckering parameters $Q = 0.45$ Å, $\Phi = 80°$, very close to those determined by the present calculations. Hydrolysis and reduction of **1** lead to **2** (Fig. 1), where a 'free' five-membered ring appears. A full MM3 calculation at $\varepsilon = 1.5$, starting from different rings and exocyclic conformations, originated many different conformers. The four most stable conformers for each ring (S or N) and ω_3 ($g = +$ or $G = -$) conformation (a total of 16) are shown as Supplementary data (Supplementary Table 1). These 16 conformers were optimized by B3LYP/6-31+G** calculations. On grounds of errors found in the energy calculations made by B3LYP (and other DFT methods)[24] for alkanes, suggesting the use of Möller-Plesset perturbation theory, and the proposal of using higher level basis sets,[25] the DFT geometries were submitted to single-point calculations at the MP2/6-311+G** level (Supplementary Table 2). Table 1 indicates the differences in energy between the most stable N and S conformers found by each method.

Table 1
Energy differences (kcal/mol) between the most stable N and S conformers found by each method for 3,6-anhydro-4-*O*-methyl-D-galactitol (**2**), and Cremer–Pople puckering parameter Φ (°) for these conformers and for others with low energy

	$E_N - E_S$	Φ_S[a]	Φ_N[a]	Range of Φ_S[b]	Range of Φ_N[b]
MM3, ε = 1.5	2.09	131	269	113–132	262–285
B3LYP/6-31+G**	4.10	118	263	114–122	263–326
MP2/6-311+G**	5.15				
MM3, ε = 80	0.20	119	271	119–135	263–271
B3LYP + PCM	0.48	119	309	119–171	277–345

[a] Data for the minimum-energy conformation in each region.
[b] Range of values found for all the conformers studied in each region (up to 8, see text).

By either MM, DFT, or HF calculations, the four most stable conformers have lower energies than any of the others (Supplementary Tables 1 and 2), followed by S+ and N− conformers. The difference is larger than 1.7 kcal/mol with MM or HF methods, but is 4.1–5.1 kcal/mol higher when using correlated methods. N+ conformers are always the least stable ones. The S conformers have rings around ${}^{6}E/E_{5}$ conformations, whereas N conformers have more scattered conformations, mostly around ${}^{5}T_{4}$, but reaching extremes up to E_6 ($\Phi = 326°$). Experimental determinations of crystal structures were carried out for some compounds related to **2**, as 3,6-anhydro-1-bromo-1-deoxy-D-galactitol[26] and peracetylated carrabiose dimethyl acetal.[27] The former, with a chemical structure very similar to that of **2**, shows exocyclic angles very close to those of S4− (the minimum after solvent simulation, see below), with puckering parameters of 0.41 Å and 123° (${}^{6}T_{5}$) and a ω_3 angle of −56°, almost identical to those determined by the present calculations. The disaccharide derivative shows puckering parameters of 0.40 Å and 163°, slightly biased toward the West (W, ${}^{6}T_{O}$, Fig. 2), whereas its ω_3 angle is −68°, also within the S− region found with lower energy.

