Density Functional Studies on the Solvation Free Energy of the Proton in Methanol

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The proton solvation free energy in methanol was calculated by B3LYP flavor of density functional calculations with the Poisson-Boltzmann solvation model. Solvents were taken into account in a hybrid manner, i.e., one to five molecules of methanol were explicitly considered while other solvent molecules were represented with an implicit solvation model.

The calculation of pK_a values is one of the subjects of extensive study in computational chemistry. Examples include carboxylic acids,[1] alcohols,[2] amines,[3] and uracil.[4] The proton solvation free energy is a central quantity in the calculation of absolute pK_a values. Tawa and coworkers calculated the free energy of proton solvation in water.[5] In contrast to the significant progress made on evaluating pK_a in aqueous solution, nonaqueous solutions have received far less attention although they are widely used in chemical reactions, separations, and characterizations. Here we report the proton solvation free energy in methanol. The structures and energetics of the protonated and neutral methanol clusters in solution have hitherto not been reported. In the gas phase, the structures of $H^+(CH_3OH)_n$ ($n = 2–5$) have been studied at the B3LYP/6-31+G* level.[6] Density functional theory (DFT) calculations on $(CH_3OH)_n$ ($n = 1–5$) clusters were reported by Hagemeister and coworkers.[7] MP2[8,9] and CCSD(T) energies[10] were also reported.

All the DFT computations reported here were done with the Jaguar v4.1 software package.[11] Solvent was taken into account in a hybrid manner. The first solvation shell was modeled explicitly and the remaining solvents were represented by a continuum. That is, the solvation free energy was calculated by monitoring the following reaction:

$$H^+(g) + (CH_3OH)_n(sol) \rightarrow H^+(CH_3OH)_n(sol), \quad (1)$$
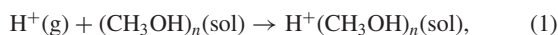
with n the number of explicit methanol molecules. The convergence was checked against n. This hybrid model allows not only faster convergence but also the inclusion of short-range directional interactions such as hydrogen bonding. The solvation free energy of proton in methanol, $\Delta G_{sol}(H^+)$, was calculated as

$$\Delta G_{sol}(H^+) = \Delta G(H^+(CH_3OH)_n, \text{sol}) \\ - \Delta G((CH_3OH)_n, \text{sol}) - \Delta G(H^+, g), \quad (2)$$

where $\Delta G(A, \text{sol})$ is the Gibbs free energy of species A in solution, which can be written as

$$\Delta G(A, \text{sol}) = \Delta G(A, g) + \Delta G_{sol}(A). \quad (3)$$

The gas phase Gibbs free energy, $\Delta G(A, g)$ was estimated from

$$\Delta G(A, g) = E_0 + ZPE + \Delta\Delta G_{0\rightarrow 298}. \quad (4)$$

The gas phase energy at $0\,K$ (E_0), zero-point energy (ZPE), the Gibbs free energy change from 0 to 298 K from the rigid-body approximation ($\Delta\Delta G_{0\rightarrow 298}$), and the electrostatic contribution to the solvation free energy ($\Delta G_{sol}(A)$) were calculated at the B3LYP/6-31++G** level. For $\Delta G(H^+, g)$, the value of -6.28 kcal/mol was

used from the consideration of the entropy using the Sackur-Tetrode equation.[5] $\Delta G_{sol}(A)$ was evaluated from the difference between the electronic energy of species A in the gas phase including nucleus-nucleus repulsion and that in solution. The implicit Poisson-Boltzmann solvation model was used for the solution phase calculation.[12] A solute was depicted as a set of ESP atomic charges located in a cavity immersed in a continuum solvent with high dielectric constant and the solute-solvent boundary was represented by the surface of closest approach as a probe sphere was rolled over the van der Waals envelope of the solute. A probe radius of 2.00196 Å and a dielectric constant of 33.62 were used for methanol. Since the difference in the solvent-accessible surface area between $H^+(CH_3OH)_n$ and $(CH_3OH)_n$ would be marginal, the nonpolar cavity contribution to the proton solvation free energy was neglected. For water, the contribution of this term was less than 0.5 kcal/mol.[5]

