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Modeling ring puckering in strained systems: application to 3,6-anhydroglycosides

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Abstract—Different conformations of methyl 3,6-anhydroglycosides with the β-D-*galacto*, α-D-*galacto*, and β-D-*gluco* configurations were studied by molecular mechanics (using the program MM3) and by quantum mechanical (QM) methods at the HF/- and B3LYP/6-31+G** levels, with and without solvent emulation. Using molecular mechanics, the energies were plotted against the ϕ, θ puckering coordinates of Cremer and Pople. In such strained systems, only two extreme conformations of the six-membered ring are likely: $^1C_4$ and $B_{1,4}$, or any one close to either of them. Results show the preponderance of a distorted chair conformation over that of the distorted boat, though the energy difference is lower and the distortions are larger for the compound with the β-D-*galacto* configuration. For derivatives of this compound, experimental data in solution indicate both chair and boat forms, depending on the compound and the solvent, whereas for the remaining compounds, experimental data always show the preponderance of the chair conformation. The more accurate DFT calculations lead to the lower energy differences, suggesting that HF and MM3 underestimate the stability of the boat-like conformations. Similar studies on model compounds depict the importance of the anomeric effect in the conformational preferences.

Keywords: Puckering; 3,6-Anhydrogalactose; DFT; Anhydro sugars; MM3

1. Introduction

In order to understand the industrial and biological functions of carbohydrates, an in-depth knowledge of their shapes is very important. The conformational analysis of carbohydrates is usually carried out by both experimental and modeling techniques.[1] The shapes of oligo- and polysaccharides are determined by the glycosidic angles between monosaccharide units, and by the actual shape of each of those monosaccharide units. Most of the hexoses and pentoses occur naturally as pyranosyl rings.[2] Experimental determinations indicate that chair forms dominate the conformer populations of most pyranoses,[2] with the exception of idose derivatives (components of many glycosaminoglycans),[3] which also present a stable skew-boat conformation.[2–4]

Several different conformations are possible for a given six-membered ring: two chairs ($^4C_1$ and $^1C_4$), a pseudorotational region of boats and skew-boats, and a group of half-chairs and envelopes,[1] with infinite intermediate conformations between them. In order to represent numerically the conformations of rings, Cremer and Pople have developed the puckering parameters (Q, ϕ, and θ),[5] which were adopted by Jeffrey and Yates into an earth-like stereographic representation,[1,6] facilitating the classification of six-membered ring conformations. A perfect $^4C_1$ chair corresponds to a $\theta = 0°$, whereas a $^1C_4$ chair shows a θ of 180°. The equatorial boat-skew region has a θ of 90°, with the parameter ϕ indicating the shape of the boat or skew (for instance, $B_{1,4}$ has a ϕ of 60°, $^1S_5$ has a ϕ of 270°, etc.).[1,6]

In 1979 the conformational space of glucopyranose was studied by molecular mechanics.[7] Seven years later,

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Ragazzi et al. plotted a projection of the isoenergy contours in the spherical surface for methyl 4-*O*-methyl-α-L-idopyranosyluronic acid 2-sulfate.[4] During the 1990's, computational advances allowed Ferro et al. at first,[8] and French and Dowd later (with another approach) to develop a methodology[9] for scanning the entire spherical conformational space. The latter one had been applied by Dowd et al. using MM3(92) to the 16 aldohexoses,[2] to some aldopentoses,[11] and to deoxy- and dideoxyhexoses,[12] among other compounds, leading to two-dimensional energy contours, which show a Pickett–Strauss *plate carée* projection of the spherical space.[10] No such study has been carried out completely with conformationally constrained ring systems like 3,6-anhydroglycosides, many of which are important constituents of polysaccharides,[13] although a partial determination was carried out with MM3(92) for methyl 3,6-anhydro-α-galactopyranoside.[14] This compound was also studied by ab initio methods.[14,15] The six-membered rings in such systems are constrained to a smaller area of the surface, and they were usually thought of as $^1C_4$-systems, as observed in crystal structures.[16,17] However, it has been shown that although 3,6-anhydro-α-D-glycosides exist in chair conformation, 3,6-anhydro-β-D-galacto- (but not gluco-) pyranosides may prefer a boat-like conformation ($B_{1,4}$) in chloroform,[18,19] or a chair conformation in more polar solvents.[20] Other bicyclo[3.2.1]octane systems substituted with an aryl group in the 3-position (equivalent to the anomeric carbon) with a configuration equivalent to the β-anomer have also been shown to adopt the boat conformation.[21] This occurs even in 8-oxa and 8-aza derivatives (related to cocaine), many of which have high bioactivities.[22,23]

In the present work, the geometries and energies of the main conformers of methyl 3,6-anhydro-β-D-galactopyranoside (**1**) and of its epimers methyl-3,6-anhydro-α-D-galactopyranoside (**2**), and -β-D-glucopyranoside (**3**) (Fig. 1) were studied by molecular mechanics (MM3 at different dielectric constants) and QM (at HF- and B3LYP/6-31+G** level) methods, with and without solvent emulation. Besides, the contour plots showing the MM3 energies against the θ and ϕ puckering parameters were also determined for the three compounds and a model hydrocarbon (**4**), and the energies and geometries of two model acetals (**5** and **6**) were determined by the above-mentioned procedures.

