

Solvation Free Energies of Small Amines: An Interpretation Thereof and Its General Significance

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It is shown that by taking into account the thermodynamic contributions due to the internal rotations, the discrepancy between the experimental and the computed values of solvation free energies of small amines reported recently could be resolved. Arguments are presented as to why such contributions do not arise in similar studies involving, e.g., ethane or propane.

Solvation free energies of small amines and amides have been the subject of several fairly recent theoretical investigations. Tannor et al.¹ have used a combination of ab initio calculations and a continuum solvation model, and Cramer and Truhlar² have applied the combined semiempirical quantum mechanical/continuum model SM2. Molecular dynamics/free energy calculations have been carried out by Morgantini and Kollman³ and, with a different force field, also by Ding et al.⁴ and by Meng et al.⁵ Although the nonadditive effects⁴ and potential polarizability⁵ bring the solvation free energies of the amines in closer agreement with experiment, significant discrepancy remains for $\text{NH} \rightarrow \text{Me}_3\text{N}$ (calculated, 3–4 kcal/mol; experimental, 1.1 kcal/mol).³ Furthermore, all the models mentioned above are generally consistent for the amides and in disagreement with experiment for acetamide (ACT) \rightarrow *trans*-*N*-methylacetamide (NMA). The disagreement with experiment for the above amines and amide is surprising, given the very good agreement (within 0.5 kcal/mol) with experiment for calculation of the solvation free energy of methane, ethane, propane,⁶ watery,⁷ methanol,⁸ and dimethyl ether.⁹

Calculation of relative solvation free energy $\Delta\Delta G_{\text{solv}}$ of two molecules, M and N, is based on the thermodynamic cycle shown in Figure 1. Since the free energy is a function of state $\Delta\Delta G_{\text{solv}}$ is given by

$$\begin{aligned}\Delta\Delta G_{\text{solv}} &= \Delta G_{\text{solv}}(\text{N}) - \Delta G_{\text{solv}}(\text{M}) \\ &= \Delta G_{\text{aq}}(\text{M} \rightarrow \text{N}) - \Delta G_{\text{gas}}(\text{M} \rightarrow \text{N})\end{aligned}\quad (1)$$

The solvation free energies $\Delta G_{\text{solv}}(\text{N})$ and $\Delta G_{\text{solv}}(\text{M})$ can be determined experimentally but are difficult to calculate. On the other hand, $\Delta G_{\text{gas}}(\text{M} \rightarrow \text{N})$ and $\Delta G_{\text{aq}}(\text{M} \rightarrow \text{N})$, which correspond to the nonphysical change of M into N in the gas phase and in aqueous solution, respectively, could be obtained by computer simulations. It is usually assumed that the contributions of the internal degrees of freedom to the free energy in the gas phase and in solution are comparable.^{3,10} $\Delta G_{\text{gas}}(\text{M} \rightarrow \text{N})$ is neglected then, and the relative solvation free energy $\Delta\Delta G_{\text{solv}}$ can in this case be determined by a free energy perturbation calculation of $\Delta G_{\text{aq}}(\text{M} \rightarrow \text{N})$.

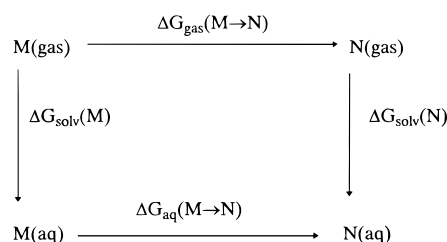


Figure 1. Thermodynamic cycle used to determine the relative free energy of solvation ($\Delta\Delta G_{\text{solv}}$) of the two molecules M and N.

In the following we shall examine more closely the contributions of internal rotations in the solvation free energy studies in question and show that, in the case of amines, these contributions in the gas phase are not the same as in water. It can be argued that attempts to resolve this problem by molecular dynamics simulations are likely to be highly demanding with regard to the required time scale. We shall base the present analysis on physical arguments instead. It should be stressed, though, that the effects which we intend to discuss here have a clearcut physical origin and can be evaluated rigorously.

We shall focus the analysis on the results of the thermodynamic perturbation calculations for the transformations $\text{NH}_3 \rightarrow \text{NH}_2\text{CH}_3$ and $\text{NH}_3 \rightarrow \text{N}(\text{CH}_3)_3$ reported in Table 3 of ref 5. These results were calculated with polarizable potential and may be regarded as being among the most accurate ones reported so far.