In Figure 1 illustrated are the minimum energy conformers of $H^+(CH_3OH)_n$ in the gas phase that are similar to those reported earlier.[6] The geometry of $H^+(CH_3OH)_1$ was that of C_s symmetry with $r(OH) = 0.98$ Å, $\theta(HOH) = 110.6°$, and $\theta(COH) = 115.3°$. For $H^+(CH_3OH)_2$, both C_i ($\tau(CO\cdots OC) = 180°$) and C_s ($\tau(CO\cdots OC) = 0°$) symmetric isomers gave an imaginary frequency. The optimized structure had $\tau(CO\cdots OC) = -101.4°$. In $H^+(CH_3OH)_3$, the excess proton was located on the central methanol. The linear chain was the most stable conformation. For $n = 4$, the linear conformer was still the most stable. For $n = 5$, the cyclic conformer had the lowest energy. However, the inclusion of ZPE and the thermodynamic correction made the linear chain conformer more stable than the cyclic one. Solution phase geometries are also depicted in Figure 1. For $n = 1$ and 2, RMS deviations from the gas phase conformers were relatively small (0.03 Å for $n = 1$ and 0.11 Å for $n = 2$). For $n = 3$, the RMS deviation was 0.39 Å and for $n = 4$, 0.34 Å. The linear conformation was most stable for $n = 5$.
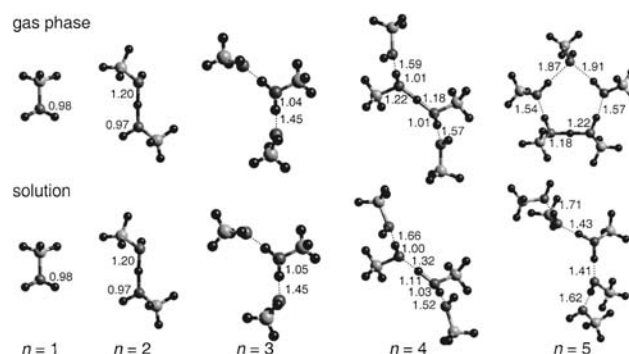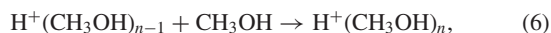

Figure 1. B3LYP/6-31++G** optimized structures of protonated methanol clusters $H^+(CH_3OH)_n$ ($n = 1–5$). The given bond lengths are in units of Å.

In order to verify the adequacy of the computation level, the free energies of clustering in the gas phase defined as

$$\Delta G_{n-1,n} = \Delta G(\text{H}^+(\text{CH}_3\text{OH})_n,\ \text{g})$$
$$- \Delta G((\text{CH}_3\text{OH})_{n-1},\ \text{g}) - \Delta G(\text{CH}_3\text{OH},\ \text{g}), \quad (5)$$

for the reaction

$$\text{H}^+(\text{CH}_3\text{OH})_{n-1} + \text{CH}_3\text{OH} \rightarrow \text{H}^+(\text{CH}_3\text{OH})_n, \quad (6)$$

were compared with other values in the literature (Table 1). The agreement is excellent considering the 10% accuracy of experimental values.[13] Since the scaling of the ZPE and thermodynamics[14] did not affect the value of $\Delta G_{n-1,n}$ by more than 0.01 kcal/mol, only the unscaled quantities are reported.

Table 1. Free energies of the clustering in the gas phase

	B3LYP/6-31++G**[a]	B3LYP/6-31+G*[b]	Experiment[c]
$\Delta G_{1,2}$	−25.43	−23.62	−24.0
$\Delta G_{2,3}$	−12.69	−11.06	−12.9
$\Delta G_{3,4}$	−6.07	−5.89	−7.5
$\Delta G_{4,5}$	−3.06	−2.68	−4.9

Unit: kcal/mol. [a]This work. [b]Reference 6. [c]Reference 13.