An equivalent exhaustive MM3 calculation was also made at $\varepsilon = 80$ (Supplementary Table 3), leading to a large reduction of the energy differences between conformers: although a slight preference for S conformers appears, the energies are within 1 kcal from each other, making these differences almost meaningless (Table 1). The low-energy conformers from Supplementary Tables 2 and 3 where submitted to a B3LYP/6-31+G** calculation with the inclusion of a solvent simulation (PCM in water), leading to the results shown in Supplementary Table 4. The differences between conformers have once more been largely reduced by the effect of solvent (Table 1), though S− ones appear to be of lower energy. The observed puckering is similar to that observed in vacuum calculations: S rings around ${}^{6}T_{5}$ ($\Phi = 119$–$135°$), with two exceptions around ${}^{6}T_{O}$ ($\Phi = 165$–$171°$), in an almost W location (Fig. 2), as that determined for the crystal structure of acetylated carrabiose dimethyl acetal.[27] The N conformations calculated by MM are around ${}^{5}T_{4}$ ($\Phi = 263$–$271°$), whereas those calculated by DFT/PCM are around ${}^{5}T_{6}$ ($\Phi = 297$–$311°$), with one exception closer to the MM calculation. The NMR three-bond H,H coupling constants for the ring atoms of an analog of **2** (without the 4-*O*-methyl group) in D_2O and of a permethylated analog of **2** (with a carboxymethyl group in C-1) in DMSO were small (<5 Hz),[28] strongly suggesting an S-like shape (expected *J*s <4 Hz) rather than an N shape (all expected *J*s >7 Hz). The experimental values for $J_{H2,H3}$ (4.6 and 5.5 Hz)[28] suggest an equilibrium between an S− conformation (negligible *J*) and an S+ one (large *J*). The energy surface with respect to Φ is shown in Figure 3a. The data at $\varepsilon = 1.5$ show the expected two-minima (N and S) feature, the S one being more stable. At $\varepsilon = 80$ the differences are markedly reduced, and a plateau in the W region appears. The highest energy appears for $\Phi = 0°$ (${}^{O}E$ conformation).

One might expect to see a change in the conformational behavior of the five-membered ring if it is present in a disaccharide, for example, if the 4-*O*-methyl group is replaced by a β-D-galactopyranosyl moiety as occurs in carrageenans.[9] The disaccharide **3** and disaccharide alditol **4** (Fig. 1) contain these structures, but in order to simplify no hydroxyl groups on C-3′ and C-4′ were added, as they are not expected to have large influences on the glycosidic linkage. On the other hand, one might also expect to find out conformational changes around the glycosidic linkages due to the opening of the 3,6-anhydro ring, as in comparing **3** to **4**. The adiabatic map of a compound similar to disaccharide **3** (the free sugar

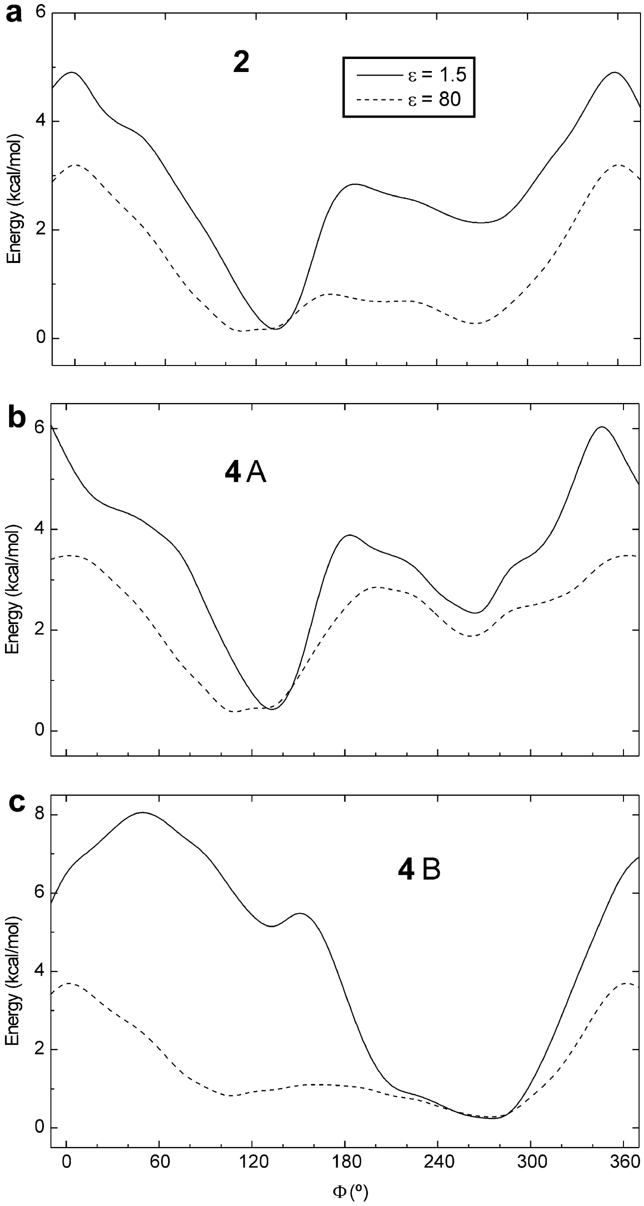

Figure 3. MM3-computed energy versus Φ plot for compounds **2** (a), **4** in the **A** region (b), and **4** in the **B** region (c). The data were binned in 15° intervals (see Section 2).