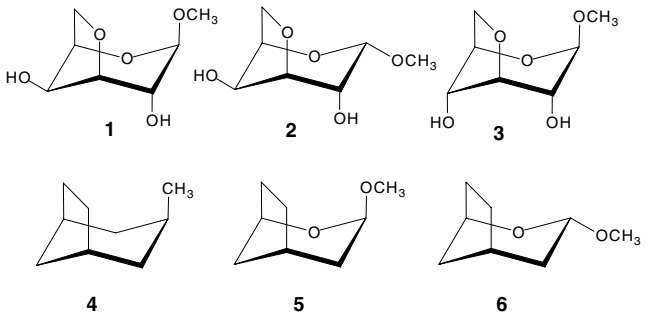

Figure 1. The compounds studied in this work, drawn as their $^1C_4$ conformers.

2. Methods

Molecular mechanics calculations were carried out using the program MM3(92) (QCPE, Indiana University, USA) developed by Allinger and co-workers,[24,25] modified as the MM3(2000) version in the O–C–C–O and O–C–O–H torsional parameters, O–H hydrogen bonding parameters, and C–H electronegativity correction.[26] Besides, a suggested modification of the MM3 routines[27] was made by changing the maximum atomic movement from 0.25 to 0.10 Å. The dielectric constant was held as indicated in Section 3. The default minimization method and termination conditions were used; each minimum was submitted to a full matrix calculation in order to check that it really corresponds to a minimum. Quantum mechanical calculations were performed using Gaussian 98W (version 5.2, revision A-7) with standard basis sets.[28] When indicated, the free energy of solvation was estimated by the polarizable continuum solvation model (PCM, with water as solvent) of Tomasi and co-workers,[29] on the gas-phase geometries obtained by the HF or DFT procedure (i.e., with no further optimization).

The methoxyl anomeric group and hydroxyl hydrogen atom orientations are indicated by χ_n, defined by the atoms H-*n*–C-*n*–O-*n*–H(O)-*n*, replacing the last atom for the methyl carbon in χ_1. Puckering in each structure was determined by the Cartesian coordinates adapting a program originally designed by Dr. L. Madsen. In order to obtain the minima with MM3 at each dielectric constant, a full conformational search was carried out with all the 27 possible starting structures (for **1**, **2**, and **3**). Those with less energy (lower than 0.5 kcal/mol above the global chair or boat minimum, not more than four of each) were tabulated, and those obtained at $\varepsilon = 1.5$ or 3 were submitted to the QM calculations. The methoxyl group in compounds **5** and **6** was oriented to the position determined to be the most stable in the previous compounds, that is, that driven by the *exo*-anomeric effect.

2.1. Generation of ring-puckering energy surfaces

The general, procedure developed by Dowd and co-workers[2,9,11,12] was followed: for each molecule, planar ring structures were generated with all nine possible staggered exocyclic orientations of the hydroxyl groups at C-2 and C-4. The methoxyl group at C-1 was left at most stable position ($\chi_1 \approx 45°$ for β-glycosides, $-45°$

for α-glycosides), driven by the *exo*-anomeric effect, as it showed to be the most stable one for all the examples studied (see Section 3). The flat rings were oriented into the *xy*-plane and puckered by moving C-2, C-4, and O-5, as well as their non-ring substituents in the *z*-direction. After some preliminary testing, it was decided to move them in 0.1 Å increments from −0.7 to +0.6 Å (for C-2 and O-5) and from −0.9 to −0.5 Å (for C-4). To better cover the small portion of the ϕ, θ surface possible for these constrained systems, new structures were generated from each starting model to include 0.05-Å increments in the areas of lower energy. The resulting structures were then submitted to MM3 minimization (block diagonal) keeping the *z*-coordinates of the six ring atoms fixed, and allowing the remaining degrees of freedom to relax. The final output contained the energies of all the resulting conformers and their Cremer–Pople puckering parameters.[5] In order to construct the Picket–Strauss representation,[10] the data was binned into $5°(\theta) \times 10°(\phi)$ regions, regardless of the value of Q or the orientation of individual exocyclic groups. The lower energy within each incremental bin was recorded against ϕ, θ angles. It should be borne in mind[11] that this planar representation of the surface distorts the true spherical surface, especially at the poles (chair conformations), which are points transformed into the horizontal boundaries of the plots. Thus, the contour lines near these boundaries can be distorted.