We first consider the $\text{NH}_3 \rightarrow \text{NH}_2\text{CH}_3$ transformation. A NH_2CH_3 molecule can be regarded as having an unsymmetrical top NH_2 attached to the rigid frame CH_3 . In vacuum the NH_2 group has three equivalent positions. In a water solution, however, the cluster is formed around the NH_2CH_3 molecule, due, in particular, to strong hydrogen bonding of water with the NH_2 group. This leads to several effects:

(a) The cluster can be regarded as being of rather low symmetry—its structure actually fluctuates. The exact symmetry number $n = 3$ of the potential function in vacuum in this case corresponds to an approximate symmetry of the potential function and not to an exact symmetry of the rotating group (NH_2 in the present case). For this reason the entropic contribution S_{ir}° due to internal rotation gains

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Table 1. Relative Free Energies for the Amine Perturbations (kcal mol⁻¹)

perturbation	$\Delta\Delta G_{\text{solv}}^a$	$\Delta\Delta G_{\text{solv}}^{b(\text{expt})}$	$\Delta\Delta G_{\text{solv}}^c$
NH ₃ → MeNH ₂	0.38 ± 0.06	-0.26	-0.26 ± 0.06
NH ₃ → Me ₃ N	2.90 ± 0.09	1.07	0.98 ± 0.09

^a Results of free energy calculations from ref 5. ^b Experimental numbers from Ben-Naim and Marcus¹³ and from Jones and Arnett (Me₃N).¹⁴ ^c Results of adding the contribution $\Delta\Delta S_{\text{ir}}$ of entropy of the internal rotation which is derived in the text to $\Delta\Delta G_{\text{solv}}^a$.

an extra term $\Delta\Delta S_{\text{ir}}^\circ$ given by¹¹

$$\Delta\Delta S_{\text{ir}}^\circ = R \ln n = R \ln 3 \cong 2.18 \text{ eu} \quad (2)$$

This term is absent in vacuum and may be neglected in the gas phase but must be taken into account in a water solution. The difference in the free energy $\Delta G_{\text{ir}}^\circ$ between the gas phase and water solution, due to the internal rotation, is then $\Delta G_{\text{ir}}^\circ = T\Delta S_{\text{ir}}^\circ \sim 0.64 \text{ kcal mol}^{-1}$ (at $T = 292 \text{ K}$). In the case of the NH₃ → N(CH₃)₃ transformation we find $\Delta G \sim 1.92 \text{ kcal mol}^{-1}$, since there are three internal rotations in this case. If the results in ref 5 are corrected for this change of the free energy contribution due to the internal rotation, very good agreement with the experimental results is obtained (Table 1).

It should be noted that the barrier of the internal rotation and also the reduced moments of inertia may also be changed due to the interactions with water molecules. These changes are generally very difficult to evaluate accurately. From the tables calculated in ref 12 it can be concluded, though, that the entropy corresponding to internal rotations is rather insensitive to moderate changes of the rotational barrier or of the reduced moment of inertia.

The above correction term in the entropic contribution due to the internal rotations does not arise in the case of, e.g., ethane or propane because in these molecules $n = 3$ is the exact symmetry number of the rotating group.¹¹ The present treatment is therefore consistent with the findings in ref 6. A methanol molecule, on the other hand, can also be regarded as having an asymmetrical top OH attached to the rigid frame CH₃, and, consequently, the term discussed above should arise in the entropy of internal rotation upon solvation. In ref 8 four models were applied to study methanol → ethane and methanol → methane transformations. Our conclusions are consistent only with the model in which equivalence was imposed on the methyl hydrogens at a particular stage of

the calculations. The correction derived above brings the results of this model reasonably close to the experimental ones. The other three models in which such equivalence was not imposed gave results close to the experimental values without having to be corrected for the symmetry breaking in the solution. Repeating these calculations for methanol with the polarizable potential model⁵ might be helpful in clarifying this situation since then a direct comparison with the two cases presently discussed could be made.

In conclusion we stress that the assumption that the contributions of internal degrees of freedom in the gas phase and in solution are comparable is not generally correct. If internal rotations exist in the molecule, possible corrections due to the symmetry breaking effects in solution must be considered. We have shown that these corrections bring the reported free energy of solvation of amines⁵ into very good agreement with experiment.

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