

## Calculation of the Solvation Free Energy of the Proton in Methanol

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The solvation free energy of proton in methanol was calculated by B3LYP flavor of density functional calculations in combination with the Poisson-Boltzmann continuum solvation model. In order to check the adequacy of the computation level, the free energies of clustering in the gas phase were compared with the experimental data. The 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.

**Key Words :** Solvation, DFT, Poisson-Boltzmann, Methanol

### Introduction

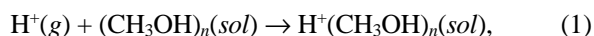
The calculation of  $pK_a$  values has been a subject of extensive studies in computational chemistry. One of the most widely using schemes for this purpose is the incorporation of solvation effects through self-consistent reaction field (SCRf) into density functional theory (DFT) electronic structure calculations.<sup>1</sup> Examples<sup>1-24</sup> include carboxylic acids,<sup>7-9,11,14,17-19</sup> alcohols,<sup>11</sup> thiols,<sup>11</sup> phenols,<sup>21</sup> pyrone derivatives,<sup>12</sup> amines,<sup>3</sup> imidazoles,<sup>5,24</sup> hydrated transition metal cations,<sup>2</sup> transition metal complexes,<sup>16</sup> phosphoranes,<sup>22</sup> and DNA (RNA) bases.<sup>6,15,23</sup> Recent applications are extended to the evaluation of  $pK_a$  values of 1) intermediate species that are not easily measured experimentally,<sup>22</sup> 2) weak organic acids with high  $pK_a$  values,<sup>13</sup> which cannot be measured experimentally in aqueous phase, and 3) molecules having multiple protonation sites.<sup>23</sup> Since the computation of  $pK_a$  involves quantum chemical calculations of the deprotonation events at the gas phase and the evaluations of the solvation free energies of the various species,<sup>20</sup> the accuracy relies on the methods for evaluating the gas phase acidity (or basicity), and for the solvation free energies. In addition, the uncertainty in the proton solvation free energy also limits the accuracy of the  $pK_a$  calculations. Since the evaluation of the solvation free energy in the continuum model involves the SCRf on the electron charge distribution, it cannot be applied to the proton directly. Therefore, experimental value is usually used when it is needed to report the absolute  $pK_a$  values. The value of  $-259.5$  kcal/mol was recommended by Lim *et al.*<sup>25</sup> However, it was estimated from five separate measurements of the absolute potential of the standard hydrogen electrode, which has 7 kcal/mol spread in the value from  $-254$  to  $-261$  kcal/mol. Tissandier and coworkers reported a value of  $-264.0 \pm 0.1$  kcal/mol from a set of cluster-ion solvation data.<sup>26</sup> Tawa and coworkers calculated the free energy of proton solvation in water.<sup>27</sup> They used the hybrid representation of the solvent and found that the free energy was converged to be  $-262.23$  kcal/mol when the number of

explicit solvents is larger than four. Mejias and Lago used the clusters up to 13 water molecules in their evaluation of the hydration free energy.<sup>28</sup> Zhan and Dixon reported a value of  $-262.4$  kcal/mol through a similar procedure with a different solvation model.<sup>29</sup> In contrast to much progress made for 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. We used the similar procedure as used for evaluating proton solvation free energy in aqueous solution.<sup>27-29</sup> Preliminary results at the B3LYP/6-31++G\*\* level<sup>30,31</sup> were reported elsewhere.<sup>32</sup> In the present study, we extend the calculation to the other basis sets and report the structure and energies of the clusters in detail. DFT calculations on  $(CH_3OH)_n$  clusters in the gas phase were reported by Hagemeister and co-workers.<sup>33</sup> MP2<sup>34,35</sup> and CCSD (T)<sup>36</sup> calculations for the small clusters were also reported.

### Computational Details

All the DFT computations reported here were done with the Jaguar v4.1 software package.<sup>37</sup> The 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:



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 specific directional interactions of short-range such as hydrogen bonding. The solvation free energy of proton in methanol,  $\Delta G_{sol}(H^+)$ , was calculated as follows:

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

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

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

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

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

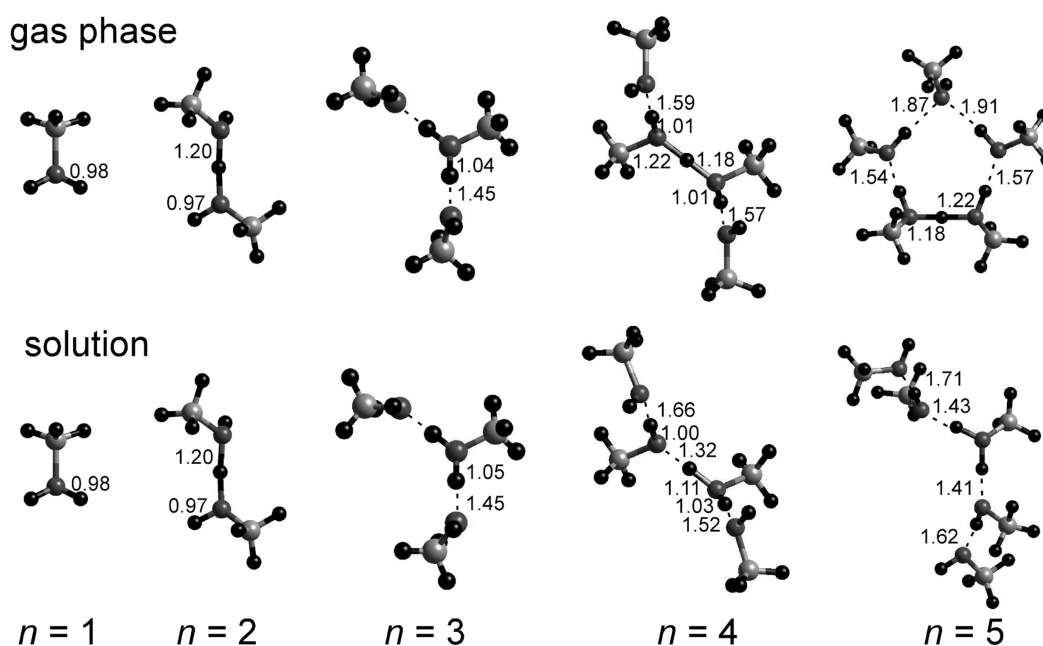
The gas phase energy at 0 K ( $E_0$ ), zero-point energy (ZPE), Gibbs free energy change from 0 K to 298 K ( $\Delta\Delta G_{0 \rightarrow 298}$ ), and the electrostatic contribution to the solvation free energy were calculated at the B3LYP<sup>38-41</sup>/6-31++G\*\* level. For the gas phase free energy of the proton,  $\Delta G(\text{H}^+, \text{g})$ , the value of  $-6.28$  kcal/mol was used from the consideration of the entropy at 298 K and 1 atm pressure using the Sackur-Tetrode equation.<sup>27</sup> The solvation free energy,  $\Delta G_{\text{sol}}(A)$  of neutral and protonated methanol clusters was calculated using the implicit Poisson-Boltzmann solvation model.<sup>42</sup> A solute was depicted as a set of 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. The probe radius of 2.00196 Å and the dielectric constant of 33.62 were used for methanol. Since the difference in the solvent accessible surface area between  $\text{H}^+(\text{CH}_3\text{OH})_n$  and  $(\text{CH}_3\text{OH})_n$  would be marginal, the nonpolar cavity contribution to the proton solvation free energy was neglected. For the aqueous proton solvation free energy, the contribution of this term was less than 0.5 kcal/mol.<sup>27</sup>

In order to get insight into basis set effects, the studies were repeated with four other basis sets (cc-pVDZ, aug-cc-pVDZ, cc-pVTZ(-f), and aug-pVTZ(-f)), using initial geometries obtained with 6-31++G\*\* basis set.

## Results and Discussion

**Protonated methanol clusters.** In Figure 1, the minimum energy conformers of protonated methanol clusters  $\text{H}^+(\text{CH}_3\text{OH})_n$  in the gas phase from B3LYP/6-31++G\*\* calculations are illustrated. (For the geometry, we only discuss the result from B3LYP/6-31++G\*\* basis set since the free energy of clustering based on this basis set is in better agreement with the experimental results than the values with other basis sets tested in this work.) The optimized structures were similar to those reported earlier.<sup>31</sup> The geometry of  $\text{H}^+(\text{CH}_3\text{OH})_1$  was of the  $C_s$  symmetry with  $r(\text{OH}) = 0.98$  Å,  $\theta(\text{HOH}) = 110.6^\circ$ , and  $\theta(\text{COH}) = 115.3^\circ$ . For  $\text{H}^+(\text{CH}_3\text{OH})_2$ , both  $C_1$  (dihedral angle  $\tau(\text{CO}\cdots\text{OC}) = 180^\circ$ ) and  $C_s$  ( $\tau(\text{CO}\cdots\text{OC}) = 0^\circ$ ) symmetric isomers gave one imaginary frequency. The optimized structure had a dihedral angle  $\tau(\text{CO}\cdots\text{OC}) = -101.4^\circ$ . The O–H<sup>+</sup> distance is calculated to be 1.20 Å, which is similar to the previous result from MP2/6-311+g(2d,2p) calculation yielding a symmetric hydrogen bond of length 2.38 Å with the proton located 1.19 Å from each oxygen.<sup>43</sup>

