

Comprehensive Studies on the Free Energies of Solvation and Conformers of Glycine: A Theoretical Study

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The stable conformers of glycine and the inter-conversions between them were studied theoretically at various levels of theory, B3LYP, MP2, CCSD and CCSD(T), in the gas phase and in aqueous solution. In aqueous solution, the structures examined by use of the conductor-like polarizable continuum model (CPCM) with various cavity models, UA0, UAHF, UAKS, UFF, BONDI and PAULING, and by use of a discrete/continuum solvation model with eight water clusters. The Gibbs free energy differences between the neutral (NE) and zwitterionic conformers (ZW), $\Delta G_{Z-N} [= G_{ZW} - G_{NE}]$, in aqueous solution were well reproduced by using the BONDI and PAULING cavity models. However the ΔG_{Z-N} values were underestimated in other cavity models, although the ZW conformers existed as stable species in aqueous solution. In the studies of a discrete/continuum solvation model with eight water clusters, gas phase results are still insufficient to reproduce the experimental findings. However the ΔG_{Z-N} values calculated by use of CPCM method in aqueous solution agreed well with the experimental ones.

Key Words : Conformers of glycine, Free energies of solvation, Cavity models in CPCM, Neutral and Zwitterionic conformers

Introduction

Amino acids have been the subject of a variety of experimental¹⁻⁹ and theoretical studies¹⁰⁻⁶⁸ because of its central role in metabolism as building blocks of proteins. Especially, among 20 amino acids, glycine has been usually preferred as a subject of theoretical studies¹⁰⁻⁴⁵ due to its small size and the existence of experimental data.¹⁻⁹ High-level *ab initio* studies demonstrated that the neutral form (NE) of glycine exists in the gas phase but the zwitterionic form (ZW) is unstable *in vacuo*.^{11-20,27,30-33} However, as is well known, the ZW of glycine predominates in crystalline or in aqueous solution,² and hence the solvent (or environmental) effects should be included in the theoretical studies to explore the glycine chemistry correctly. Therefore the theoretical studies of glycine in aqueous solution have been mainly carried out by three different approaches; (i) calculations of the solute surrounded by some discrete water molecules¹⁰⁻²¹ (ii) calculations by statistical approaches such as Monte Carlo (MC)²⁵ or molecular dynamics (MD),^{14,19,22-24} and (iii) calculations by use of a dielectric continuum methodology.²⁶⁻³³ Nevertheless, the experimental findings¹⁻⁹ could not be successfully reproduced by most of these approaches, although some qualitative characteristics were consistent with the experimental findings.^{2,5} For example, it has been shown that the ZW of glycine exists as an energy minimum when at least two water molecules are included. However, an accurate description such as energy difference between the NE and ZW species would be achieved by introducing an immense numbers of water molecules due to the long-range property of electrostatic interactions, but these systems could not be actually handled even at a semi-empirical level

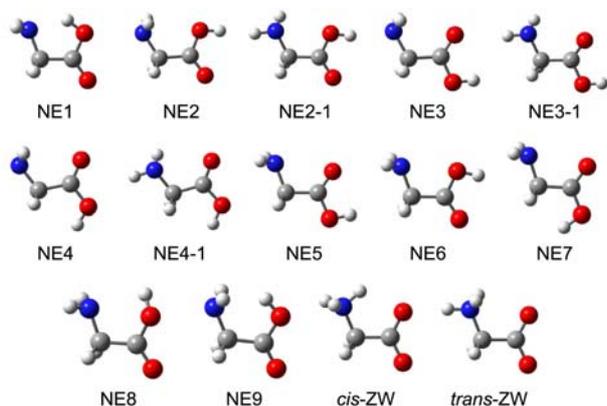
of quantum mechanical calculations. On the other hand, a great number of water molecules could be treated by using the MC or MD simulations,^{14,19,22-25} and some works on the ZW of glycine in water have been reported.¹³⁻²⁵ However, these simulations could be difficult to apply directly to a chemical process such as the intramolecular proton transfer of glycine, since the potential energy functions employed in these approaches might be hardly suitable to a chemical process. Recently, the mixed quantum mechanical/molecular-mechanical methods (QM/MM) have been developed to overcome these limitations,⁶⁹ but the methods could still include some inaccuracies associated with the MM region and the approximate treatment of electrostatic interactions at the boundaries between QM and MM regions.

