Monte Carlo Results for the Effect of Solvation on the Anomeric Equilibrium for 2-Methoxytetrahydropyran

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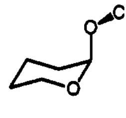
The anomeric effect is central to understanding the conformational preferences of carbohydrates.[1] Solvation may be an important moderator that typically leads to diminished favoring of the axial disposition of alkoxy substituents with increasing solvent polarity.[2] However, quantitative data on the magnitude of the solvent effects are limited and debate continues about their significance in general. For example, two recent computational studies revealed approximately no hydration effect on the equilibrium between α- and β-D-glucose,[3] while two earlier, technically related studies found significantly more attractive solute–water interactions for the β anomer.[4] We have pursued the issue by performing Monte Carlo simulations to obtain the changes in free energy of solvation for conversion between the axial and equatorial forms of 2-methoxytetrahydropyran (MTP). The analysis is particularly thorough since complete torsional profiles have been obtained for rotation about the C2–OCH_3 bond in water for both anomers. The results compare favorably with new experimental data[5] and show significant discrepancies with AM1/SM2 predictions.

The OPLS/AMBER united-atom potential functions for ethers[6] were readily extended to acetals; an atom type for the acetal carbon was added along with bond stretching, angle bending, and torsional terms selected to reproduce the structures and relative energetics from ab initio 6-31G* calculations[7] for conformers of dimethoxymethane (DMM).[8] Further testing included Monte Carlo simulations of pure liquid DMM and 1,3-dioxolane; the average errors in the computed densities and heats of vaporization are 1% at 25 °C and 1 atm. Gas-phase optimizations of all intramolecular variables for the six conformers of MTP yielded the relative energies in Table 1. The OPLS/AMBER findings are similar to 6-31G*//6-31G* results[5] with the axial sc, sc and equatorial t, –sc forms separated by 1–2 kcal/mol. The AM1[9] calculations give a larger energy difference for this pair and erroneously predict the t, sc conformer to be lower in energy than the t, –sc form.

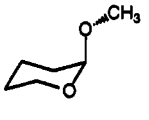
Table 1. Computed Relative Energies (kcal/mol) for Conformers of MTP in the Gas Phase and Aqueous Solution

	gas phase			water	
conformer	OPLS/ AMBER	6-31G*// 6-31G*	AM1	OPLS/ AMBER	AM1 + SM2
sc, sc	0.00	0.00	0.00	0.0	0.00
sc, t	5.11		3.25[a]	3.3	2.80[a]
sc, –sc	12.21		3.69	9.2	2.39
t, –sc	1.81	1.47	2.52	–0.3	2.19
t, t	7.81		6.63[b]	2.7	5.39[b]
t, sc	4.80	4.38	2.42	2.4	1.91

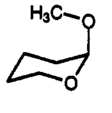
[a] Not a gas-phase minimum; C–C–O–CH_3 angle constrained to be –60°. [b] Not a gas-phase minimum; C–C–O–CH_3 angle constrained to be 60°.



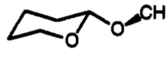
sc, sc



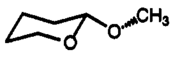
sc, t



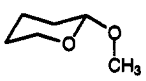
sc, -sc



t, -sc



t, t



t, sc

Monte Carlo simulations were then carried out with statistical perturbation theory to interconvert the sc, sc and t, –sc conformers in carbon tetrachloride,[10] acetonitrile,[11] and TIP4P water.[12] Ten simulations were performed in each case with double-wide sampling to perturb by epimerization between the gas-phase optimized structures using the BOSS program.[13] The numbers of solvent molecules were 126 for CCl_4, 265 for acetonitrile, and 260 for water, which were contained in cubic cells with periodic boundary conditions. Computational details are similar to those in related studies,[10] though it is noted that each simulation entailed 1 × 10^6 configurations of equilibration and (2–4) × 10^6 configurations of averaging in the NPT ensemble at 25 °C and 1 atm. The key result is that the equatorial t, –sc form is predicted to be better solvated than the axial sc, sc conformer by 0.11 ± 0.04, 1.6 ± 0.1, and 2.1 ± 0.2 kcal/mol in CCl_4, acetonitrile, and water, respectively. The recent thermodynamic study of Wiberg and Marquez on 4,6-dimethyl-MTP found the equatorial form to be better solvated than the axial isomer by 0.2, 0.8, and 1.5 kcal/mol in these three solvents.[5] A prior computational study for MTP with an ab initio reaction field method gave corresponding differences of 0.6 kcal/mol in CCl_4 and 1.4 kcal/mol in water.[14] This model would not predict a difference between high dielectric media such as acetonitrile and water. NMR and optical rotation measurements found preferential solvation of the equatorial form by 0.6 kcal/mol more in acetonitrile than in CCl_4 and by 0.9–1.5 kcal/mol more in water than in CCl_4.[2]

The analysis of the solvent effects in water was extended by computing free energy profiles for rotation about the C2–OCH_3 bond for both anomers. The details of the simulations were the same as above, and the perturbations were performed in steps of 7.5°. The results are summarized in Figure 1, which shows the modification of the gas-phase energies with the relative free energies of hydration to give the total relative free energies in water. The results for the six conformers are also given in Table 1. The gas-phase energy change of 1.81 kcal/mol for sc, sc → t, –sc becomes –0.3 ± 0.2 kcal/mol upon addition of the –2.1 kcal/mol hydration effect. Averaging over the entire free energy profiles in water (eq 1) only changes the net ΔG to –0.4 ± 0.2