3. Results and discussion

Three methyl 3,6-anhydroglycosides (Fig. 1) were submitted to a full conformational search with MM3. As expected, these strained systems can only appear as a chair ($^1C_4$), a boat ($B_{1,4}$) or conformations close to either

Table 1. Relative energies (kcal/mol), torsion angles (°), and Cremer–Pople puckering parameters[5] for the main conformers of methyl 3,6-anhydro-β-D-galactopyranoside (**1**)

Method/conformer	E_{rel}	Torsion angles			Puckering parameters		
		χ_1	χ_2	χ_4	Q (Å)	θ (°)	ϕ (°)
MM3, ε = 1.5							
C1	0.00	46	−31	49	0.64	152	61
C2	0.03	46	24	46	0.64	152	62
C3	0.15	45	36	−37	0.64	152	62
B1	3.10	45	−53	151	0.84	99	62
MM3, ε = 3							
C1	0.00	45	−36	49	0.64	152	61
C2	0.03	45	35	47	0.64	152	61
C3	0.08	45	40	−43	0.64	152	61
B2	3.45	46	−50	52	0.85	99	57
B3	3.78	45	−49	−42	0.85	99	57
MM3, ε = 80							
C2	0.00	44	44	48	0.64	153	60
C3	0.01	44	44	−47	0.64	153	60
C1	0.05	44	−41	48	0.64	153	60
C4	0.07	44	−41	−47	0.64	153	61
B2	3.76	44	−50	49	0.84	99	58
B3	3.76	44	−50	−49	0.84	99	58
B4	3.89	42	44	−49	0.84	99	58
B5	3.90	42	43	49	0.84	99	58
B3LYP/6-31+G**							
C1	0.00 (0.00)[a]	52	−43	66	0.66	147	62
C3	0.42 (0.13)[a]	51	51	−47	0.66	146	64
C2	0.49 (0.66)[a]	52	41	65	0.66	146	64
B1	0.56 (3.45)[a]	52	−58	157	0.81	104	62
B2	1.33 (2.75)[a]	52	−56	70	0.81	105	57
B3	2.14	52	−55	−49	0.81	106	57
HF/6-31+G**							
C1	0.00 (0.00)[a]	53	−42	63	0.65	147	61
C2	0.62	52	36	62	0.65	147	62
C3	0.71	51	48	−47	0.65	147	62
B1	1.60 (3.87)[a]	53	−55	153	0.80	104	60
B2	1.67 (2.55)[a]	54	−52	67	0.81	105	56
B3	2.67	54	−51	−48	0.80	105	56

[a] In parentheses, relative energy considering the polarizable continuum model in water.

of them. Any other possibility is almost prohibited by the five-membered ether ring joining C-3 and C-6. Simple six-membered rings like cyclohexane or tetrahydropyran give a chair conformation 5.6–5.8 kcal more stable than the skew form, with potential barriers above 10 kcal/mol, either by experimental or calculational methods.[2] Molecular mechanics calculations (with MM3) indicate that 9 out of the 16 hexopyranoses show similar energy differences (4.2–7.9 kcal/mol) between the most stable chair and the most stable skew ($^{O}S_2$, $^{3}S_1$, $^{1}S_3$, $^{2}S_O$, or $^{1}S_5$, depending on the sugar), though β-Alt, β-Gul, β-Ido, and α-Tal give differences around 2.9–3.7 kcal/mol (about the same as most pentopyranoses),[11] α-Gul and α-Alt between 1.2 and 1.5 kcal/mol, and for α-Ido, the skew $^{O}S_2$ has a stability similar to that of both chairs.[2] The minima are always located close to either chair or skew forms. In some few cases, the skew forms had some boat character,[2,11] which was important only for α-L-Rha,[12] which carries a fourth minimum with conformation $^{3,O}B$.