The dielectric continuum model could be one of the popular choices for elucidating the solvent effects, and has predicted correctly that the ZW of glycine is a predominant species in aqueous solution. However, the continuum models could not reproduce accurately the characteristics of glycine such as the experimental energy difference between the NE and ZW species.^{27,30-33} Moreover, the main drawback of the continuum model could be the lack of microscopic information such as specific interactions between solute and solvent molecules.⁶⁹ Recently, Bandyopadhyay and Gordon⁴⁵ have reported that the energy difference between the NE and the ZW structures is $-8.6 \text{ kcal mol}^{-1}$ by applying a discrete/continuum solvation model combined with the effective fragment potentials (EFP) and isodensity polarizable continuum model (IPCM). This result seems to agree well with the experimental Gibbs-free energy differences of -7.27 or $-7.67 \text{ kcal mol}^{-1}$.² Moreover, they also reported the hydrogen-bonded NE and ZW clusters of glycine with eight water

molecules. Nonetheless, the energy difference ($-8.6 \text{ kcal mol}^{-1}$) obtained from their model was the sum of the differences in electronic energies (ΔE) and in solvation free energies (ΔG) between the NE and ZW forms, but the experimental findings^{2,3} were exclusively Gibbs free energy difference. Therefore, the direct comparison between these two values might be somewhat questionable.

Besides these works, many theoretical¹⁰⁻⁴⁵ and experimental^{2,6,8} works were performed to explore the glycine structures. In earlier works,^{11,17,19,20,27,31-33,38,39} various conformers for the NE of glycine shown in Scheme 1 were considered in the gas phase, and the NE3 structure was found to be the global minimum. In the NE2, NE3, and NE4 structures, the NH_2 group bisected the molecular plane, denoted hereafter as C_s -like conformers, while the NH_2 group in the NE2-1, NE3-1, and NE4-1 structures positioned in the same plane, labeled as C_1 conformers. Similarly, Falzon and Wang³⁸ also confirmed that the NE3 species was the global minimum in the gas phase. Interestingly, these works have also reported that the NE1 is more stable than the NE3 in aqueous solution. This indicates that the solvent effects play an important role for the stabilities of the neutral conformers as well as the appearance of the ZW form of glycine. However, even if the studies on the conformers of glycine have been reported,^{15,16,19,30} the exhaustive studies for inter-conversions between them at a sophisticated level of theory were relatively rare.

Therefore, in this work, among all possible structures of glycine shown in Scheme 1, the first seven NE conformers, NE1 ~ NE4-1, and the inter-conversion between them have been examined in aqueous solution as well as in the gas phase. The last five NE conformers, NE5 ~ NE9, were not considered because they were clearly unstable due to repulsive interaction between lone pairs on nitrogen and oxygen or between hydrogens facing each other.³¹⁻³³ For the calculations in aqueous solution, all the structures have examined by use of the conductor-like polarizable continuum model (CPCM) with various cavity models and by use of a discrete/continuum solvation model with eight water clusters. In the continuum model, the choice of a cavity model is very important because the free energy of solvation, G_s , largely depends on the choice of cavity



Scheme 1

model.⁷⁰⁻⁷² Therefore this study could provide comprehensive information about glycine chemistry.

Computational Methods

The structures of the seven NE conformers of glycine and transition structures for inter-conversions between these conformers were fully optimized in the gas phase without any geometrical constraints at the B3LYP level with the 6-311+G(d,p) and 6-311+G(3df,2p) basis sets and the MP2 and CCSD levels with the 6-311+G(d,p) basis set. The energetics were then refined using the CCSD(T)/6-311+G(d,p) level on geometries optimized at the CCSD/6-311+G(d,p) level. In aqueous solution, the seven NE and ZW conformers were firstly optimized at the CPCM-B3LYP/6-311+G(d,p) level with various cavity models (UA0, UAHF, UAKS, UFF,^{72,73} PAULING,⁷⁴ and BONDI⁷⁵) in order to choose the most reliable model. After selecting the best model, we performed aqueous phase optimizations by use of the CPCM methodologies. All the optimized structures were characterized by frequency calculations at the B3LYP and MP2 levels.

