Ab Initio Studies on the Relative Stabilities of Neutral and Ionic Forms of Acetic Acid–Methylamine Complex and *β*-Alanine in Various Solvents

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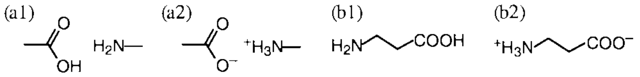
The preference between neutral and ionic forms of acetic acid–methylamine complex and *β*-alanine in solution was studied quantum mechanically. The solvents studied were water, methanol, CH_2Cl_2, and hexane, representing various polarities.

When the carboxyl (–COOH) and amino (–NH_2) groups are present together in solution, it is not always obvious whether they exist in a neutral or an ionic form. Although much known of their relative stabilities in water,[1,2] less is known in nonaqueous solvents. Since many experimental analyses and syntheses are performed in nonaqueous solvents, it is important to know which form is dominant for the understanding of experimental results and underlying interactions.

In this work, we tried to figure out which charge form of amine–carboxylic acid pair is more stable in various solvents by ab initio quantum mechanical calculations. The two functional groups of interest were represented by simple models (Scheme 1). In one approach, they were modeled by CH_3COOH and CH_3NH_2 and in the other by a single molecule *β*-alanine ($NH_2CH_2CH_2COOH$). The relative stability between the neutral-pair and the ion-pair complexes of trimethylamine and formic acid,[1] and the influence of benzene on the relative stability of ammonium formate complex[2] have been studied quantum mechanically. Calculations on *β*-alanine in aqueous solution have also been reported based on various theories.[3,4]



Scheme 1. (a1) Neutral and (a2) ionic forms of acetic acid and methylamine and (b1) neutral and (b2) zwitterionic forms of *β*-alanine.

The standard Gibbs free energy of a solute in solution was evaluated[5] by

$$\Delta G(\text{sol}) = E_0 + \text{ZPE} + \Delta\Delta G_{0\rightarrow 298} + \Delta G_{\text{solv}}. \qquad (1)$$

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 of the free energy of solvation (ΔG_{solv}) were calculated at the B3LYP/6-31++G** level,[6–9] using Jaguar v4.0.[10] The continuum solvation approach[11–13] with numerical solution of the Poisson–Boltzmann equation[14] was employed to calculate ΔG_{solv}. The solute was depicted as a set of atomic charges located in a low-dielectric cavity ($\varepsilon_{\text{QM}} = 1$) immersed in a continuum solvent of high dielectricity 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.[13] The probe radius and the dielectric constant (ε) of each solvent are listed in Table 1. The "nonpolar" contributions due to the creation of a solute cavity[13] were almost the same for neutral and ionic forms since their molecular surface areas were almost the same. This was verified by comparing the "total" solvation free energy difference between the two forms and the "polar" contribution difference (see Tables 1, 2, and 4). This result is important in calculations using the current version of Jaguar,[10] since the nonpolar contributions are not calculated for nonaqueous solvents.

Table 1. Solvent properties and differences in the solution phase free energies between the neutral and ionic forms of acetic acid–methylamine complex at infinite separation[a]

Solvent	Gas	Hexane	CH_2Cl_2	CH_3OH	Water	Water[b]
Probe radius/Å		2.97	2.33	2.00	1.40	1.40
ε	1	1.89	8.93	33.62	80.43	80.43
$\Delta\Delta G$	129.7	63.3	2.7	–8.2	–12.8	–12.8

[a] $\Delta\Delta G$ at 298 K in kcal/mol. Positive values indicate that the neutral species is more stable than the charged species. [b] Including the cavity contribution to the solvation energy.

First calculated was the difference in the solution phase energies between neutral and ionic forms in each solution of infinite dilution, the difference between $\Delta G(\text{sol},CH_3COO^-)$ + $\Delta G(\text{sol},CH_3NH_3^+)$ and $\Delta G(\text{sol},CH_3COOH)$ + $\Delta G(\text{sol},CH_3NH_2)$. Table 1 shows that the relative stability is in order of the solvent dielectric constant, and acetate and methylammonium would be in the ionic form both in methanol and in water. The fitting of the relative stability vs $1/\varepsilon$ yielded a linear correlation coefficient R of 0.9999, which indicates that the electrostatic term prevailed. The fitted data (intercept = –13.2, and slope = 143.1) show that two forms would have the same free energy at $\varepsilon = 10.8$. Note that the inclusion of the cavity terms did not affect the free energy differences. This suggests that the electrostatic term of the solvation free energy can be used at least for the relative stability without further parameterization of the cavity term. This perfect correlation is related to the fact that the geometry of each molecule (CH_3COOH, CH_3COO^-, CH_3NH_2, and $CH_3NH_3^+$) was almost the same in each solvent, and thus that the internal energy was almost the same. Only the differences in solute–solvent interactions mattered. As the first approximation these interactions can be written

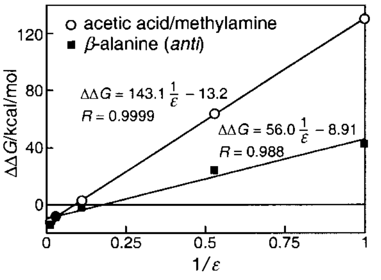


Figure 1. Plot of the calculated free energy difference between the ionic and neutral forms of acetic acid and methylamine (circle) vs the inverse of the solvent dielectric constant, and the same plot for *β*-alanine (square). Positive value indicates the neutral form is more stable than the (zwitter)ionic one.

as classical electrostatic terms. Then one can easily estimate the relative energy between neutral and ionic forms at infinite separation in a new solvent from the curve plotting the relative stability vs $1/\varepsilon$ provided that the geometry of the molecule remains the same in different solvents, i.e., for molecules with restrained torsional freedom and without multiple protonation sites.

