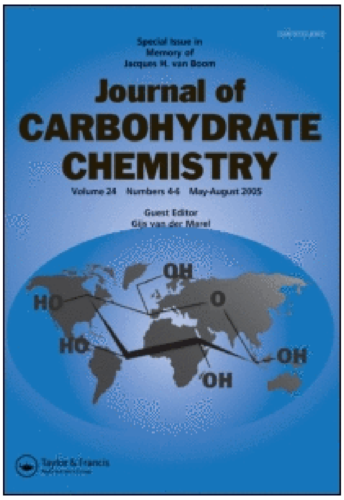

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THE NMR COUPLING CONSTANTS, AND CONFORMATIONAL AND STRUCTURAL PROPERTIES OF FLEXIBLE ALDOPYRANOSYL RINGS: α- AND β-D-IDOPYRANOSE[1]

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ABSTRACT

The flexible ring structures of α- and β-D-idopyranose have been investigated by conformational analysis using structures generated by MacroModel and GMMX search protocols. The lowest energy structures found during the conformer search for the $^4C_1$, $^1C_4$, $^OS_2$ and the $^3S_1$ structures were then examined by AM1 and Gaussian ab initio methods at the HF/6-311G** and HF/6-31+G* levels. The $B_{2,5}$ conformer found for β-D-idopyranose at 14 kJ/mol by GMMX and 29.5 kJ/mol for α-D-idopyranose by MacroModel would not contribute to Boltzmann-averaged ^{1}H NMR coupling constants. The Merck MMFF force field tends to overweight the $^1C_4$ structures, making these the lowest energy conformers for both anomers. Boltzmann-averaged coupling constants are heavily weighted by this structure in the MMFF search conformer ensemble. Averaged proton coupling constants determined using MMFF fit very well for α-D-idopyranose compared to the observed values, but fit poorly for the β-anomer. Ab initio results place the $^1C_4$ conformer at lowest energy for the α-anomer and place the $^4C_1$ conformer at lowest energy for the β-anomer. The GMMX and MM3* force fields find the $^4C_1$ conformer to have the lowest energies for both anomers.

INTRODUCTION

Most all aldopyranosyl ring structures show considerable energy differences between the $^4C_1$ and $^1C_4$ conformers, with the $^4C_1$ structure typically having the lower energy by 21.0 kJ/mol or more. However, the pyranose rings of several sugars such as D-idopyranose, D-altropyranose and D-talose exhibit significant flexibility. These characteristics were suggested in early NMR and computational studies[2-6] where varied relative energies for the $^4C_1$ and $^1C_4$ structures were reported. The study of flexible carbohydrate rings provides an ideal way to examine the relationship between search conformer ensembles generated by different force fields and physical properties such as NMR proton coupling constants. Recent studies[7-13] demonstrated that conformational searching programs now work relatively well with polyhydroxyl compounds. Ernst et al.[14] have recently examined iduronate conformational flexibility. D-Idopyranose is a good monosaccharide to examine since there is no question that a number of different conformers are significantly populated. However, there is some question about the ordering of relative energies for these conformers.

Vijayalakshmi and Rao[4] found that the energies for the α-D-idopyranose $^4C_1$ and $^1C_4$ conformers were nearly equal ($^1C_4$, 0.08 kJ/mol lower), and for β-D-idopyranose that the $^4C_1$ conformer energy was lower than that of the $^1C_4$ conformer by 3.8 kJ/mol. Angyal and Pickles[3] found that the $^1C_4$ conformer was lower by 2.1 kJ/mol for α-D-idopyranose, and that the $^4C_1$ conformer was lower in energy than the $^1C_4$ conformer by 5.4 kJ/mol for β-D-idopyranose. These workers reported that in terms of population, 70% of α-D-idopyranose molecules were in the $^1C_4$ conformation and that 90% of the β-D-idopyranose molecules were in the $^4C_1$ form. In these earlier studies, twist conformers were not considered, which would have an important bearing on the analysis of conformer populations. The ^{1}H NMR coupling constants of Snyder and Serianni[6] supported a low energy $^1C_4$ conformer and the possibility that lower energy twist conformers might be present. They considered only the presence of a $^3S_5$ (currently labeled $^OS_2$) conformer, however.