In the CPCM method, the non-electrostatic terms are important because the computed energies depend on the cavity size, one of the major components of the non-electrostatic terms.⁷⁰⁻⁷⁵ Therefore, in this work, the Gibbs free energies in aqueous solution were obtained by use of eq. (1), where G_s is the Gibbs free energy of solvation including the non-electrostatic terms such as cavitation and dispersion. In eq. (1), E_{el} is the gas-phase electronic energy obtained from the geometry optimized at the CPCM calculation and E_{ZPVE} , E_{Th} , and S are the zero-point vibration energy, thermal energy and entropy terms, respectively, obtained from the CPCM calculation. Since the CCSD(T) calculations were inapplicable to the CPCM method, all the structures in aqueous solution were optimized at the CPCM-CCSD/6-311+G(d,p) level and thus the ΔG_s values were obtained at the CPCM-CCSD levels.

$$G(\text{at } 298 \text{ K}) = E_{el} + E_{ZPVE} + E_{Th} + PV - TS + G_s \\ = E_{el} + G_{corr} + G_s \quad (1)$$

The discrete/continuum solvation model was employed for systems with eight water molecules in the gas phase and in aqueous solution at the B3LYP and MP2 levels with the 6-311+G(d,p) basis set. In aqueous solution, the geometry optimization was carried out by use of opt = loose option to overcome convergence problems. All calculations were performed with Int(grid = ultrafine) option by using the Gaussian 03 program.⁷⁶

Results and Discussion

As reported earlier,^{2,27,30-33} the ZW form in aqueous solution existed as a stable species in all the cavity models employed in this work. However, the relative stabilities of two conformers, *cis*-ZW and *trans*-ZW shown in Scheme 1, were dependent on theoretical levels as well as cavity

models. In the CPCM-B3LYP calculations using UA0, UAHF, UAKS and UFF cavity models,^{72,73} the *cis*-ZW form existed solely as a stable conformer but the *trans*-ZW form could not be located as a stable conformer. On the other hand, both conformers existed in the cases of the PAULING⁷⁴ and BONDI⁷⁵ cavity models, but the relative stabilities were dependent on the method chosen: The Gibbs free energy of the *cis*-ZW form was 1.4 kcal mol⁻¹ lower than that of *trans*-ZW at the CPCM-B3LYP/6-311+G(d,p) level in the former cavity model. In contrast, the *trans*-ZW form was 0.4 kcal mol⁻¹ more stable than the *cis*-ZW at the same level in the latter cavity model. However, the *trans*-ZW existed only as a stable species at the CPCM-MP2 and CPCM-CCSD levels. This indicates that the stability of the ZW conformers of glycine is highly sensitive to the theoretical levels as well as the cavity models, which suggests that C-NH₃⁺ bond might be a free rotatable bond.

The relative Gibbs free energies, ΔG , for the seven NEs and ZWs at the CPCM-B3LYP/6-311+G(d,p) level using the six cavity models in aqueous solution are summarized in Table 1. As shown in Table 1, the NE1 form was the most stable conformer among the neutral conformers in all cavity models except the UA0 model. In the UA0 cavity model, the NE3 was the most stable. The UA0 result was, however, inconsistent with the results reported in earlier works.^{17,19,30-33} In all the calculations at the CPCM-B3LYP/6-311+G(d,p) level, the electronic energies of the NE3 form, E_{el} in eq. (1), were slightly more stable (within 0.1 kcal mol⁻¹) than those of the NE1, but the free energies of solvation of the NE1, G_s in eq. (1), were *ca.* 2.0 kcal mol⁻¹ more favorable than those of the NE3 in all cavity models except the UA0 cavity model.^{72,73} As a result, the NE1 became the most stable neutral conformer due to the favorable G_s in aqueous solution. In the UA0 cavity model, the E_{el} and G_s values of the NE3 were slightly more favorable (by 0.4 kcal mol⁻¹) than the corresponding values of the NE1. Therefore, the result for the UA0 cavity model disagreed with the results obtained