Tables 1–3 show the main conformers appearing for the methyl 3,6-anhydroglycosides with β-D-*galacto* (**1**, Table 1), α-D-*galacto* (**2**, Table 2), and β-D-*gluco* (**3**, Table 3) configuration, after a calculation with MM3 at $\varepsilon = 1.5$, 3, and 80, with a search of all possible conformations of the exocyclic groups. The tables also show the results of submitting the main conformers obtained in the above study to a DFT study at the B3LYP/6-31+G** level and to an HF calculation with the same basis set, and the effect of adding to the most important chair and boat forms of both calculations of solvent emulation by the polarizable continuum method.[29] Csonka[30] has shown that carbohydrates can be modeled accurately using B3LYP/6-31+G**. Table 4 shows the results of submitting model compounds **4**, **5**, and **6** to the same calculations. Table 5 summarizes the energy differences found between the boat and chair forms for the six compounds. All of the calculations led to boat conformers having higher energy than the chair conformers (Table 5). Using MM3 at $\varepsilon = 3$, the differences in energy range from 3.45 kcal/mol for **1**, to 4.46 kcal/mol for **3**, up to 6.12 kcal/mol for **2**. The HF procedure led to about one-half of that difference (Table 5) for the three carbohydrates, obviously with a similar trend, whereas the DFT calculations indicate an even smaller difference for **1** and **2**, suggesting that both the HF and the MM calculations may be overestimating the energy of the boat conformers. Application of the solvation model of Tomasi and co-workers[29] to both QM procedures indicates that the chair is better stabilized

Table 2. Relative energies (kcal/mol), torsion angles (°), and Cremer–Pople puckering parameters[5] for the main conformers of methyl 3,6-anhydro-α-D-galactopyranoside (**2**)

Method/conformer	E_{rel}	Torsion angles			Puckering parameters		
		χ_1	χ_2	χ_4	Q (Å)	θ (°)	ϕ (°)
MM3, $\varepsilon = 1.5$							
C1	0.00	−47	−84	48	0.66	161	61
B1	6.40	−44	−158	152	0.80	102	63
B2	6.56	−44	−154	54	0.80	102	59
MM3, $\varepsilon = 3$							
C1	0.00	−46	−75	48	0.66	161	62
C2	0.30	−46	−73	−38	0.66	162	62
B2	6.12	−43	−161	51	0.80	102	60
B3	6.30	−43	−163	−44	0.80	102	60
MM3, $\varepsilon = 80$							
C1	0.00	−44	−56	49	0.66	162	63
C2	0.02	−45	−56	−47	0.66	162	63
B4	5.57	−42	−51	−49	0.80	102	60
B5	5.58	−42	−51	49	0.80	102	60
B3LYP/6-31+G**							
C1	0.00 (0.87)[a]	−54	−83	59	0.66	156	58
C2	0.46 (0.00)[a]	−53	−81	−40	0.66	156	58
B1	0.91 (2.76)[a]	−47	−149	157	0.79	105	60
B2	1.62 (2.22)[a]	−47	−142	68	0.79	107	54
B3	2.32	−45	−145	−43	0.80	106	55
HF 6-31+G**							
C1	0.00 (0.00)[a]	−55	−79	58	0.66	156	57
C2	0.65 (0.03)[a]	−54	−78	−40	0.66	156	57
B1	3.03 (4.37)[a]	−49	−150	153	0.79	105	58
B2	3.13 (3.76)[a]	−49	−143	67	0.79	107	54
B3	3.99	−48	−147	−43	0.79	106	54

[a] In parentheses, relative energy considering the polarizable continuum model in water.

Table 3. Relative energies (kcal/mol), torsion angles (°), and Cremer–Pople puckering parameters[5] for the main conformers of methyl 3,6-anhydro-β-D-glucopyranoside (**3**)

Method/conformer	E_{rel}	Torsion angles			Puckering parameters		
		χ_1	χ_2	χ_4	Q (Å)	θ (°)	ϕ (°)
MM3, $\varepsilon = 1.5$							
C1	0.00	46	46	−178	0.61	155	67
B1	5.47	45	−52	−78	0.81	99	55
MM3, $\varepsilon = 3$							
C1	0.00	45	46	179	0.61	155	65
C2	0.25	44	177	54	0.61	154	66
C3	0.40	45	−173	−44	0.61	155	64
C4	0.41	45	−27	−175	0.61	155	66
B1	4.46	44	−52	−63	0.80	99	56
B2	4.99	44	−52	52	0.80	99	57
MM3, $\varepsilon = 80$							
C5	0.00	44	45	−56	0.61	154	62
C6	0.06	44	−42	−58	0.61	154	62
C7	0.09	44	47	54	0.61	154	63
C8	0.18	44	−42	54	0.61	154	63
B1	4.29	43	−50	−55	0.80	99	57
B2	4.33	43	−50	55	0.80	99	57
B3	4.44	43	43	−55	0.80	99	57
B4	4.47	43	44	55	0.80	99	57
B3LYP/6-31+G**							
C2	0.00 (0.00)[a]	49	161	134	0.66	148	69
C1	1.36	51	59	−164	0.64	149	66
C4	1.69	52	−50	−154	0.64	149	65
C3	1.99	50	176	−34	0.64	150	64
B1	3.98 (1.76)[a]	53	−56	−117	0.75	111	54
B2	5.66	50	−57	58	0.78	106	63
HF 6-31+G**							
C2	0.00 (0.00)[a]	50	169	82	0.63	147	65
C1	0.56 (0.27)[a]	51	57	−168	0.63	150	66
C4	0.78	53	−43	−155	0.63	149	64
C3	1.27	50	178	−34	0.63	149	63
B1	2.79 (1.03)[a]	53	−53	−85	0.77	107	56
B2	4.48	52	−54	56	0.77	105	62