Table 2. Difference in the solution phase energies of the neutral and ionic contacting pairs of acetic acid and methylamine

Solvent	Gas	Hexane	CH_2Cl_2	CH_3OH	Water	Water[b]
$\Delta\Delta E$	N/A[c]	N/A[c]	–2.5	–5.0	–6.5	–6.5

[a]Unit: kcal/mol. Negative values indicate the ionic form is more stable. [b]Including the cavity contribution to the solvation energy. [c]Not available since the ionic form is not an energy-minimum structure.

We then calculated the relative stability of the "contact" ionic pair with respect to the "contact" neutral pair in various solvents. For both neutral and ionic pairs, two forms of pairs were considered; one involves one hydrogen bond, and the other two hydrogen bonds. In the gas phase, the ionic forms were not stable, and the geometry optimization led to neutral pairs. The conformation with two hydrogen bonds had a free energy as much as 11.6 kcal/mol higher than the conformation with one hydrogen bond. Earlier calculations on $NH_4^+/HCOO^-$ pair showed similar proton transfer without an apparent barrier.[2] Recent calculations on trimethylamine–formic acid complex showed that the neutral complex was as much as 7.0 kcal/mol ($\Delta\Delta G_{298}$) more stable than the ionic pair in a vacuum at the level of MP4SDQ/6-311+G(3df,2p)//HF/6-31+G*.[1] However, the ionic form was not a "true" energy-minimum conformation with addition of polarization functions on hydrogen. On the contrary, the most stable form in water was an ionic pair that has one hydrogen bond between methylammonium and acetate. The optimized geometry is shown in Figure 2. Some bond lengths and angles of the complex are listed in Table 3. Unlike the infinite separation case, the ionic form was more stable than the neutral one in CH_2Cl_2 (Table 2). Note that this is not conclusive since neither ZPE nor the thermodynamic correction is included in the values in Table 2. The absence of the cavity contribution did not affect the relative energy between two charge states of the complex as in the case of infinite separation.

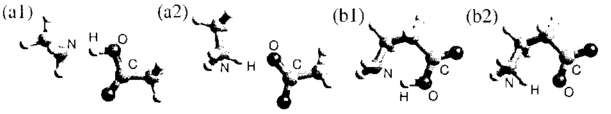


Figure 2. Optimized structures of (a1) acetic acid–methylamine in the gas phase, (a2) acetic acid–methylamine in water, (b1) β-alanine (*syn*) in the gas phase, and (b2) β-alanine (*syn*) in water.

Table 3. Selected geometric parameters of optimized structures[a]

	R(N···H)	R(H···O)	R(N···O)	θ(N···H···O)	θ(H···O···C)
(a1)	1.74 Å	1.01 Å	2.75 Å	176°	110°
(a2)	1.05 Å	1.85 Å	2.82 Å	162°	131°
(b1)	1.78 Å	1.00 Å	2.70 Å	152°	109°
(b2)	1.04 Å	1.78 Å	2.64 Å	137°	108°

[a]See Figure 2 for the labeling of the atoms and the molecules.

In the second approach, the two functional groups are linked by a C–C single bond resulting in β-amino acid. The neutral form of β-alanine in the extended form was more stable than the ionic form in the gas phase, whereas the ionic form was more stable in water due to its large solvation energy. Hexane stabilized the neutral form whereas CH_2Cl_2 and methanol stabilized the ionic form. Again the relative stability was proportional to the inverse of the solvent dielectric constant. Since two end groups were located away from each other in this conformation, the behavior of β-alanine was expected to be similar to the infinite separation case of methylamine and acetic acid to a first approximation. The linear correlation coefficient for β-alanine was 0.988 with a slope of 56.0 and an intercept of –9.81 (see Figure 1 and Table 4). The smaller value of R compared with the result for acetic acid–methylamine pair is due to geometry changes of β-alanine in different solvents. In the syn conformation, two functional groups were close to each other. In the gas phase and in hexane, the ionic form was not stable and the proton was transferred from $–NH_3^+$ to $–CO_2^-$, resulting in the neutral form.[3,4] However, in water, due to its favorable solvation, the ionic form was more stable than the neutral form. In CH_2Cl_2 and methanol, the ionic form was more stable due to the more favorable interaction between the two end groups, but the stabilization was not as much as in water.

Table 4. Energy differences between neutral and ionic forms of the *anti*- and *syn*-β-alanines[a]

	Gas	Hexane	CH_2Cl_2	CH_3OH	Water	Water[b]
$\Delta\Delta G$ (*anti*)	43.4	24.8	–1.4	–8.1	–13.4	–13.5
$\Delta\Delta E$ (*syn*)	N/A[c]	N/A[c]	–7.3	–11.5	–16.2	–16.6

[a]Unit: kcal/mol. Negative values indicate the ionic form is more stable. [b]Including the cavity contribution to the solvation energy. [c]Not available since the ionic form is not an energy-minimum structure.

In summary, we calculated the relative stabilities between neutral and ionic pairs of alkylamine–carboxylic acid in various solvents using quantum mechanical methods with a continuum representation of the solvent. The stability was directly related to the solvent dielectric constant. Polar solvent with a high dielectric constant preferred the ionic pair whereas nonpolar solvent stabilized the neutral pair. Proper parameterization of the nonpolar cavity term of the solvation free energy would give further insight on the conformational preference of the molecule. We are currently working on this line of research.

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