Table 1. The relative Gibbs free energies, ΔG in kcal mol⁻¹, at 298 K for seven NEs and ZW species at the CPCM-B3LYP/6-311+G(d,p) level adopting the six cavity models in aqueous solution

Cavity	NE1	NE2	NE2-1	NE3	NE3-1	NE4	NE4-1	ZW
UA0	0.9	0.8	2.0	0.0	0.9	2.6	3.6	1.2 ^a
UAHF	0.0	1.3	2.5	0.5	1.7	1.9	3.2	1.0 ^a
UAKS	0.0	1.4	2.6	0.7	1.8	2.0	3.3	1.8 ^a
UFF	0.0	3.7	4.6	2.7	3.6	4.9	5.7	-0.6 ^a
BONDI	0.0	2.8	3.6	1.9	2.7	3.6	4.5	-7.2 ^b
PAULING	0.0	3.2	4.0	2.2	3.2	4.3	5.2	-8.2 ^a

^aValues were taken from the *cis*-ZW conformer. ^bValue was taken from the *trans*-ZW conformer.

by use of other cavity models and reported in earlier works.^{17,19,30-33}

For the calculations adopting the UAHF and UAKS cavity models,^{72,73} the NE1 were more stable than the ZW by 1.0 and 1.8 kcal mol⁻¹, respectively, even if the ZW form exists as a stable species. This result was also inconsistent with the general experimental findings^{2,3,5} that the ZW of glycine predominates in aqueous solution. It implies that the united atom topological models with implicit hydrogens of the UA0, UAHF and UAKS cavity models^{72,73} could be inadequate in the studies of glycine chemistry. On the contrary, the ZW form was more stable than the NE1 for the calculations adopting the UFF, PAULING⁷⁴ and BONDI⁷⁵ cavity models with explicit hydrogens. Especially, the ΔG values between the ZW and NE1 species, $\Delta G_{Z-N} [=G_{ZW} - G_{NE}]$, agreed quite well with the experimental values of -7.3 (or -7.7) kcal mol⁻¹ in the PAULING⁷⁴ (-8.2 kcal mol⁻¹) and BONDI⁷⁵ (-7.2 kcal mol⁻¹) cavity models, even if the ΔG_{Z-N} value in the UFF cavity model⁷²⁻⁷⁴ was largely underestimated (-0.6 kcal mol⁻¹).

The differences in the ΔG_{Z-N} values among the cavity models with implicit hydrogens and explicit hydrogens could be caused from the large differences in the G_s values.

Table 2. The E_{el} , G_{corr} , ΔG_s and G values in eq. (1) for the NE1 and the ZW form at the CPCM-B3LYP/6-311+G(d,p) level adopting the six cavity models in aqueous solution

Cavity	Species	E_{el} ^a	δE_{el} ^{b,c}	G_{corr} ^a	δG_{corr} ^{b,d}	G_s ^b	δG_s ^{b,e}	G ^a	ΔG_{Z-N} ^{b,f}
UA0	NE1	-284.52802	22.8	0.04930	0.7	-10.1	-23.3	-284.49488	0.2
	ZW ^g	-284.49166		0.05040		-33.4		-284.49453	
UAHF	NE1	-284.52757	22.4	0.04794	1.1	-16.3	-22.5	-284.50555	1.0
	ZW ^g	-284.49188		0.04976		-38.8		-284.50391	
UAKS	NE1	-284.52746	22.3	0.04796	1.1	-17.1	-21.7	-284.50682	1.8
	ZW ^g	-284.49189		0.04975		-38.8		-284.50392	
UFF	NE1	-284.52801	22.2	0.05087	1.1	-7.1	-24.0	-284.48844	-0.6
	ZW ^g	-284.49257		0.05266		-31.1		-284.48939	
BONDI	NE1	-284.52768	28.7	0.05068	0.9	-15.4	-36.8	-284.50156	-7.2
	ZW ^h	-284.48189		0.05205		-52.2		-284.51304	
PAULING	NE1	-284.52749	26.1	0.05033	0.6	-17.2	-35.0	-284.50455	-8.2
	ZW ^g	-284.48586		0.05128		-52.2		-284.51769	