Table 2
Torsion angles (°), relative strain energies (kcal/mol), and exocyclic angles for the minimum-energy conformations obtained for disaccharide **3**, using the MM3 force-field at two different dielectric constants

Minimum	E_{rel}	ϕ, ψ	Exocyclic torsion angles	
			$\chi_{2'}\omega_{6'}\chi_{6'}$	$\chi_1\chi_2$
ε = 1.5				
A	0.00	−82, 168	GgG	GG
B	1.07	−72, 99	GgG	GG
C	6.42	−70, −47	GgG	GG
ε = 80				
A	0.00	−81, 168	GgT	GG
B	0.63	−90, 77	GgT	GG
C	8.28	−75, −45	GgT	GG
Fiber diffraction[a]		−97, 108 −89, 109 −91, 104		

[a] Fiber diffraction analysis for κ- and ι-carrageenan (Ref. 29).

instead of the methyl glycoside of a dideoxy derivative) was already studied[21] at ε = 3. The ϕ,ψ adiabatic maps (around the glycosidic linkage) of **3** at ε = 1.5 and 80 are shown as Supplementary data (Supplementary Fig. 1), whereas the data for the minima are shown in Table 2. The results are similar to those determined previously for β-carrabiose.[21] Fiber diffraction analysis of polysaccharides containing the carrabiose unit gives rise to a structure with the glycosidic angle within the **B** region,[21] but NOESY determinations indicate that a conformation similar to that of the **A** minimum prevails in solution.[21,30] The adiabatic maps for the disaccharide **4** with an open 3,6-anhydro ring are shown in Figure 4, whereas the data for the minima are shown in Table 3. A notable difference is observed for the map determined at ε = 1.5, where the **B** minimum is more stable than the **A** minimum. This was experimentally reflected in the crystal structure of acetylated carrabiose dimethyl acetal,[27] which shows precisely this arrangement (ϕ,ψ = −92°, 72°). These values are almost identical to those calculated for the **B** minimum at ε = 80, and very close to those calculated at ε = 1.5 (Table 3).

Table 3 also shows that whereas the five-membered ring in both **A** minima has an S conformation (as occurred with the lower-energy conformers of **2**), those corresponding to **B** and **C** minima show an N conformation. This fact is independent of the dielectric constant employed, and thus it is probably produced by torsional effects, and not by dipolar or hydrogen bonding effects. Moreover, the puckering parameter Φ for the five-membered ring was determined for all the points that gave rise to the adiabatic maps of **4**. Some points are only N conformations, others are S, others are intermediate (W, Φ between 145° and 234°), and a few have an N and an S conformer with similar energies (within 0.20 kcal/mol). The distribution of those points is shown in Figure 5. The energy versus Φ surface was also calculated for compound **4** in the **A** and **B** disaccharidic regions. Figure 3b shows that when the glycosidic linkage of the disaccharide is held in the **A** region, the energy pattern is very similar to that of the unsubstituted alditol (cf. Fig. 3a and b). On the other hand, in the **B** region at ε = 1.5, the pattern changes sharply: the global minimum appears in the N region (as previously shown in Table 3), and the other conformations carry very high energies. At ε = 80 though the minimum in the N region also carries lower energies, the differences are very small, especially for Φ between 80° and 280°.