Recently, Dowd et al.,[7] using MM3 (92), reported relative conformational energies for the α-D-idopyranose $^{O}S_2$, $^{1}C_4$, and $^{4}C_1$ conformers as 0.00, 0.75 and 2.30 kJ/mol, respectively, placing the twist conformer at lowest energy. In their study, the relative conformer energies for β-D-idopyranose for the $^{4}C_1$, $^{1}C_4$, $B_{2,5}$ and $^{3}S_1$ conformers were 0.00, 9.87, 12.97 and 18.82 kJ/mol, respectively. Dowd et al. used systematic variation of hydroxyl and hydroxymethyl torsional angles to explore conformational space rather than random searching methods. Having different conformer energies so close together allows testing of both conformational searching protocols and force fields. This study applies the MacroModel and GMMX searching protocols to examine the conformer ensembles for α- and β-D-idopyranose. Low energy conformers are examined using the semi-empirical AM1 and ab initio quantum methods. All calculations are full structural optimizations using the Polak-Rabiere congruent gradient method. A significant goal is the determination of computed Altona-Haasnoot-modified[15] Karplus ensemble-averaged NMR vicinal proton coupling constants of the conformer ensemble utilizing their Boltzmann distribution. Theoretical results are then compared with observed proton coupling constants. The furanose structures present in solution are not considered in this study.

COMPUTATIONAL TECHNIQUES

The two methods applied in this study for searching conformational space were GMMX[16] and MacroModel[17] version 5.5. The GMMX program using the MMX force field was applied in the mixed mode of atom coordinate movement and bond rotation. The computations were carried out with a dielectric constant of 4.0 and with the hydrogen bonding function turned off. The runs were repeated with different starting structures and re-minimized until a consistent set of ^{1}H NMR coupling constants was determined. Typically, 5000 to 8000 structures were examined. The underlying proton coupling constants were based on the modified Karplus vicinal coupling constant work of Haasnoot et al.[15] MacroModel was applied in the Monte Carlo (MC) multiple minimum searching mode using the MM3*[18-19] and Merck force fields (MMFF).[20] The MM3* force field is modified from MM3 (91), Allinger et al.,[18] except that point charges are used instead of bond moments for the electrostatics. Typically, 5000 MC steps were used within a 30 kJ/mol energy window using the GB/SA[21] water solvent model. Sometimes a 50 kJ/mol energy window was used for the collection of conformer structures over a wider range of energies. All flexible torsion angles for both anomers were rotated and were allowed to vary between 0° and ±180°. These included the pyranose ring internal torsion angles. Between two and nine bonds were randomly selected for rotation. The searching procedure was started with different initial structures and MC random numbers (SEED). Conformers were determined to gradients of 0.04 kJ/mol-Å or less.

For the quantum mechanical calculations, HyperChem 5.1[22] AM1 and PM3 methods were applied in the gas phase using the lowest energy distinct structural conformers found from each MC searching study. Structures were completely optimized in all quantum mechanical methods. Energies were taken to a gradient less that 0.4 kJ/mol-Å. Ab initio calculations were conducted with the Spartan 5.0[23] package on an Indigo SGI workstation, and the Gaussian calculations were performed using G94W[24] on PC 266 to 300 MHz machines. Ab initio computations were carried out in the gas phase to full convergence, and dipole moments were taken from the ChelpG[25] calculations.

RESULTS AND DISCUSSION

α-D-Idopyranose. The GMMX results for α-D-idopyranose indicate that the $^4C_1$ conformer has the lowest energy, followed by the $^1C_4$ conformer with a relative energy of 0.84 kJ/mol. The relative energy of the twist conformer, $^OS_2$, is 1.2 kJ/mol. A MacroModel search using the MM3* force field also found the $^4C_1$ conformer to be lowest in energy. The relative energies obtained from MacroModel with this force field for the $^OS_2$ and $^1C_4$ structures are 8.8 kJ/mol and 10.5 kJ/mol, respectively. The GMMX search shows low percentages of $^OS_2$ and $^1C_4$ conformers in the ensemble made up of conformers in the lowest 8 kJ/mol. This factor lowers the coupling constants, as shown in Table 1. The computed coupling constant rms deviation is 1.7 Hz. It should be noted here that coupling constant calculations based on the single energy differences given in Table 2 for GMMX would still be lower than observed ($J_{1,2}$ = 4.8 Hz, $J_{2,3}$ = 7.4 Hz, for example). Note that the coupling constant results shown in the footnotes of Table 1 are computed this way. In the MacroModel MM3* search, the relatively high $^1C_4$ and $^OS_2$ energies (see Table 2) lead to Boltzmann-averaged ^1H NMR ring coupling constants that are much smaller than the observed values (see Figure 1).

Table 1. The GMMX and MacroModel conformational Boltzmann-averaged (300K) NMR coupling constants (Hz) compared to the experimental values (Hz) for α-D-idopyranose and β-D-idopyranose.