^aValues in Hartree. ^bValues in kcal mol⁻¹. ^c $\delta E_{el} = [E_{el}(ZW) - E_{el}(NE1)]$. ^d $\delta G_{corr} = [G_{corr}(ZW) - G_{corr}(NE1)]$. ^e $\delta G_s = [G_s(ZW) - G_s(NE1)]$. ^f $\Delta G_{Z-N} = G(ZW) - G(NE1)$. ^gValues were taken from the *cis*-ZW conformer. ^hValues were taken from the *trans*-ZW conformer.

Table 3. The E_{el} , G_{corr} , G_{s} , and G values in eq. (1) for the NE1 and the ZW at various levels of theory adopting the PAULING cavity models in aqueous solution

Levels	Species	E_{el}^a	G_{corr}^a	ΔG_{s}^b	G^a	$\Delta G_{\text{Z-N}}^{b,c}$	ΔG^d
CPCM-B3LYP/6-311+G(d,p)	NE1	-284.52749	0.05033	-17.2	-284.50455	-6.8	7.9
	ZW	-284.48142	0.05279	-54.5	-284.51542		
CPCM-B3LYP/6-311+G(3df,2p)	NE1	-284.54652	0.05032	-16.0	-284.52173	-6.3	7.9
	ZW	-284.50041	0.05295	-52.9	-284.53175		
CPCM-MP2/6-311+G(d,p)	NE1	-283.78604	0.05113	-18.1	-283.76379	-6.2	7.6
	ZW	-283.73856	0.05486	-56.4	-283.77359		
CPCM-CCSD/6-311+G(d,p)	NE1	-283.80944	0.05113 ^e	-18.7	-283.78819	-5.5	9.2
	ZW	-283.75839	0.05486 ^e	-58.6	-283.79699		
CCSD(T)/6-311+G(d,p) ^(f)	NE1	-283.84305	0.05113 ^e	-18.7 ^g	-283.82179	-6.4	8.8
	ZW	-283.79336	0.05486 ^e	-58.6 ^g	-283.83197		

^aValues in Hartree. ^bValues in kcal mol⁻¹. ^c $\Delta G_{\text{Z-N}} = G(\text{ZW}) - G(\text{NE1})$. ^d $\Delta G^{\ddagger} = G(\text{TS}) - G(\text{ZW})$. ^eValues at the CPCM-MP2 level were used. ^fGeometries at the CPCM-CCSD level were used. ^gValues at the CPCM-CCSD level were used.

The E_{el} , G_{corr} and G_{s} values for the NE1 and the ZW species are summarized in Table 2. Table 2 shows that the differences in G_{corr} values between the NE1 and ZW species, $\delta G_{\text{corr}} = [G_{\text{corr}}(\text{ZW}) - G_{\text{corr}}(\text{NE1})]$, are much smaller than $\delta E_{\text{el}} = [E_{\text{el}}(\text{ZW}) - E_{\text{el}}(\text{NE1})]$ and δG_{s} values regardless of the cavity models. The magnitude of δE_{el} and δG_{s} values were similar for the cases of UA0, UAHF, UAKS, and UFF cavity models.^{72,73} However, in the BOND1⁷⁵ and PAULING⁷⁴ models, the δG_{s} values were somewhat larger than the corresponding δE_{el} values. This indicates that the solvent stabilizing effects are much larger for the BOND1⁷⁵ and PAULING⁷⁴ cavity models, and hence the $\Delta G_{\text{Z-N}}$ values obtained by these two models agree well with the experimental ones.^{2,5} Based on these findings, all other calculations were done using the PAULING cavity model and the results are summarized in Table 3. Table 3 shows that the computed $\Delta G_{\text{Z-N}}$ values between the NE1 and ZW forms in aqueous solution are in consonant with the experimental findings.