[a] In parentheses, relative energy considering the polarizable continuum model in water.

by water solvation in compounds with the *galacto* configuration (**1** and **2**), thus increasing the energy difference, but the boat is better stabilized by solvation in compound **3**, with the *gluco* configuration (Tables 3 and 5). Calculations made with MM3 but increasing the dielectric constant did not change much the differences between the chair and boat energies, but the trend shown for all compounds (but **2**) is the same as that observed by adding a solvation model to the QM calculations (Table 5).

Figure 2 shows the energy surfaces (as θ, ϕ puckering maps) for the three 3,6-anhydroglycosides, as well as for the model compound **4** (3-methylbicyclo[3.2.1]octane, Fig. 1). They all have similar shapes, but those corresponding to **1** or **4** extend more throughout the boat region ($\theta < 120°$) than those of **3** or (especially) **2**. As expected, the plot for **4** is symmetric around $\phi = 60°$. This compound shows very similar geometries and energies by MM and QM methods (Table 4, Fig. 2), with a $^1C_4$-like conformer having a $\theta = 150$–$151°$, and a boat-like form carrying a $\theta = 101$–$102°$.

The boats and chairs obtained are not 'perfect' (Figs. 2 and 3). Boats are expected to show a θ puckering parameter of 90°. Molecular mechanics calculations give boats with the C-1 slightly raised ($\theta = 99$–$102°$, Tables 1–3). The QM calculations yield even more distorted boats ($\theta = 104$–$107°$, with one exception at $\theta = 111°$, Table 3). By the same token, chairs are also distorted toward the same direction (flattening at C-1), leading to structures that are actually intermediate between the 'perfect' chair ($\theta = 180°$) and an E_4 envelope ($\theta = 125°$). MM3 gives a distortion of more than 25° for β-anomers (**1**, **3**, and **5**, $\theta = 152$–$155°$), but lower for the α-anomers **2** and **6** ($\theta = 161°$, Tables 2 and 4). QM calculations give the same trend, but rings are ca. 5° more distorted for the sugars **1**–**3**, and a little less for the model acetals (Table 4). The geometries obtained by HF and DFT calculations are very similar (Tables

Table 4. Relative energies (kcal/mol) and Cremer–Pople puckering parameters[5] for the main conformers of the bicyclo model compounds **4**, **5**, and **6**

Method/compound/conformer	E_{rel}	Puckering parameters		
		Q (Å)	θ (°)	ϕ (°)
MM3, $\varepsilon = 1.5$				
4-chair	0.00	0.64	150	60
4-boat	1.16	0.83	101	60
5-chair[a]	0.00	0.63	153	58
5-boat[a]	4.71	0.82	100	58
6-chair[a]	0.00	0.65	161	59
6-boat[a]	3.80	0.77	105	56
B3LYP/6-31+G**				
4-chair	0.00	0.64	151	60
4-boat	0.51	0.82	101	60
5-chair	0.00 (0.00)[b]	0.64	151	58
5-boat	3.99 (2.97)[b]	0.79	104	56
6-chair	0.00 (0.00)[b]	0.64	159	58
6-boat	1.51 (3.09)[b]	0.78	106	53
HF/6-31+G**				
4-chair	0.00	0.64	151	60
4-boat	0.78	0.82	102	60
5-chair	0.00 (0.00)[b]	0.63	151	57
5-boat	4.06 (3.09)[b]	0.79	103	54
6-chair	0.00 (0.00)[b]	0.64	158	56
6-boat	2.18 (3.73)[b]	0.77	106	52

[a] The geometries at $\varepsilon = 3$ and $\varepsilon = 80$ are the same, whereas their relative energies are given in Table 5.
[b] In parentheses, relative energy considering the polarizable continuum model in water.