	α-D-Idopyranose				β-D-Idopyranose			
Constant	GMMX[a]	MacroMod[a]		Obs.[b]	GMMX[a]	MacroMod[a]		Obs.[b]
		MMFF	MM3*			MMFF	MM3*	
$J_{1,2}$	4.7	7.3	2.9	6.0[c,d]	1.6	3.1	1.5[c,d]	1.6
$J_{2,3}$	7.2	8.8	4.5	8.1[d]	3.2	7.4	3.3[d]	3.8
$J_{3,4}$	5.1	8.7	4.0	7.9	3.2	7.3	3.3	3.7
$J_{4,5}$	2.8	5.5	1.7	5.0	1.2	4.4	1.0	1.8
$J_{5,6R}$	6.8	9.0	3.0	8.8	7.5	9.6	6.1	7.5
$J_{5,6S}$	5.3	3.7	6.1	3.9	4.8	3.5	3.0	4.4

a. GMMX, no solvent; MacroModel (V5.5)/MMFF, GB/SA water solvent model. b. Snyder and Serianni.[6] A long-range coupling constant was observed for β-D-idopyranose, $J_{2,4}$ = 1.2 Hz. c. $J_{1,2}$ = 5.6 Hz.[5] d. Coupling constants calculated by Dowd et al., MM3 (92):[7] α-D-idopyranose: $J_{1,2}$ = 5.1 Hz; $J_{2,3}$ = 8.3 Hz; for β-D-idopyranose: $J_{1,2}$ = 1.3 Hz; $J_{2,3}$ = 3.5 Hz.

With the MMFF force field, the $^1C_4$ structure is lowest in energy and represents 97% of the conformers in the ensemble found in the lowest 20 kJ/mol. The $^OS_2$ conformer at 13.4 kJ/mol represents only 3% of these conformers. No $^4C_1$ conformer was present in that energy window. The percentage in the distribution and relative lowest conformer energies in a 50 kJ/mol energy window are: $^1C_4$ (28%, 0.0 kJ/mol); $^OS_2$ (25%, 13.4 kJ/mol); $^3S_1$ (10%, 22.0 kJ/mol); $^4C_1$ (20%, 25.5 kJ/mol); and $B_{2,5}$ (1%, 29.5 kJ/mol). The percents listed here are summed from the lowest energy given for the conformer over the remainder of the 50 kJ/mol energy window.

The high relative energies of all conformers compared to the $^1C_4$ structure represent an ensemble that gives NMR coupling constants that are too large, but overall are a good fit. Figure 2 shows this for the $J_{1,2}$ and $J_{2,3}$ values as well as for several structures from the primary MMFF search results. The mole percent values listed with the figures are those collected in the filter over the 30 kJ/mol energy window. For example, the coupling constant fit for α-D-idopyranose is very good with an rms deviation of 0.7 Hz (see Table 1). This result indicates that the $^1C_4$ structure is indeed the lowest

Table 2. Comparison of the GMMX and MacroModel search relative energies (kJ/mol) with the AM1 and ab initio energies (kJ/mol) for α- and β- D-idopyranose $^4C_1$, $^1C_4$ and $^OS_2$ conformers.

	α-D-Idopyranose[a]			β-D-Idopyranose[a]		
Parameter/Method	$^4C_1$[b]	$^1C_4$	$^OS_2$	$^4C_1$	$^1C_4$	$^OS_2$
			Molecular Mechanics			
GMMX	0.00	0.84	1.23	0.00	7.36	16.40
MMFF	25.55	0.00	19.03	5.93	0.00	16.72
MM3*	0.00	10.50	8.82	0.00	12.79	19.37
			AM1			
AM1 (GMMX)	5.48	11.49	0.00	11.90	0.00	12.24
AM1 (MMFF)	0.00	30.87	19.29	9.39	0.00	13.60
AM1 (MM3*)	1.99	0.00	2.87	5.12	0.00	18.86
			Ab initio			
6-311G**(MMFF)	0.68	0.00	12.70	0.00	10.46	26.35
6-311G**(MM3*)[b]	0.00	4.15	15.15	3.66	0.00	26.09
6-31+G* (MMFF)	5.26	0.00	12.00	0.00	10.52	27.46
6-31+G* (MM3*)	0.00	0.93	12.46	3.36	0.00	24.52

a. The reference energy taken as 0.0 kJ/mol is the lowest energy found by each method.

b. The energy difference between the α- and β-forms of the $^4C_1$ D-idopyranose conformers is 2.80 kJ/mol based on the MM3* structures and at the HF/6-311G** level of computation. α-D-idopyranose is lower in energy and the $^4C_1$ α-anomer is 0.86 kJ/mol higher in energy than the $^1C_4$ β-anomer.