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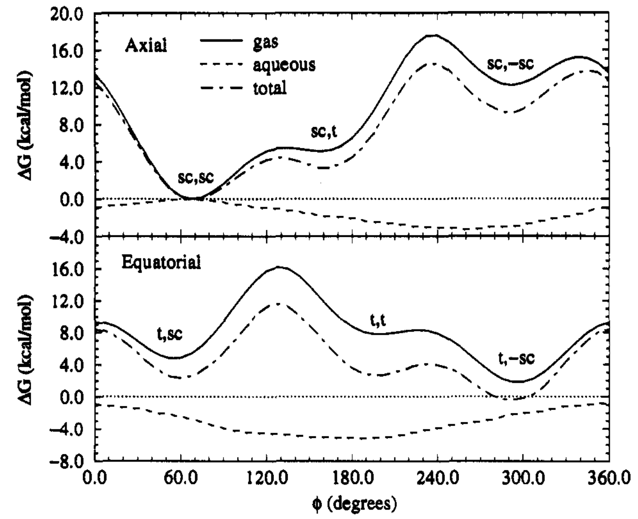

Figure 1. Computed energy profiles for rotation about the C2–OCH$_3$ bond in axial and equatorial MTP. Results are shown for the gas-phase optimizations, the change in free energies of hydration, and their sum. All values are relative to the sc, sc conformer.

kcal/mol between axial and equatorial.

$$\Delta G = -k_B T \ln[[\int \exp(-\Delta G_{\text{equ}}(\phi)/k_B T)\, d\phi] / [\int \exp(-\Delta G_{\text{ax}}(\phi)/k_B T)\, d\phi]] \quad (1)$$

This reflects the small populations of the other conformers at 25 °C and the similar curvature of the sc, sc and t, –sc wells in Figure 1. Experimental values for the net ΔG in water are +0.1 kcal/mol from NMR for MTP,[2] –0.7 kcal/mol from optical rotation for MTP,[2] and –0.3 kcal/mol from the recent thermodynamic study on 4,6-dimethyl-MTP.[5]

The free energies in water were also evaluated with the AM1/SM2 method[15] for the six conformers, as listed in Table 1.[16] The effects of hydration are predicted to be comparatively minor with this semiempirical continuum model for the solvent. Hydration decreases the gas-phase energy difference between the sc, sc and t, –sc forms by only 0.3 kcal/mol, and the t, sc conformer is still predicted to be the most stable equatorial form, 1.9 kcal/mol above the axial sc, sc conformer. The underestimation of the hydration effect compounds the favoring of the axial conformer by AM1 such that the stability of the axial form in water is significantly overestimated. 6-31G* calculations using a simple SCRF dipolar model with a spherical cavity also give a low estimate (0.4 kcal/mol) of the effects of hydration on the anomeric equilibrium for MTP.[17] It may be noted that replacement of the methoxy group in MTP by ammonium leads to a 2 kcal/mol hydration effect favoring the equatorial isomer with SM2 calculations.[18]

The origin of the 2.1 kcal/mol preferential hydration of the t, –sc conformer over the sc, sc one was pursued by performing hydrogen-bonding analyses on configurations saved during Monte Carlo simulations for these forms with fixed MTP geometries in TIP4P water. A hydrogen bond was defined by an MTP–water attraction of at least 2.25 kcal/mol and an MTP O–water H distance of ≤2.5 Å. Within the statistical limits of the calculations, the results for the two conformers were the same. Both have nearly one hydrogen-bonded water molecule on each oxygen, which is normal for ether oxygens,[19] with an average hydrogen bond strength of –4.1 kcal/mol. So, differential hydrogen bonding is not operative. However, the average MTP–water total interaction energies are –29.0 and –31.2 kcal/mol for the sc, sc and t, –sc rotamers. Thus, the interactions with the many non-hydrogen-bonded water molecules are responsible for the hydration effect. The key component is undoubtedly electrostatic as reflected in Figure 2, which shows that the computed relative free energies of hydration parallel remarkably the changes in dipole moment for MTP.

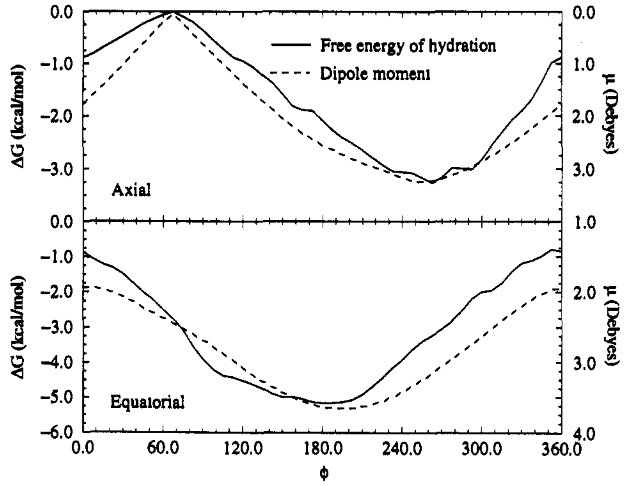

Figure 2. Comparison of the computed free energies of hydration relative to the sc, sc conformer and the change in dipole moment for axial and equatorial MTP upon rotation about the C2–OCH$_3$ bond.

Overall, the present calculations support the existence of a substantial (2 kcal/mol) effect of hydration, which preferentially stabilizes the equatorial form of MTP over the axial anomer. The effect originates from the higher dipole moment for the t, –sc conformer (2.7 D, OPLS; 1.9 D, 6-31G*) than for the sc, sc form (0.1 D, OPLS; 0.3 D, 6-31G*) and associated more favorable interactions with many water molecules. The effect emerges readily in the simulations with explicit solvent molecules in contrast to the results from simple continuum models.[20]

Supplementary Material Available: OPLS/AMBER parameters for acetals, computed thermodynamic results for liquid acetals, and plots of the free energy changes for the sc, sc to t, –sc conversions (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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