Table 5. $E_{boat} - E_{chair}$ (kcal/mol) for the compounds under study

Compound	Config	MM3 $\varepsilon = 1.5$	MM3 $\varepsilon = 3$	MM3 $\varepsilon = 80$	B3LYP/6-31+G** (+ PCM in water)	HF/6-31+G** (+ PCM in water)
1	β	3.10	3.45	3.76	0.56 (2.75)	1.60 (2.55)
2	α	6.40	6.12	5.57	0.91 (2.22)	3.03 (3.76)
3	β	5.47	4.46	4.29	3.98 (1.76)	2.79 (1.03)
4	β	1.16	1.16	1.16	0.51	0.78
5	β	4.71	4.50	4.30	3.99 (2.97)	4.06 (3.09)
6	α	3.80	4.01	4.22	1.51 (3.09)	2.18 (3.73)

1–4), with few exceptions (like χ_4 in the B1 conformer of **3**, Table 3). Those results show that the chair and boat conformations obtained by QM calculations are closer to each other than those obtained by MM calculations. It can be shown that the direction of distortion is always through movement of C-1, as the ϕ parameter is always around 60° (Tables 1–4). Probably, it does not give a value of exactly 60° due to the asymmetry caused by the presence of two oxygens in the bridged structure. The crystal structure of **2** exhibits a shape[16] very similar to that determined herein using calculations ($\theta = 158°$, $\phi = 63°$, $Q = 0.67$ Å, $\chi_1 = -47°$, cf. Table 2 and Fig. 2), as it occurs with the crystal structure of a disaccharide containing the structure of **2** at the non-reducing end ($\theta = 161°$, $\phi = 58°$, $Q = 0.67$ Å).[31] Izumi has determined the solution conformation of **2**.[32] Although he postulated a highly distorted chair using an old parameterization of the Karplus equation, a reassessment of the data using the parameterization of Haasnoot et al.[33] is compatible with a chair only slightly distorted ($\theta \approx 162°$, $\phi \approx 75°$) from our MM3 calculations. It should be noted that Schafer et al. have already made a computational study on **2**, using a different ab initio basis set, and a different parameterization of the MM3 program.[14] Some crystal analysis of 3,6-anhydro-α-D-gluco derivatives was also made. Besides the methyl glycoside,[17] a disaccharide was studied,[34] indicating a near-chair ($\theta = 166°$, $\phi = 69°$, $Q = 0.66$ Å), and also a couple of modified cyclodextrins: the one as a cyclic octasaccharide ($\theta = 161$–$163°$, $\phi = 67$–$75°$, $Q = 0.63$–0.64 Å),[35] and the other as a cyclic heptasaccharide, but complexed to potassium hydroxide and including molecules of water and acetone, leading to a slightly larger dispersion of puckering parameters ($\theta = 153$–$163°$, $\phi = 64$–$86°$, $Q = 0.57$–0.69 Å), always within the chair domain.[36]

The arrangement of exocyclic groups for the minima is similar by MM and QM methods: angle χ_1 (H-1–C-1–O-1–CH_3) is governed by the *exo*-anomeric effect, as expected, yielding values of about 45–54° for β-anomers, and −42 to −55° for α-anomers. As explained earlier, the crystal structure of **2** gave the same χ_1 as that calculated.[16] Several conformers are produced by different