Figure 2 shows the minimum energy conformers of neutral methanol clusters that are also similar to those reported in references.[7–10] Cyclic conformers had the lowest energy for $n = 3$–5, as is consistent with the recent calculation.[10] Tables 2 and 3 show the relative energies between various conformers of the
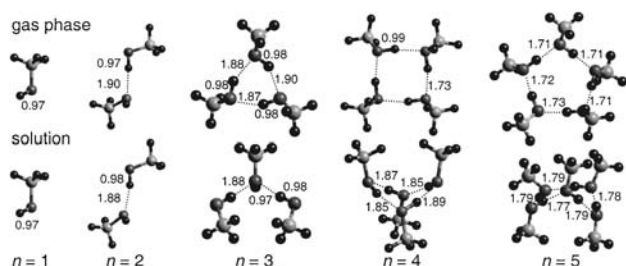

Figure 2. B3LYP/6-31++G** optimized structures of neutral methanol clusters $(\text{CH}_3\text{OH})_n$ ($n = 1$–5). The given bond lengths are in units of Å.

Table 2. Differences in the gas phase energy, ΔE_0, and the gas phase Gibbs free energy, $\Delta\Delta G(\text{g})$, and the free energy in solution, $\Delta\Delta G(\text{sol})$, between various conformers of $(\text{CH}_3\text{OH})_4$

Conformer	ΔE_0	$\Delta\Delta G(\text{g})$	$\Delta\Delta G(\text{sol})$
(4)	0.00	0.00	0.00
(3) + 1	7.23	5.64	3.01
4	7.42	5.77	0.49
3 + 1₂	10.78	7.53	1.06
3 + 1₁	12.52	9.64	0.20

Unit: kcal/mol.

Table 3. Differences in the gas phase energy, ΔE_0, and the gas phase Gibbs free energy, $\Delta\Delta G(\text{g})$, and the free energy in solution, $\Delta\Delta G(\text{sol})$, between various conformers of $(\text{CH}_3\text{OH})_5$

Conformer	ΔE_0	$\Delta\Delta G(\text{g})$	$\Delta\Delta G(\text{sol})$
(5)	0.00	0.00	0.00
(4) + 1	3.86	3.76	0.08
5	7.33	5.64	0.59
(3) + 2	8.30	8.91	4.60
(3) + 1 + 1	10.61	9.62	5.36
4 + 1₃	11.40	8.84	0.61
4 + 1₂	12.12	9.45	2.27
4 + 1₁	12.58	11.10	2.93

Unit: kcal/mol.

methanol tetramer and pentamer. The conformers are designated according to the nomenclature of Hagemeister and co-workers:[7] (n) represents a cyclic conformer, $\underline{n}$ a linear chain, $(n) + m$ a branched cylic, $n + m_x$ a chain of n units long with a branch at molecule x of chain length m units attached. In solution, free energy differences between various conformers of methanol clusters were much smaller than those in the gas phase, although the cyclic conformer was still the most stable one.

In Table 4, the proton solvation free energy in methanol calculated from Eq. (2) is listed as a function of the number of explicit methanol molecules. The most stable conformer is considered in the calculation. The inclusion of the conformational entropy can be done by Boltzman averaging over the conformers.[15] This is ~0.4 kcal/mol in the present case and it is smaller than the usual error associated with the quantum chemical calculations. The solvation free energy converged within 1.0 kcal/mol when $n > 3$. The converged value of −263.4 kcal/mol is comparable to the value for water, which was calculated to be −262.23 kcal/mol[5] and in the range of −256.6 to −262.5 kcal/mol from experiments.

Table 4. Solvation free energy of proton in methanol as a function of the number of explicit methanol molecules

n	1	2	3	4	5
$\Delta G_{\text{sol}}(\text{H}^+)$	−247.42	−255.40	−259.65	−263.46	−263.36

Unit: kcal/mol.

In summary, the absolute value of proton solvation free energy in methanol was calculated using a hybrid model. The solvation free energy converged when the number of explicit methanol molecules was greater than 3. Computations with a larger basis set and evaluation of the nonpolar term with additional parameterization are in progress.

References and Notes

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