As mentioned above, in the gas phase, the NE3 was the global minimum at all levels of theory as reported in many works.^{17,19,20,30-33,38,39,41} However, as noted above, the NE1 was more stable than the NE3 in aqueous solution. Such a reversal in stability could be clearly caused by the differences in dipole moments, i.e., the calculated dipole moments of the NE1 and the NE3 forms were 6.06 and 1.88 Debye, respectively, at the CCSD/6-311+G(d,p) level in the gas phase and were changed to 8.35 and 2.20 Debye, respectively, at the CPCM-CCSD/6-311+G(d,p) level in aqueous solution. As a result, the ΔG_{s} value was expected to favor the NE1 with respect to the NE3 by 2.0 kcal mol⁻¹ in aqueous solution. This could be the reason why *the NE1 becomes more stable than the NE3 in aqueous solution*. When we compared the relative stabilities for various neutral conformers of glycine, the C_{s} -like conformers were slightly more stable than the corresponding $C_{1\text{-}}$ conformers both in the gas phase and in aqueous solution. For example, the NE3 with C_{s} -like conformation in the gas phase was 1.7 kcal mol⁻¹ more stable than the NE3-1 with $C_{1\text{-}}$ conformation at the CCSD(T)/6-311+G(d,p)//CCSD/6-311+G(d,p) level. This

indicates that the major conformers of neutral forms could be the four C_{s} -like conformers and the reasons for this have been well demonstrated.^{31,38} The respective terms of eq. (1) calculated at various levels of theory in the gas phase and in aqueous solution are summarized in Supporting Materials, S1 and S2.

In an earlier work, Tuñón and coworkers³⁰ have reported the inter-conversions between three NE conformers, NE1, NE2-1 and NE3, and the tautomerization process, $\text{ZW} \rightleftharpoons \text{NE}$, at the PCM-B3LYP/6-31+G(d,p) level of theory. However studies on the inter-conversions among the neutral conformers at a sophisticated level of theory (such as QCISD or CCSD levels) have been relatively rare as compared to the studies on the tautomerization processes. Therefore, in this work, the activation barriers for the inter-conversions of the seven neutral conformers were examined at various levels of theory in the gas phase and the results are shown in Figure 1. All the results calculated at other levels of theory were similar to those at the CCSD(T) level. The calculated energetics for the inter-conversion transition states (TS) in the gas phase are summarized in Supporting Material, S3. As expected, the activation barriers, ΔG^{\ddagger} , for the inter-conversion processes between the C_{s} -like conformers and

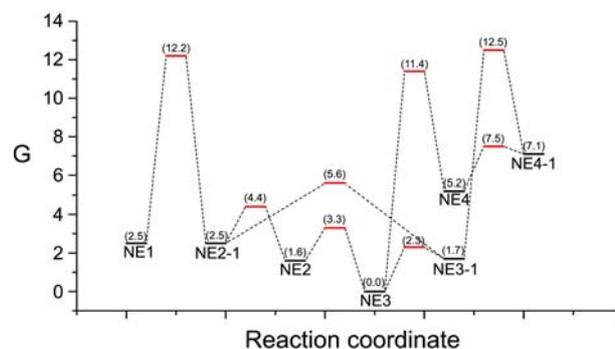


Figure 1. The activation free energy barriers for the inter-conversions of the seven neutral conformers in the gas phase at the CCSD(T)/6-311+G(d,p) level. Relative Gibbs energies are in kcal mol⁻¹.

the corresponding the C_1 -conformers were relatively low (about 1-2 kcal mol⁻¹), which indicates that these processes could be achieved easily. Moreover, the NE2 → NE3 process (and/or the NE2-1 → NE3-1 process) involved near free-rotation, because the ΔG^\ddagger value on going from the NE2 to the NE3 form (and/or from the NE2-1 to the NE3-1) was only 1.1 (0.8) kcal mol⁻¹. These activation barriers were quite similar to the well-known free-rotation barrier of ethane (*ca.* 3 kcal mol⁻¹).⁷⁷ On the other hand, the ΔG^\ddagger values for the NE1 → NE2-1 process and the NE3 → NE4 process (and/or the NE3-1 → NE4-1 process) were somewhat higher (13.8 and 8.9 (8.9) kcal mol⁻¹, respectively). However these inter-conversion processes might not be so important in glycine chemistry, because the relatively unstable NE4 species (and NE4-1) could be minor species in dynamic equilibrium processes.