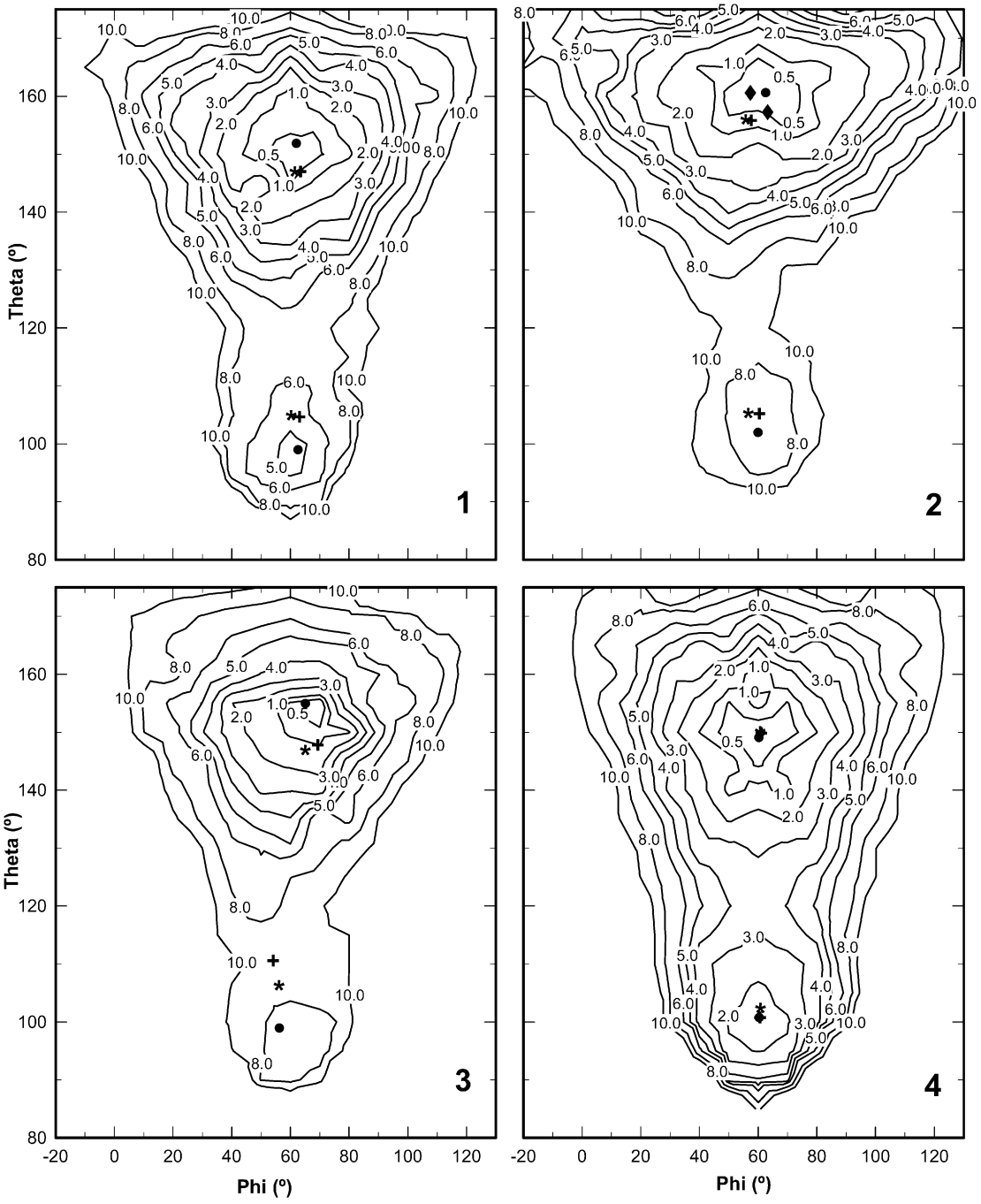

Figure 2. MM3-computed adiabatic θ, ϕ puckering maps for compounds **1**–**4** at $\varepsilon = 3$. Iso-energy contour lines are graduated at 0.5, 1, 2, 3, 4, 6, 8, and 10 kcal/mol increments above the global minimum. Symbols: (●) MM3 local minima, (+) B3LYP/6-31+G** local minima, (★) HF/6-31+G** local minima, (♦) crystal structures of compounds related to **2** (Refs. 16 and 31).

arrangements of the remaining exocyclic groups at C-2 and C-4. Hydrogen bonding causes the presence of different minima at different dielectric constants: for the boat forms of **1** and **2**, a conformation where H(O)-4 is directed toward O-6 is preferential only at $\varepsilon = 1.5$ (or the equivalent QM gas phase calculations, B1 in Tables 1 and 2), but not important at higher dielectric constants. Besides, for the boat form of **2**, the conformation where H(O)-2 can reach O-1 (H(O)-2 *anti* with respect to H-2) is stabilized at $\varepsilon = 1.5$ or 3, but at $\varepsilon = 80$ steric factors do not stabilize that conformation. For the chair conformer of **3**, the axial substituents at C-2 and C-4 can hydrogen bond to each other, giving a variety of conformers presenting this bonding, whereas at higher dielectric constant this arrangement is disadvantageous.

QM calculations on model compounds **5** and **6** (3-methoxy-2-oxabicyclo[3.2.1]octane) should show the consequences of the anomeric effect without the influence

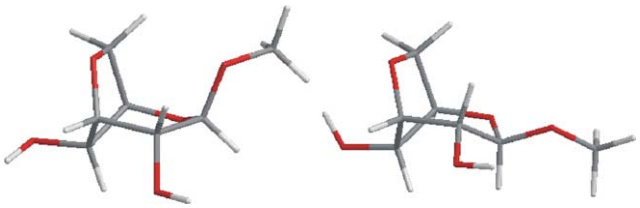

Figure 3. Molecular drawings for the main chair (left) and boat (right) conformations of methyl 3,6-anhydro-β-D-galactopyranoside (**1**), calculated by B3LYP/6-31+G**.