In  $\text{H}^+(\text{CH}_3\text{OH})_3$ , the excess proton was located on the central methanol. In contrast to the neutral methanol cluster, the linear chain was the most stable conformation. Its structure can be understood that  $\text{H}^+(\text{CH}_3\text{OH})_1$  has two first-nearest neighbors since it can donate two hydrogen bonds. For  $n = 4$ , the linear conformer was still the most stable. Recent vibrational predissociation spectroscopy (VPS) study of protonated methanol cluster shows the linear isomer is more stable than the cyclic one which is consistent with our calculation.<sup>30</sup> For  $n = 5$ , the cyclic conformer had the lowest energy. However, the inclusion of ZPE and thermodynamic correction at 300 K made the linear chain conformer more



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

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

	B3LYP/ 6-31++G** <sup>a</sup>	B3LYP/ cc-PVDZ <sup>a</sup>	B3LYP/ aug-cc-PVDZ <sup>a</sup>	B3LYP/ cc-PVTZ <sup>a</sup>	B3LYP/ aug-cc-PVTZ <sup>b</sup>	B3LYP/ 6-31+G** <sup>c</sup>	Experiment <sup>d</sup>
$\Delta G_{1,2}$	-25.43	-28.40	-23.22	-25.04	-23.34	-23.62	-24.0
$\Delta G_{2,3}$	-12.69	-15.13	-11.36	-13.35	-11.89	-11.06	-12.9
$\Delta G_{3,4}$	-6.07	-9.33	-4.52	-6.64	-4.79	-5.89	-7.5
$\Delta G_{4,5}$	-3.06	-6.25	0.66	-2.47	-0.06	-2.68	-4.9

Unit: kcal/mol. <sup>a</sup>This work. <sup>b</sup>ZPE and thermodynamic corrections at B3LYP/cc-PVTZ. <sup>c</sup>Reference<sup>31</sup> <sup>d</sup>Reference<sup>44</sup>

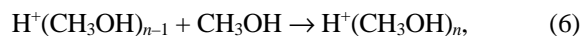
stable than the cyclic one. VPS study shows that the linear isomer is more stable at 300 K and that the peak corresponds to the cyclic one appears in a colder beam (250 K),<sup>30</sup> which shows excellent agreement with our computation results.

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  $n = 5$ .

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

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

for the reaction



are compared with other literature values (Table 1). The agreement is excellent considering the 10% accuracy of experimental values.<sup>44</sup> Since the scaling of the ZPE (0.9806) and thermodynamics (0.9989) according to reference<sup>45</sup> did not affect the value of  $\Delta G_{n-1,n}$  more than 0.01 kcal/mol, only the unscaled quantities are reported. Of the five basis sets tested in this work, B3LYP/6-31++G\*\* gives better agreement than other basis sets.

**Table 2.** The gas phase energy,  $E_0$ , and differences in the gas phase Gibbs free energy,  $\Delta\Delta G(g)$ , and the free energy in solution,  $\Delta\Delta G(sol)$ , between various conformers of  $(\text{CH}_3\text{OH})_4$ . See the text for the notation of the isomer.

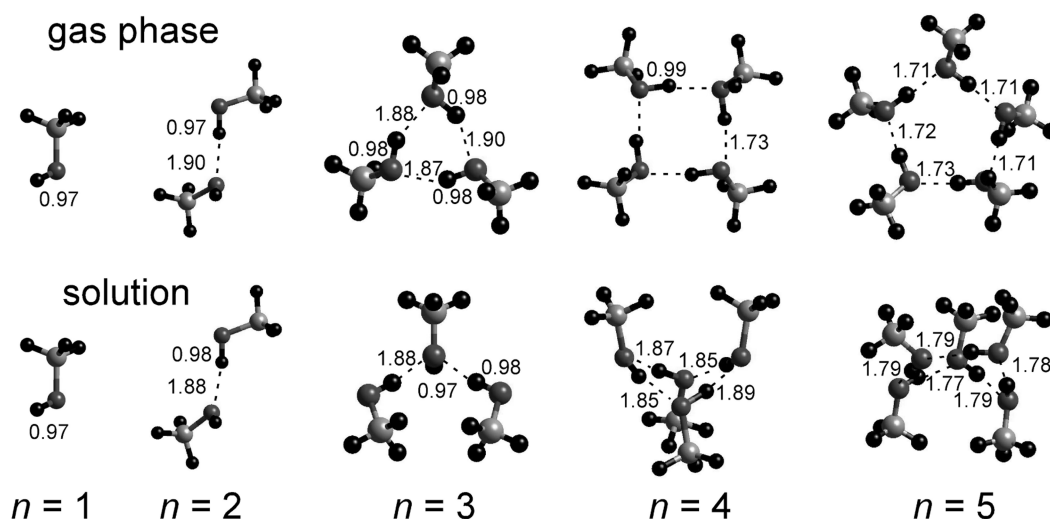
isomer	$\Delta E_0^b$	$\Delta\Delta G(g)^b$	$\Delta\Delta G(sol)^b$
(4)	0.00	0.00	0.00
(3)+1	7.23	5.64	3.01
4	7.42	5.77	0.49
$\underline{3}+1_2$	10.78	7.53	1.06
$\underline{3}+1_1$	12.52	9.64	0.20