Some conformers in the **A** and **B** minimum-energy regions of **4** carrying the five-membered ring in different conformations were submitted to B3LYP/6-31+G** analysis. Table 4 shows that the main geometrical features of the MM3 minima were kept after DFT minimization. Only slight variations occurred (small shifts in the exocyclic angles, less puckered rings), but the energy differences between the minima were reduced sharply. However, in the **A** region, the S conformer was more stable than the N conformer by either method. The same fact occurred for the **B** region and the N conformer, but always the BN conformer (Table 4) was the most stable one. This is probably due to the strong inter-residue hydrogen bonds between H(O)-5 and O-6′, and between H(O)2′ and O-1, only occurring for BW and BN conformers (Fig. 6). The other conformers only exhibit intra-residual hydrogen bonds, the more relevant being those between H(O)-5 and O-2 (AS and BS), H(O)-2 and O-1 (AS, BS and AN), and H(O)-1 and O-6 (AN). The crystal structure obtained for an analog of **4** corresponds to an acetylated compound,[27] not capable of producing hydrogen bonds, helping thus to explain why it did not reach a BN conformation.

In order to find out if the solution conformation of analogs of **4** is represented by the previous calculations (which indicated an **A** minimum, with the five-membered ring in S conformation), the

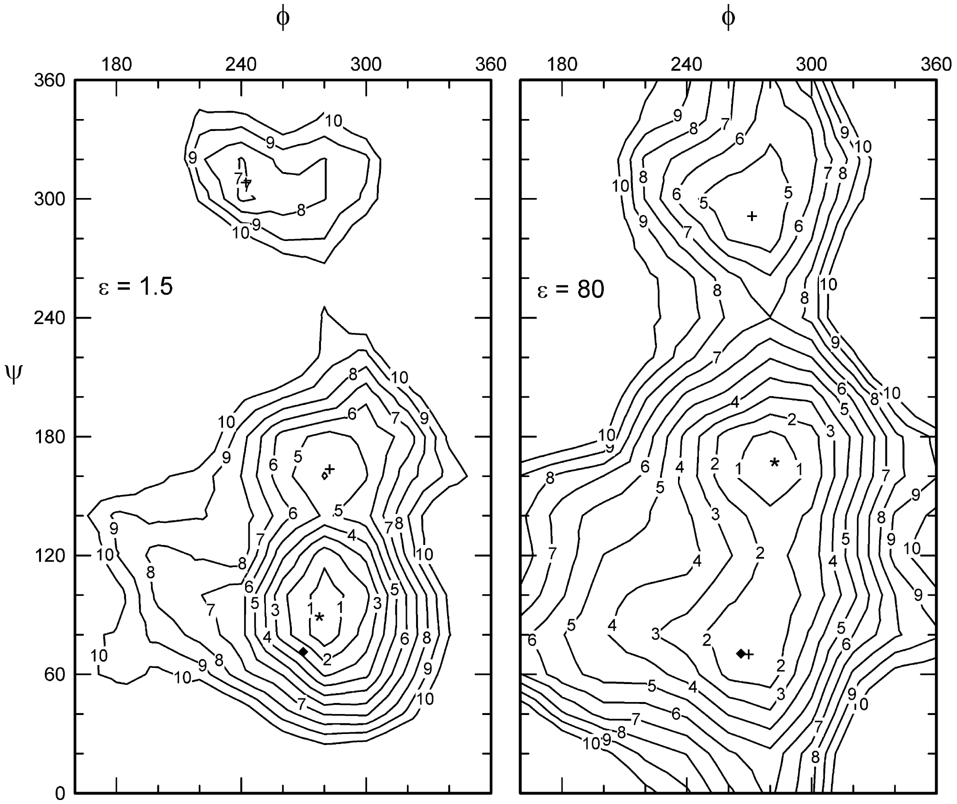

Figure 4. MM3-computed adiabatic ϕ, ψ maps for compound **4** at ε = 1.5 and 80. Iso-energy contour lines are graduated at 1 kcal/mol increments above the global minimum (up to 10 kcal/mol). Symbols: (∗) global minimum, (+) local minimum, (♦) crystal structure of a compound related to **4** (Ref. 27).