energy conformer. In Table 2 for each model, the conformer (not always the $^4C_1$ conformer) with the lowest energy is assigned the 0.0 kJ/mol reference value. From examining the energies in Table 2, it is clear that the ab initio values support the $^1C_4$ structure as the lowest energy for the α-anomer for MMFF search conformers. However, the low energy $^4C_1$ conformers from GMMX and MM3* ensembles, found at even higher relative energy with the MMFF force field, show lower energies with the ab initio results for both the HF/6-311G** and the HF/631+G* basis sets (Table 3). This may be due to no solvent model being used with the ab initio methods. Preliminary ab initio results on the MM3*

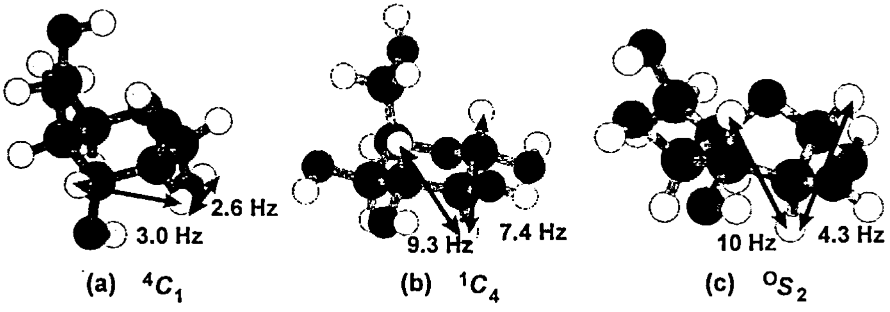


Figure 1. The lower energy conformers found for α-D-idopyranose in the MacroModel search with the MM3* force field consist of the (a) $^4C_1$ (48%), (b) $^1C_4$ (17%) and (c) $^OS_2$ (15%) in a 30 kJ/mol energy window. Variations of the $J_{1,2}$ and $J_{2,3}$ constants with change in conformation are shown here. Boltzmann-averaged NMR proton coupling constants are given in Table 1 and the relative energies are shown in Table 2.

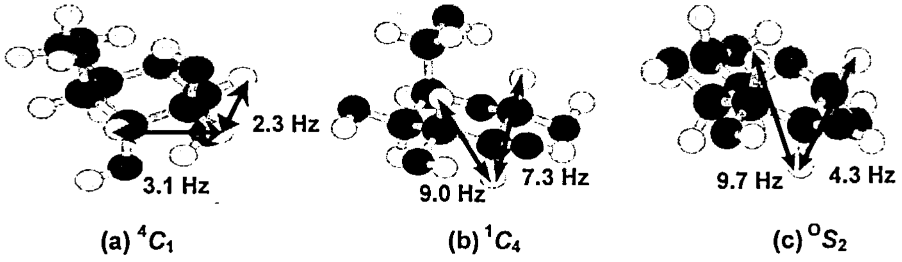


Figure 2. The lower energy common conformers found for α-D-idopyranose in the MacroModel search with the MMFF force field consist of the (a) $^4C_1$ (12%), (b) $^1C_4$ (17%) and (c) $^OS_2$ (15%) in a 30 kJ/mol energy window. These percentages do not reflect the full nature of the energy distribution curve. Variations of the $J_{1,2}$ and $J_{2,3}$ constants with changes in conformation are shown here. The Boltzmann-averaged NMR proton coupling constants are given in Table 1 and the relative energies are shown in Table 2.

conformers, using the SCRF/PCM solvent method[24] with the HF/6311G** basis set, places the lowest $^1C_4$ conformer lower than the lowest $^4C_1$ conformer. Further solvent-modeled computational results are needed to better establish the relative energies.

In Table 3, the absolute AM1 and ab initio energy values and respective dipole moments for selected conformers are given. The variation of the dipole moments demonstrates that there is considerable variation in the OH bond rotations with the related