The inter-conversion between NE1 and NE2-1 could be one of the key processes in aqueous solution, because the tautomerization process of $ZW \rightleftharpoons NE$ could be actually achieved in the NE1 form and the inter-conversion between NE1 and NE2-1 might be competitive with the tautomerization. The inter-conversion between the NE1 and the NE2-1 form was confirmed by the intrinsic reaction coordinate (IRC) calculations. To compare with the gas phase results, the activation barriers for the inter-conversions of the neutral conformers and for the tautomerization process were examined in aqueous solution using the same levels of theory and the results at the CCSD(T)/6-311+G(d,p) level are shown in Figure 2. The calculated energetics for TS corresponding to the inter-conversions are summarized in Supporting Material, S4. All the trends for the inter-conversions in aqueous solution were similar to those in the gas phase except for the fact that the NE1 (not the NE3) was the most stable conformer as noted above, i.e., the ΔG values for the inter-conversions between the C_s -like conformers and the corresponding the C_1 -conformers were relatively low (about 1-2 kcal mol⁻¹) and the inter-conversion between the NE2 and NE3 species was also low. Anyway, this strongly implies that the inter-conversion between them (and/or the NE2-1 and the NE3-1) could involve free-rotation as noted in the gas phase.

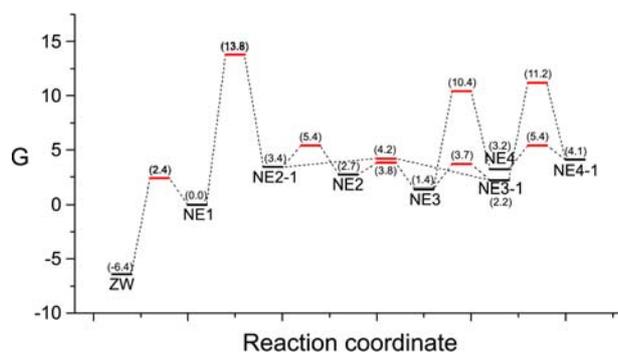


Figure 2. The activation free energy barriers for the inter-conversions of seven neutral and zwitterionic conformer in aqueous solution at the CPCM-CCSD(T)/6-311+G(d,p) level. Relative Gibbs energies are in kcal mol⁻¹.

As shown in Figure 2, the inter-conversion between NE1 and NE2-1 was more difficult than the tautomerization on going from NE1 to ZW, i.e., the ΔG^\ddagger value for the former was higher than that of the latter by 11.4 kcal mol⁻¹. Therefore, in aqueous solution, the tautomerization process producing the ZW species from the most stable neutral NE1 form could be the most favorable process in terms of the thermodynamic (ΔG) and kinetic (ΔG^\ddagger) points of view. These results agree well with the general experimental findings^{2,3,5} that the ZW predominates in aqueous solution. One thing to note is that the ΔG^\ddagger values of 9.2 and 8.8 kcal mol⁻¹ for the ZW → NE1 process at the CPCM-CCSD and CPCM-CCSD(T) levels, respectively, were fairly consistent with the experimental value³ of 14.6 kcal mol⁻¹.

As noted above, the CPCM method adopting the PAULING cavity model⁷⁴ could be well applied to the glycine chemistry, but it has been well known that a main drawback of continuum models is the lack of microscopic information such as specific interactions between solute and solvent molecules. One way to solve this problem could be using a microsolvation model,^{11,12,14-16,18} in which a solute was surrounded by some discrete number of water molecules. Recently, Bachrach¹² has shown that the NE and the ZW

