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Note

Crystal-solution structural equivalence of methyl 3,6-anhydropyranosides

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In the application of a recently developed chiroptical method of conformational analysis to anhydro sugars [1], it was found that the optical rotations calculated for the crystal structure geometries of a series of methyl 3,6-anhydro-D-pyranosides, with approximately $^1C_4$ ring forms, did not match the observed rotation values in solution. The calculated values were brought into line with experiment when the ring conformation was changed in the direction of the envelope E_4 form. Therefore, a solvent induced conformational change was proposed.

In a series of molecular modeling studies, originally intended to provide supporting evidence for such a conclusion, we have found, to the contrary, significant evidence for crystal-solution structural equivalence, indicating that the optical rotation model used earlier [1] is not directly applicable to 3,6-anhydro sugars (see later).

Methyl 3,6-anhydro-α-D-galactopyranoside was taken as representative of the series. First, an ab initio geometry optimization of the molecule's ground state was carried out with the package GAMESS [2], starting with the crystal structure determined by X-ray [3]. The molecular energy was calculated at the single configuration Hartree–Fock self-consistent field level, with a "triple zeta valence" basis set, (5s)/[3s] for H, (10s 6p)/[5s 3p] for C,O. The geometry was optimized using the Newton–Raphson method with analytical energy gradients.

The ab initio geometry optimization converged after 27 iterations to within 0.03 kcal mol^{-1}. The optimized structure is very similar to the X-ray structure. The structures are described in Table 1 in terms of Cremer–Pople ring-puckering parameters [4,5]. Q, ϕ

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Table 1
Methyl 3,6-anhydro-α-D-galactopyranoside conformations and some calculated molecular properties

Conformation	Cremer–Pople parameters			Ab initio	MM3(92)	$[M]_D$ [b]	J_{12} [c] Hz
	Q Å	ϕ deg	θ deg	Energy [a] kcal mol^{-1}	Energy kcal mol^{-1}	°cm^2 dmol^{-1}	
Idealized $^1C_4$			180.0				
Crystal structure [3] "$^1C_4$"	0.672	63.5	158.3			-44	
Ab initio optimized "$^1C_4$"	0.653	56.0	156.2	-8.09		-41	
Dynamics simulation, average (sd)	0.668(2)	58.6(11)	159.7(5)			-46(2)	
MM3(92) optimized "$^1C_4$"	0.654	63.4	159.1		26.84	-47	2.4
	0.635	57.7	149.6		27.86	-17	3.2
	0.640	58.6	136.5		30.67	41	4.6
"E_4"	0.672	59.1	124.6		32.52	122	5.9
	0.717	59.4	114.4		32.05	198	6.0
	0.775	59.6	105.4		31.10	229	5.3
"B_{14}"	0.848	59.8	97.5		32.53	232	4.5

[a] Referenced to the *ab initio* energy of the crystal structure. [b] The observed value in solution is 145° cm^2 dmol^{-1} ($c = 1$, water, 20° C) [9]. [c] The observed value in solution is 2.8 Hz.(5-10%, deuterium oxide, 20° C).[11]

and θ are a set of spherical polar coordinates in which Q is a measure of the displacement of ring atoms from a defined plane, and ϕ and θ together specify the ring shape; e.g. the polar positions, $\theta = 0°$ and $\theta = 180°$, correspond to $^4C_1$, and $^1C_4$ ring forms respectively, and the equator, $\theta = 90°$, encompasses six boat and six skew conformations through variation in ϕ. The X-ray structure, and the ab initio optimized structure are "distorted" $^1C_4$ rings.

A molecular dynamics simulation in vacuo was also carried out, taking the initial structure to be that found in the crystal. The TRIPOS force field was used, without electrostatics. The calculation interval was 1 fs. After temperature ramping of 50 ps per step with a 50-K step size, the system was equilibrated at 300 K for 100 ps. Dynamics were run for 1 ns with 100 fs sampling intervals. There was no significant departure from the ring conformation of the crystal structure (Table 1, Fig. 1). Q fluctuated within an interval of approximately 0.01 Å, ϕ and θ fluctuated within approximately 4 and 2°, respectively. It appears that crystal packing forces do not play a major role in determining the ring conformation found in the solid state.