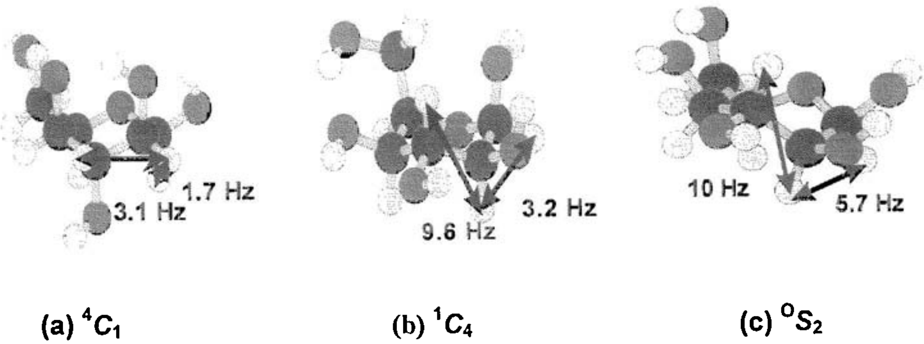
Table 3. Comparison of the absolute AM1 (kJ/mol) and ab initio (au) energies and dipole moments in Debyes for α-D-idopyranose $^{4}C_{1}$, $^{1}C_{4}$, and $^{O}S_{2}$ conformers.

	α-D-Idopyranose		
Parameter Method	$^{4}C_{1}$[a]	$^{1}C_{4}$	$^{O}S_{2}$
		AM1	
AM1 (GMMX)	-1251.98/3.58	-1245.95/1.49	-1257.46/2.21
AM1 (MMFF)	-1258.38/4.30	-1260.39/2.46	-1257.50/2.20
AM1 (MM3*)	-1276.74/3.17	-1262.31/2.33	-1252.60/2.60
		Ab initio	
6-311G**(MMFF)[a]	-683.534076/5.43	-683.534336/2.65	-683.529244/0.38
6-311G**(MM3*)[b]	-683.537926/5.69	-683.536345/2.57	-683.531451/3.24[c]
6-31+G* (MMFF)	-683.347928/5.81	-683.349932/2.68	-683.345363/0.33
6-31+G* (MM3*)	-683.352365/5.87	-683.352011/2.56	-683.347262/3.26

a. A boat structure is at 16.6 kJ/mol (-683.528004 au). b. The difference between the α- and β-forms of the $^{4}C_{1}$ D-idopyranose conformers is 3.66 kJ/mol based on the MM3* structures at the HF/6-311G** level of computation. The α-D-idopyranose is lower in energy. c. A higher energy conformer at -683.527526 au had a dipole moment of 2.97 Debyes, and the same hydroxymethyl geometry. This is a $^{3}S_{1}$ conformer (ring torsion angles of 34.3°, -61.5°, 23.4°); see torsion angles in Table 5.

force field. Both the AM1 and PM3 methods applied to carbohydrates give ring distortion problems,[26] but can show some interesting aspects of the hydroxyl orientation with relatively fast calculations. For example, the PM3 calculation for the α-D-idopyranose, MM3* force field, puts the $^{4}C_{1}$ conformation at lowest energy (0.00, $^{4}C_{1}$; 5.52 kJ/mol, $^{1}C_{4}$ and 15.28 kJ/mol, $^{O}S_{2}$). Compared to AM1 ordering of energies (Table 1), the PM3 calculation switches the $^{4}C_{1}$ to the lowest energy (0.00, $^{4}C_{1}$; 8.69 kJ/mol, $^{1}C_{4}$ and 14.45 kJ/mol, $^{O}S_{2}$). PM3 inverts the MMFF ensemble $^{4}C_{1}$ and $^{1}C_{4}$ energy values, too.

The AM1 values for a given conformer type would be expected to be the same if the structures converged to the same geometry. Utilizing computed dipole moments is a very quick way to tell if the basic structure is different. A more detailed relationship to the torsion angles can be seen in Table 5, and will be discussed later.



(a) $^4C_1$ (b) $^1C_4$ (c) $^OS_2$

Figure 3. The low energy conformers found for β-D-idopyranose in the MacroModel search with the MM3* force field using a 30 kJ/mol energy window consist of the (a) $^4C_1$ (45%), (b) $^1C_4$ (18 %), (c) $^OS_2$ (8%) and $^3S_1$ (8%). The Boltzmann-averaged NMR proton coupling constants are shown in Table 1 and the energies in Table 2.

It is important to examine the general fit of the hydroxymethyl proton coupling constants. Note how well the MMFF field reproduces the $J_{5,6S}$ and $J_{5,6R}$ values (Table 1), yielding an average of only 6% error when compared with the observed values. Although the GMMX ensemble fits the general trend in the coupling constants, it does not yield the mole percentage of $^1C_4$ and $^OS_2$ structures needed to fit the coupling constants. The MM3* determined ensemble cannot reproduce the coupling constants because the $^1C_4$ and $^OS_2$ relative energies are so large. The MM3 (92) relative energies[7] and, therefore, the coupling constants seem to fit better, although we observe the ordering of the energies to be different.