Table 3
Torsion angles (°), relative strain energies (kcal/mol), exocyclic angles, and puckering parameters for the minimum-energy conformations obtained for disaccharide alditol **4**, using the MM3 force-field at two different dielectric constants

Minimum	E_{rel}	ϕ, ψ	Exocyclic torsion angles			Puckering parameters		Conformations
			$\chi_{2'}\omega_{6'}\chi_{6'}$	$\omega_2\omega_3$	$\chi_1\chi_2\chi_5$	Q (Å)	Φ (°)	
ε = 1.5								
A	3.86	−78, 165	GgG	TG	TGT	0.40	132	$^6T_5 \rightarrow {}^6E$
B	0.00	−82, 89	GgT	Gg	GgG	0.41	275	$^5T_4 \rightarrow {}^5E$
C	6.36	−118, −52	ggG	Gg	GgG	0.45	273	$^5T_4$
ε = 80								
A	0.00	−79, 166	GgT	Tg	TgG	0.39	119	$^6T_5 \rightarrow E_5$
B	0.85	−90, 72	ggT	Tg	Tgg	0.42	271	$^5T_4$
C	3.71	−90, −67	GgT	TG	TGG	0.43	264	$^5T_4 \rightarrow E_4$
Crystal[a]		−92, 72		−G		0.40	163	^6T_O

[a] Crystal data for acetylated carrabiose dimethyl acetal (Ref. 27). ω_2 is meaningless for this compound.

literature was searched for proper data. The ^{1}H and ^{13}C NMR chemical shifts for κ-carrabiitol are fully reported,[31] but (to the best of our knowledge) no coupling constants were provided. In an agar-like oligosaccharide, Usov and Elashvili reported small coupling constants (<4.5 Hz) for the five-membered ring hydrogens,[32] indicating an S-like conformation. New attempts to determine the coupling constants of κ-carrabiitol were unsuccessful (Navarro and Stortz, unpublished results), given the severe overlapping of signals in the ^{1}H NMR spectrum. The small shift (ca. 0.8 ppm) observed for the δ of C-1 of the β-D-Gal unit when passing from its linkage to a closed 3,6-AnGal to that to a 3,6-AnGalol[31] suggests that both have similar ϕ, ψ angles, as changes in ψ angle are expected to induce a larger chemical shift displacement.[33] Calculations for **3** and **4** at ε = 80 (Tables 2 and 3) have shown that the global minima for both are in the **A** region. The chemical shifts of most of the five-membered ring carbon atoms show a large downfield displacement when passing from a strained 3,6-AnGal system to an open alditol or hydrate.[14,31] The question is: is this displacement originated in a conformational change of this ring? In order to answer this question, we have calculated the ^{13}C and ^{1}H chemical shifts for compound **3** in their **A** and **B** minima, and for compound **4** in the five minima reported in Table 4 (i.e., taking into account different glycosidic angles and different five-membered ring shapes), using the NMR shielding tensors determined by the gauge-independent atomic orbital (GIAO) method.[34] The calculated chemical shifts have shown good predictive capacity not by their absolute values (values relative to TMS were supplied as Supplementary Table 5) but by their differences.[35] Table 5 shows both the observed experimental displacements (when passing from analogs of **3** and **4**) and the calculated ones for each combination of conformations of **3** and **4**. Results confirm some previous predictions: the displacement for C-1′ is compatible with retention of the