A broader survey of pyranosyl ring conformations was carried out with the MM3(92) force field. For each ring form examined, the molecular energy was minimized starting from twenty-seven different conformations of exocyclic conformers, which allows for a three-fold staggered rotational sampling of the methoxy group and the two hydroxyl groups. Ring conformations were sampled along the pseudorotational itinerary [6,7] passing from the region near the crystal structure, through the E_4 region, to the B_{14} form. Structures were generated by constraining the optimization of ring atoms, as previously described [7]. Electrostatic contributions to the energy were evaluated with a dielectric constant of 4.0 [8]. The MM3(92) geometry optimization results (Table 1) in a ring conformation very similar to the X-ray crystal structure. Although a shallow

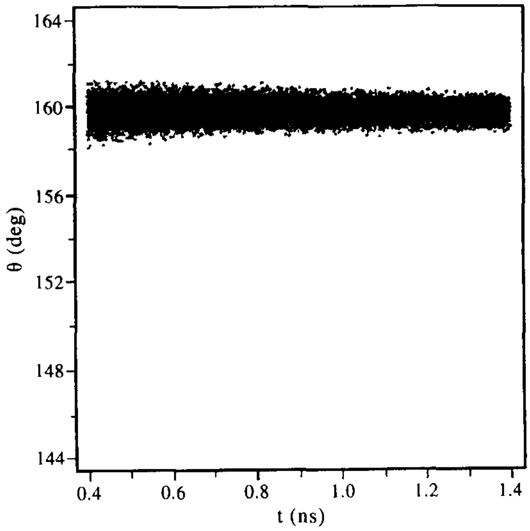

Fig. 1. A 1-ns time evolution of the θ ring puckering parameter of methyl 3,6-anhydro-α-D-galactopyranoside.

secondary energy minimum appears near $\theta = 105°$, it is > 4 kcal mol^{-1} higher than the crystal structure conformer.

Thus, all three modeling methods support crystal-solution structural equivalence, in spite of the significant differences in the three methods. Electrostatic interactions are included in the MM3(92) calculation, but not in the molecular dynamics simulation. A continuous solvent was simulated in the MM3(92) calculation by using a dielectric constant of 4.0. Solvent was not included in the molecular dynamics and ab initio calculations. Explicit hydrogen-bonding interactions are included in MM3(92), absent in the dynamics simulation, and implicitly allowed in the ab initio calculation. The fact that such disparate models produce the same energy-optimized structure must be considered significant, and indicates that, to the extent that there is an equilibrium mixture of ring conformations, it is strongly weighted in favor of the crystal structure.

Optical rotations, calculated with the algorithm MOLROT as previously described [1] (Table 1), confirm the earlier result that the rotation calculated for the crystal structure geometry is very much different from the value observed in solution [9]. Although a pyranosyl ring conversion in solution to the envelope E_4 form would bring the observed and calculated rotations into agreement (Table 1), the modeling calculations argue for crystal-solution structural equivalence.

The $J_{1,2}$ coupling constants, calculated with the method of Haasnoot et al. [10] (Table 1), also agree with the observed value [11] for ring conformations near that found in the crystal. Other calculated coupling constants for the MM3(92) optimized ring conformation, in Hz, and the observed values (parentheses) are: $J_{2,3}$ 5.0 (5.8), $J_{3,4}$ 1.0 (< 0.5), $J_{4,5}$ 2.1 (2.0), $J_{5,6}$ 1.2 (< 0.5), $J_{5,6'}$ 3.6 (2.9). The agreement is within expected values.

In reviewing the earlier application of MOLROT to 3,6-anhydro sugars [1] it now seems likely that the C–O polarizability parameters that were optimized for ring C–O bonds cannot be used for the ether C–O bonds of the 3,6-anhydro bridge; they must be applied only to acetal C–O bonds. In 1,6-anhydro sugars, the anhydro bridge C–O bonds are part of the acetal group, which explains why the optical rotation analysis confirmed crystal-solution structural equivalence, in agreement with a substantial amount of ^{1}H NMR data [12]. The rotations of 3,6-anhydro sugars are not correctly evaluated with the MOLROT algorithm because at this time it lacks polarizability parameters for ether C–O bonds, other than those of acetal groups. The present work again illustrates the importance and the uniqueness of the acetal group in determining the optical rotation of saccharides.

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