β-D-Idopyranose. The three basic conformers from each search have been examined using HyperChem (AM1), Spartan and Gaussian 94W at the 6-311G** level. For example, the relative energies found from 6-311G** (MM3* β-D-idopyranose structures) with $^1C_4$ lowest in energy are the $^4C_1$ and $^OS_2$ structures at 3.7 kJ/mol and 26.0 kJ/mol, respectively. A comparison of NMR ensemble-averaged proton coupling constants are shown in Table 1 and the relative energies are in Table 2. The absolute energies and dipole moments from the quantum calculations are given in Table 4. Selected torsion angles for the structures are reported in Table 5. The MMFF force field again gives too much weight to the $^1C_4$ structures here, placing this conformer at the

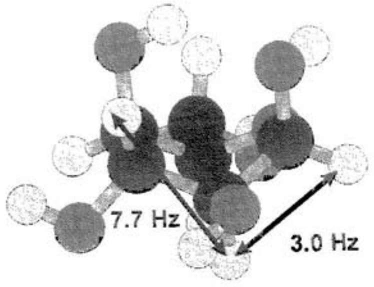


Figure 4. The lowest energy β-D-idopyranose $B_{2,5}$ boat structure found at 14 kJ/mol above the $^4C_1$ conformer using a GMMX search. This relative energy is high enough that it would not contribute to the NMR proton coupling constants. The ring torsion angles C(1)C(2)C(3)C(4), C(2)C(3)C(4)C(5), and C(3)C(4)C(5)O(5) are 43.9°, 10.6° and -58.0°.

Table 4. Comparison of the absolute AM1(kJ/mol) and ab initio (au) energies, and dipole moments in Debyes for β-D-idopyranose $^4C_1$, $^1C_4$ and $^OS_2$ conformers. Results are given as Energy/Debyes.

		β-D-Idopyranose	
Parameter/Method	$^4C_1$[a]	$^1C_4$	$^OS_2$
		AM1	
AM1 (GMMX)	-1256.58/1.33	-1269.22/0.97	-1256.96/1.38
AM1 (MMFF)	-1257.29/1.39	-1253.07/2.71	-1253.07/2.71
AM1 (MM3*)	-1263.74/3.41	-1268.88/1.99	-1250.01/1.97
		Ab initio	
6-311G**(MMFF)	-683.539149/2.10	-683.535165/2.80	-683.529106/1.90
6-311G**(MM3*)	-683.536860/5.52	-683.538254/2.64	-683.528324/1.59
6-31+G* (MMFF)	-683.353831/2.20	-683.349823/2.90	-683.343372/1.55
6-31+G* (MM3*)	-683.351755/5.64	-683.353037/2.67	-683.343699/1.70

a. The difference between the α and β forms of the $^4C_1$ D-idopyranose conformers is 3.66 kJ/mol based on the MM3* structures at the HF/6-311G** level of computation. The α-D-idopyranose is lower in energy. Compare values to those in Table 3. b. A higher energy conformer at -683.5291902 au had a dipole moment of 0.44 Debyes and the same hydroxymethyl geometry. c. The energy of $^3S_1$ completed at the 6-311G** level is 683.527526/2.97 au, with torsion angles of 30.2°, -59.0°, 25.0°, -177.6° and 53.3°.

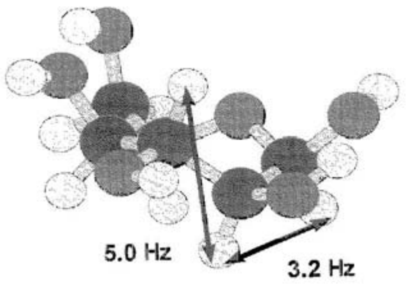


Figure 5. The β-D-idopyranose ${}^{3}S_{1}$ structure found using the MMFF parameters. It has ring torsion angles in the range of 28.5°, -59.5°, 27.5°. The $J_{1,2}$ and $J_{2,3}$ vicinal coupling constants are shown. The relative energy was 14.1 kJ/mol.

lowest energy. Having no contribution from the ${}^{4}C_{1}$ structures leads to coupling constants that are much too large (Tables 1 and 2). The MMX force field places the ${}^{4}C_{1}$ structures 7.4 kJ/mol lower than the ${}^{1}C_{4}$, which gives an rms deviation of 0.4 Hz in the coupling constants. The hydroxymethyl group coupling constants show that the distribution in the MMX ensemble is predicted well. The MM3* ensemble does not seem to fit the hydroxymethyl distribution for either the α- or the β-anomers. A $B_{2,5}$ structure is found at 14.0 kJ/mol for β-idopyranose while the ${}^{O}S_{2}$ twist structure is found at 19.4 kJ/mol for MM3*. The small presence of these latter structures in the conformational ensemble would not affect the solution NMR proton coupling constants. The difference in energy between the MM3* α- and β-anomers for the ${}^{4}C_{1}$ structures is 2.80 kJ/mol, calculated at the 6-311G** level. This value is too large considering the nearly equal intensities shown in the ^{1}H NMR spectra.[6] For the dominant structures in solution by energy, the α-anomer ${}^{4}C_{1}$ is 0.86 kJ/mol higher in energy than the ${}^{1}C_{4}$ β-anomer.