of hydrogen bonding. The anomeric effect should lead to a relatively higher stability of the chair forms of the β-anomers and of the boat forms of the α-anomers, all of which have the polar methoxyl group *anti* to one electron pair of the ring oxygen. This effect indeed occurs: DFT calculations lead to a boat–chair energy difference 2.5 kcal higher in **5** (β-anomer) than in **6** (α-anomer, Table 5). The difference also occurs, but with smaller magnitude in HF and MM calculations (Table 5). The higher stability of the chair in **5** occurs in spite of the larger steric interactions occurring for the β-compound, alleviated in part by a larger distortion of the chair (Table 4). Furthermore, the nature of the effect is also reflected by solvation, which diminishes sharply the differences between **5** and **6**, leading to a chair slightly more stable (in relationship with the boat) in **6** than in **5** (Table 5). It is a known fact that the anomeric effect is sharply diminished in polar solvents. These effects are also shown when looking at the relative energies of compounds **5** and **6** (Table 6): the chair of the β-compound is more stable when the anomeric effect is preponderant (gas-phase calculations), whereas the α-compound becomes more stable when steric factors dominate (solvent emulations or higher dielectric constants, Table 6).

A different picture is observed when looking at compounds **1** and **2**. In these cases, steric effects and especially hydrogen bonding become more important than the anomeric effect. Thus, in gas phase calculations the chair is relatively more stable in **2** (α-anomer) than in **1** (β-anomer) with respect to the boat (Table 5), using any method of calculation, as a product of the expected destabilizing effect of the 1,3-diaxial steric interactions in **1** (diminished by distorting the chair). DFT gives rise to a very small difference in energy between the chair and the boat in both compounds (Table 5), probably due to the relevance that this method gives to the presence of an additional hydrogen bond between H(O)-4 and O-6 in the boat forms. When the molecules are modeled in aqueous solution, the boat forms appear less stabilized (Table 5) as an expected effect of the decrease of their hydrogen-bonding capabilities. The determination of the relative energies of the more stable chair conformer of **1** with respect to that of **2** also reflects the importance of hydrogen bonding: in gas-phase calculations the α-anomer (**2**) is more stable (Table 6), probably due to hydrogen bonding between H(O)-2 and O-1. With solvent emulation, the β-anomer appears to be the most stable. The same trend is reflected in MM calculations (Table 6).

3,6-Anhydro-α-D-galactopyranosides are usual constituents of red seaweed galactans,[13] with a known $^{1}C_{4}$ conformation, proven by different experimental procedures.[14,16,32] Attempts to justify a distortion toward the boat or envelope,[32,37] proved to be wrong.[14] For its β-anomer (**1**), it was shown by NMR spectroscopy in chloroform that the $B_{1,4}$ form is preferred over the chair form,[18] a fact ascribed to lowering the 1,3- and 1,5-diaxial repulsions present in the chair form,[18] although present calculations may also indicate the contribution of hydrogen bonding (see above). In a recent paper, it was assumed that the same boat form was predominant in water,[19] but an analysis of the NMR H–H coupling constants of a 3,6-anhydro-β-galactoside determined in a water–methanol mixture showed that it clearly corresponds to a $^{1}C_{4}$ conformation.[20] The inclusion of solvent in the QM calculations of **1** shows the behavior expected according to the experimental data: an increase in the relative stability of the chair form (Tables 1 and 4). For the C-4 epimer of **1** (**3**, with *gluco* configuration), the chair form also appears even more stable, probably due to the strong flagpole interaction between O-4 and H-1 that would appear in the boat conformation, and to the stronger hydrogen bonding effect between the hydroxyl groups in O-4 and O-2 in the chair than in the boat form. As expected from the second term, the difference is strongly diminished in the presence of water (Tables 3 and 5).

The present work shows preponderant chair conformations for the three compounds. However, the calculations for **1** (reported to have a dominant boat conformation in chloroform[18]) yield the lower difference in energy between both conformations, especially with gas-phase DFT calculations (Table 1), which give comparable energies for the boat and chair forms. Compound **1** also exhibits the more distorted chair (Table 1), comparable to other β-substituted models like **4** and **5**. This distortion certainly appears to diminish diaxial interactions.

Table 6. Differences in energies of the most stable conformers of β and α anomers ($E_{\beta} - E_{\alpha}$, kcal/mol)

Compound	MM3 $\varepsilon = 1.5$	MM3 $\varepsilon = 3$	MM3 $\varepsilon = 80$	B3LYP/6-31+G** (+ PCM in water)	HF/6-31+G** (+ PCM in water)
1 – **2**	2.69	1.37	0.35	2.62 (−1.32)	2.94 (−0.93)
5 – **6**	−0.08	0.13	0.34	−0.45 (0.91)	−0.22 (1.14)

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