<sup>a</sup>Unit: kcal/mol. <sup>b</sup>Relative to cyclic conformer (4).

**Table 3.** The gas phase energy,  $E_0$ , and differences in the gas phase Gibbs free energy,  $\Delta\Delta G(g)$ , and the free energy in solution,  $\Delta\Delta G(sol)$ , between various conformers of  $(\text{CH}_3\text{OH})_5$ . See the text for the notation of the isomer

	$\Delta E_0^b$	$\Delta\Delta G(g)^b$	$\Delta\Delta G(sol)^b$
(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
$\underline{4}+1_3$	11.40	8.84	0.61
$\underline{4}+1_2$	12.12	9.45	2.27
$\underline{4}+1_1$	12.58	11.10	2.93

<sup>a</sup>Unit: kcal/mol. <sup>b</sup>Relative to cyclic conformer (5).

**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 angstroms.

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

$\Delta G_{\text{sol}}(\text{H}^+)$	$n = 1$	2	3	4	5
B3LYP/6-31++G**	-247.42	-255.40	-259.65	-263.46	-263.36
B3LYP/cc-PVDZ	-252.51	-261.98	-265.86	-264.87	-265.24
B3LYP/aug-cc-PVDZ	-246.73	-254.02	-258.80	-261.56	-260.19
B3LYP/cc-PVTZ(-f)	-250.01	-256.32	-264.94	-265.41	-261.82
B3LYP/aug-cc-PVTZ(-f) <sup>d</sup>	-247.67	-253.95	-261.12	-265.19	-263.93

Unit: kcal/mol. <sup>d</sup>ZPE and thermodynamic corrections at B3LYP/cc-PVTZ(-f) level

**Neutral methanol clusters (CH<sub>3</sub>OH)<sub>n</sub>.** Figure 2 shows the minimum energy conformers of neutral methanol clusters that are similar to those from references.<sup>33-35</sup> Cyclic conformers had the lowest energy for the trimer through the pentamer. All O atoms in the cyclic conformers were in plane and the hydroxyl H atoms were nearly in the plane of the O atoms in the gas phase.

Tables 2 and 3 show the relative energies between various conformers of the methanol tetramer and pentamer calculated from B3LYP/6-31++G\*\* level of theory. The conformers are designated according to the nomenclature of Hagemester and co-workers:<sup>33</sup> (*n*) represents a cyclic conformer, *n* a linear chain, (*n*) + *m* a branched cyclic, *n* + *m*<sub>*x*</sub> a chain of *n* units long with a branch at molecule *x* of chain length *m* units attached. In solution, free energy differences among linear, branched-chain, and cyclic conformers of methanol clusters were much smaller than those in the gas phase, although the cyclic conformer was still the most stable one. The O atoms were not in plane contrary to the gas phase conformers.

**Proton solvation free energy in methanol.** In Table 4, the solvation free energy of proton in methanol is listed as a function of the number of explicit methanol molecules. B3LYP/6-31++G\*\* results give better convergence than the other basis sets. The solvation free energy converged within 1.0 kcal/mol when *n* > 3. The converged value of -263.4 kcal/mol (from B3LYP/6-31++G\*\*) is comparable to the value for water. The aqueous value was calculated to be -262.23 kcal/mol,<sup>27</sup> while experimentally it was reported in the range of -256.6 to -262.5 kcal/mol. (-259.5 kcal/mol<sup>25</sup>)

### Summary

In summary, we have demonstrated that the combined DFT and continuum dielectric theory is a useful tool for calculating molecular properties in solution even for methanol. The absolute value of proton solvation free energy in methanol was calculated using a hybrid representation of the solvent. The solvation free energy converged when the number of explicit methanol was greater than 3. The converged value of -263.4 kcal/mol (from B3LYP/6-31++G\*\*) is comparable to the value for water.

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