Examination of torsion angles in Table 5 shows some interesting trends and problems in this type of multiple force field analysis. First, note that the hydroxymethyl group angles vary considerably between the different searches. For example, in the MM3* calculation with α-D-idopyranose ${}^{4}C_{1}$ and ${}^{O}S_{2}$ conformers, the hydroxymethyl group is rotated into a different geometry from those of the other force fields. In addition, the C(4)-OH as listed and other OH groups are in very different orientations. Dipole

Table 5. Comparison of the molecular mechanics search structures with ab initio structure torsional angles for the $^4C_1$, $^1C_4$, and $^OS_2$ conformers.

	α-D-Idopyranose			β-D-Idopyranose		
Parameter	$^4C_1$	$^1C_4$	$^OS_2$	$^4C_1$	$^1C_4$	$^OS_2$
			GMMX[a]			
C(1)C(2)C(3)C(4)	-45.7	53.7	61.4	-48.3	54.4	43.9^b
C(2)C(3)C(4)C(5)	48.5	-53.4	-26.7	48.1	-54.4	10.6
C(3)C(4)C(5)O(5)	-55.8	54.9	-35.4	-54.3	53.8	-58.0
C(4)C(5)C(6)O(6)	-171.4	179.1	-171.0	-168.8	172.2	-172.2
H(4)C(4)O(4)H	56.5	53.5	61.0	-177.7	57.5	-177.1
			MMFF[c]			
C(1)C(2)C(3)C(4)	-52.5	53.6	60.7	-51.4	53.9	59.9^d
C(2)C(3)C(4)C(5)	53.0	-52.8	-27.3	50.7	-54.4	-27.6
C(3)C(4)C(5)O(5)	-55.1	52.5	-34.0	-55.4	51.9	-33.5
C(4)C(5)C(6)O(6)	-175.3	-176.3	-174.6	-175.8	-178.7	-174.8
H(4)C(4)O(4)H	46.2	69.1	62.5	165.4	69.2	-62.9
			MM3*			
C(1)C(2)C(3)C(4)	-54.4	53.9	61.5	-53.6	55.4	60.2
C(2)C(3)C(4)C(5)	55.7	-54.7	-35.4	54.6	-54.1	-34.3
C(3)C(4)C(5)O(5)	-56.8	55.1	-27.3	-58.3	51.1	-28.1
C(4)C(5)C(6)O(6)	46.7	-174.5	59.8	46.3	-69.2	59.9
H(4)C(4)O(4)H	-71.5	61.8	55.4	-71.2	59.5	55.5
			Ab initio (6-311G**)[e,f]			
C(1)C(2)C(3)C(4)	-50.7	55.3	63.6	-50.3	53.9	64.9
C(2)C(3)C(4)C(5)	49.7	-53.7	-34.9	50.6	-54.4	-34.8
C(3)C(4)C(5)O(5)	-52.9	50.5	-26.6	-54.6	51.9	-25.9
C(4)C(5)C(6)O(6)	-173.9	-177.4	-166.6	-176.3	-178.7	-173.6
H(4)C(4)O(4)H	57.3	65.3	61.3	165.1	69.9	61.1

a. The torsion angles are from the GMMX search with the MMX force field using $\varepsilon=4.0$ and no H-bond function. b. This is a boat structure; a $^OS_2$ structure was observed at ΔE = 16.4 kJ/mol with angles 61.5, -23.9 and -37.7°. c. The torsion angles are from the MacroModel search with water solvent and the MMFF field. d. There is a $^3S_1$ structure close to the $^OS_2$ structure at 16.7 kJ/mol with torsion angles of 26.8, -58.6, 27.1, -178.6, -46.8°. e. The ab initio values are computed from minimum energy structures taken mainly from the MMFF search. f. The torsion angles for the 16.4 kJ/mol boat conformer are 28.8, 28.4, -63.6°.

moments vary greatly with different hydroxyl and hydroxymethyl group orientation. All the β-anomer searches place the $^{O}S_2$ conformer at a high energy. Again, the torsion angles for the MM3* results are different. It is also noteworthy that the GMMX pyran ring torsion angles show more distortion than those of the other methods, which is true also for the β-idopyranose $^{4}C_1$ conformer. In fact, these variations present problems when running a number of higher-level quantum mechanical calculations; for example, exploring which OH configuration would produce the lowest energy structure. This is especially troublesome since the QM energy calculations are thought to be accurate only to 4 kJ/mol. This problem arises since the OH configuration depends considerably on the hydrogen bonding model used within the force field as well as solvent model characteristics. It would appear that temperature dependent results would be essential for clarifying the experimental order of the energies for these conformers.