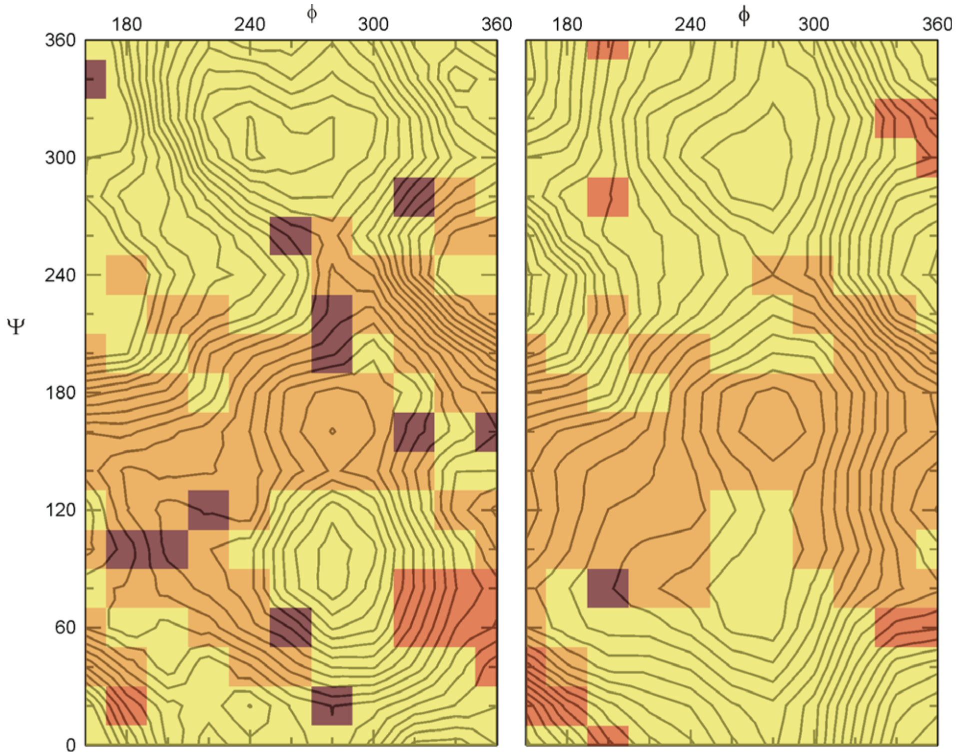

Figure 5. Color-coded shape of the five-membered ring conformation at each grid point, overimposed on the MM3-computed adiabatic ϕ,ψ maps for **4** at $\varepsilon = 1.5$ and 80. Codes: yellow = N conformations (Φ = 234–306°), light orange = S conformations (Φ = 54–144°), dark orange = W conformations (Φ = 145–234°), brown = about the same energy (within 0.20 kcal/mol) for an N and an S conformation.

Table 4
Torsion angles (°), relative strain energies (kcal/mol), exocyclic angles, and puckering parameters for minimum-energy conformations obtained for disaccharide alditol **4** in the **A** and **B** regions, with different shapes of the five-membered ring, using DFT and MM3[a]

	E_{rel}	ϕ, ψ	Exocyclic torsion angles			Puckering parameters	
			$\chi_{2'}\omega_{6'}\chi_{6'}$	$\omega_2\omega_3$	$\chi_1\chi_2\chi_5$	Q (Å)	Φ (°)
BN	0.00 (0.00)	−77, 87 (−82, 89)	−59, 61, −173 (−62, 63, −178)	−55, 64 (−52, 70)	−58, 71, −54 (−55, 63, −54)	0.35 (0.41)	289 (275)
BS	1.49 (4.57)	−65, 98 (−70, 101)	−60, 64, −58 (−61, 63, −54)	−177, −67 (178, −62)	165, −78, −166 (180, −70, −176)	0.36 (0.39)	122 (132)
BW	1.89 (3.59)	−68, 90 (−73, 92)	−61, 62, −54 (−67, 62, −50)	−55, 64 (−51, 71)	−60, 70, 177 (−57, 62, 169)	0.38 (0.43)	189 (200)
AS	2.28 (3.86)	−71, 161 (−78, 165)	−59, 61, −59 (−59, 62, −55)	−177, −67 (178, −62)	165, −78, −165 (180, −70, −174)	0.36 (0.40)	117 (132)
AN	2.39 (5.38)	−44, 178 (−54, −175)	−60, 71, −61 (−60, 68, −47)	−77, −69 (−69, −65)	61, −143, −60 (62, −157, −68)	0.37 (0.43)	279 (276)

[a] First, the B3LYP/6-31+G** data; in parentheses, MM3 data at $\varepsilon = 1.5$.