The variations in the aqueous solvation energies that arise from the MacroModel study are also of interest. Consider the results for the α-anomer using the MMFF parameter set. The low energy $^{1}C_4$ conformer with all hydroxyl groups counterclockwise has an aqueous solvation energy of –73.1 kJ/mol, which changes to –98.2 kJ/mol for the higher energy $^{4}C_1$ conformer in which all hydroxyl groups are counterclockwise. The lowest energy $^{1}C_4$ conformer which has the four hydroxyl groups counterclockwise has a solvation energy of -79.2 kJ/mol. For a total clockwise set of hydroxyl groups (MMFF) in the $^{1}C_4$ conformer, the solvation energy is lowered to –89.6 kJ/mol and the total relative energy increases by 8 kJ/mol over the lowest energy. For the MM3* force field results, the lower energy $^{4}C_1$ conformer, with all of the hydroxyl groups clockwise, has a solvation energy of -62.0 kJ/mol. The value for the $^{1}C_4$ conformer is –53.8 kJ/mol with all hydroxyl groups clockwise. The lowest energy $^{4}C_1$ MM3* conformer, having hydroxyl groups 1 and 3 counterclockwise and 2 and 4 clockwise in hydrogen bonded pairs, has a solvation energy of -40.0 kJ/mol.

Interestingly, if one uses the MMFF parameter set to minimize the low energy $^{4}C_1$ MM3* conformer which has the hydroxyl groups clockwise, the solvation energy is –79.5 kJ/mol, and the conformer energy jumps by 12.0 kJ/mol over the $^{1}C_4$ value. Likewise, when the low energy MMFF $^{1}C_4$ conformer with all hydroxyl groups counterclockwise is minimized with the MM3* parameter set, the solvation energy is changed to –49.8 kJ/mol and the energy jumps 20.0 kJ/mol over the lowest energy $^4C_1$ conformer. The largest solvation energy was –101 kJ/mol for the MMFF $^4C_1$ conformer β-anomer with all hydroxyl groups clockwise. The results show that the solvation energies are all more negative when using the MMFF parameter set compared to MM3*, and that calculated solvation energies vary considerably with the hydroxyl group orientation being generally more negative with all of the hydroxyl groups clockwise.

CONCLUSION

It has been shown in this study that conformational searching methods using MacroModel and GMMX coupled with quantum mechanical methods can lead to useful interpretation of ^{1}H NMR coupling constants. The MMFF parameter set used with MacroModel applied with GB/SA water solvent leads to a good explanation of the complete set of proton coupling constants for α-D-idopyranose. However, the $^1C_4$ conformation is overweighted in the conformer ensemble for β-D-idopyranose, leading to a poor set of coupling constants. The MM3* parameter set, on the other hand, gives a poor fit to the proton coupling constant set for α-D-idopyranose, and a satisfactory fit for the β-D-idopyranose except for the hydroxylmethyl constants. The GMMX search finds reasonable relative energies but not a good percentage distribution of conformers. The mole percent distribution of $^1C_4$ in the ensemble is too small. The GMMX coupling constants, including the hydroxylmethyl constants, however, do show a good fit for the β-D-idopyranose. Ab initio results generally support the relative energies found for each molecular mechanics method. However, on an absolute basis there are inconsistencies between the ordering of the ab initio conformer energies, the force field data, and the proton coupling constant predictions of relative energies. This may be due to the non-solvent treatment of hydrogen bonding by the ab initio method. A preliminary ab initio SCRF/PCM water model treatment of α-D-idopyranose places the $^1C_4$ lowest energy MM3* conformer lower than the lowest energy $^4C_1$ conformer. The use of dipole moments is also shown to be quite effective in determining when conformers do not have the same hydroxyl group configuration. Finally, when dealing with energies that are within 4 to 6 kJ/mol, it is important to remember that variation in the methods themselves can lead to problems in obtaining the correct ordering of conformer structures by energy.

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