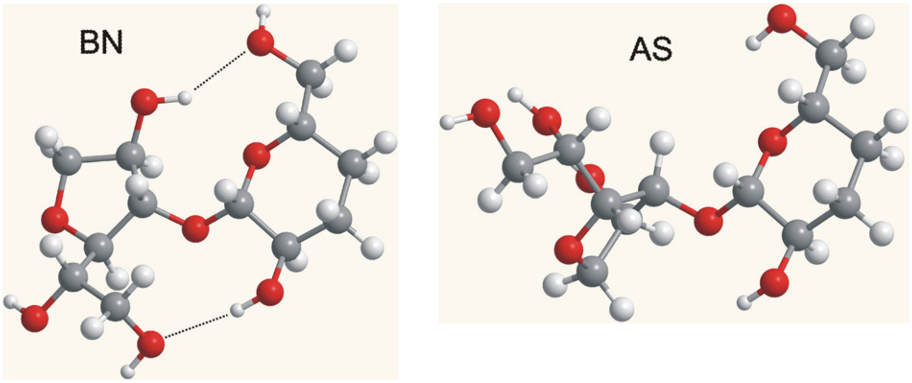

Figure 6. Molecular drawings for conformations BN and AS of compound **4** (analog of carrabiitol), calculated by B3LYP/6-31+G**. The inter-residue hydrogen bonds in BN are indicated by a dotted line.

glycosidic angle (**A** or **B**) characteristics from **3** to **4**. The displacement for the remaining carbons is compatible with changes from **B** to BS, from **B** to BN, or from **A** to AS (Table 5, see the averages). On the other hand, for protons, the displacement fits better with the calculated data for **A**→AS and **B**→BS transitions (Table 5). Taking into account that experimental NOE data for a carrabiose

Table 5

Calculated chemical shift displacements (ppm) for the 3,6-anhydro five-membered ring atoms when passing from the strained structure in **3** to the open one in **4**, for different combinations of conformations

Atom	Experimental data	From **A** to					From **B** to				
		BN	BS	BW	AS	AN	BN	BS	BW	AS	AN
C-1′	−0.8	−3.9	−3.8	−4.5	+1.2	+2.0	−0.8	−0.7	−1.4	+4.3	+5.1
C-3	−4.4	−2.4	−3.6	−3.1	−2.9	−6.3	−1.7	−2.9	−2.4	−2.2	−5.6
C-4	−9.2	−13.9	−12.9	−14.6	−6.7	+0.4	−10.3	−9.3	−11.0	−3.1	+4.0
C-5	+0.7	+1.5	−0.4	−4.4	+0.2	+2.0	+3.1	+1.2	−2.8	+1.8	+3.6
C-6	−3.5	−1.9	−6.0	−6.1	−6.7	−0.8	−2.4	−6.5	−6.6	−7.2	−1.3
H-1′	+0.10	+0.25	−0.01	+0.19	+0.12	+0.04	+0.36	+0.10	+0.30	+0.23	+0.15
H-3	+0.54	+0.04	+0.64	+0.39	+0.47	+0.26	−0.05	+0.55	+0.30	+0.38	+0.17
H-4	+0.46	+1.41	+0.73	+1.68	+0.09	−0.35	+1.05	+0.37	+1.32	−0.27	−0.71
H-5	+0.17	−0.25	0.00	−0.21	+0.19	−0.27	−0.24	+0.01	−0.20	+0.20	−0.26
H-6	+0.13	+0.25	+0.16	+0.32	+0.07	+0.14	+0.18	+0.09	+0.25	0.00	+0.07
H-6′	+0.23	−0.09	+0.04	−0.02	+0.04	−0.07	−0.06	+0.07	+0.01	+0.07	−0.04
Avg. C[a]		2.4	2.2	3.6	1.9	3.7	1.5	1.0	2.2	3.6	5.1
Avg. H[a]		0.41	0.15	0.38	0.12	0.32	0.37	0.08	0.34	0.22	0.39

Data for the anomeric carbon and proton of the attached unit are also included. The experimental data (Ref. 31) for the passage from the chain unit in κ-carratetraitol and the alditol terminus in κ-carrabiitol are added for comparison.

[a] Average difference (ppm) between the calculated and the experimental displacements.

derivative are indicating that the **A** conformation is more stable, these results are compatible with the carrabiitol in solution having also a glycosidic **A** conformation and the five-membered ring in S-like conformation (AS), as predicted by our MM calculations.

The present results show that when accurate calculations are helped by experimental determinations, the conformational features of flexible systems (as those of a 3,6-AnGalol moiety) can be estimated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.04.037.

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