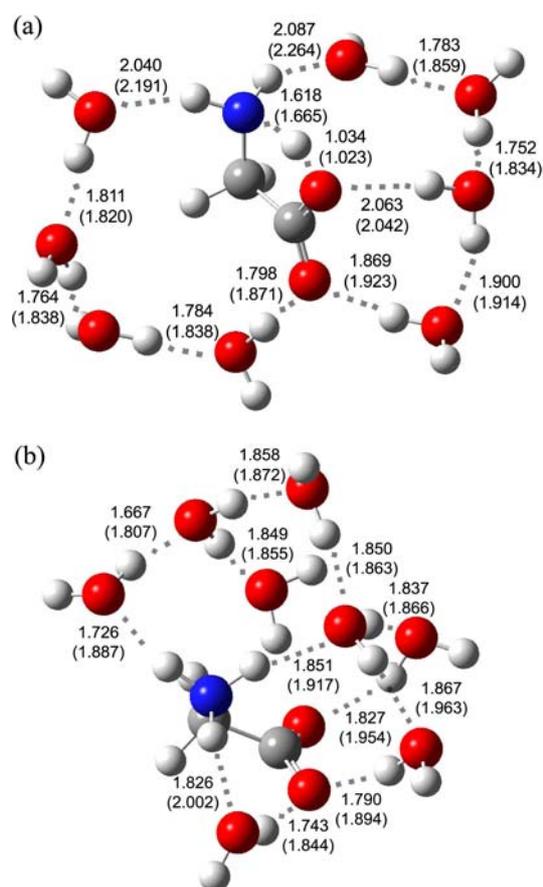


Figure 3. The optimized geometries of the clusters with eight water molecules at the MP2/6-311+G(d,p) level. (a) the NE1 cluster and (b) the ZW cluster. Values are in Å, and the values shown in parentheses are obtained in aqueous solution at CPCM-MP2/6-311+G(d,p) level.

Table 4. The relative energetics for the clusters of NE1 and ZW with eight water molecules

Phase	Level	Cluster	E_{el}^a	G_{corr}^a	ΔG_s^b	G^a	$\Delta G_{Z-N}^{b,c}$	$\Delta E_{Rex}^{b,d}$
Gas	B3LYP /6-311+G(d,p)	NE1	-896.31771	0.21429	-	-896.10342	-0.9	-2.5
		ZW	-896.33270	0.22788	-	-896.10482		-6.0
	B3LYP/6- 311+G(3df,2p)	NE1	-896.36037	0.21308	-	-896.14729	1.0	-
		ZW	-896.37305	0.22734	-	-896.14570		-
	MP2 /6-311+G(d,p)	NE1	-894.11649	0.22215	-	-893.89434	-2.2	-1.9
		ZW	-894.13099	0.23311	-	-893.89788		-3.5
Aqueous	CPCM-B3LYP /6-311+G(d,p)	NE1	-896.31372	0.21429 ^e	-25.2	-896.13953	-3.8	-
		ZW	-896.32310	0.22788 ^e	-31.6	-896.14554		-
	CPCM-MP2 /6-311+G(d,p)	NE1	-894.11347	0.22215 ^f	-38.7	-893.95301	-7.0	-
		ZW	-894.12540	0.23311 ^f	-45.1	-893.96412		-

^aValues in Hartree. ^bValues in kcal mol⁻¹. ^c $\Delta G_{Z-N} = G(ZW) - G(NE1)$. ^d $\Delta E_{Rex} = E(\text{gas}) - E(\text{gas, geometry optimized in aqueous solution})$. ^eValues at the B3LYP/6-311+G(d,p) level in the gas phase were used. ^fValues at the MP2/6-311+G(d,p) level in the gas phase were used.

species are nearly isoenergetic when associated with seven water molecules in the gas phase. Moreover, using a combined microsolvation-continuum approach at the PCM-MP2//RHF/6-311+G(d,p) level of theory, Christine and coworker¹¹ reported that the ZW is about 7-9 kcal mol⁻¹ more stable than the NE structures and thus becomes a global minimum when associated with seven or eight discrete water molecules. Therefore it could be expected that the first-solvation shell could be roughly made up by seven or eight discrete water molecules.

However, to complement the earlier results,^{11,45} the clusters of the NE1 and ZW species with eight water molecules were re-examined in the gas phase and in aqueous solution. The optimized structures and the relative energies are given in Figure 3 and Table 4, respectively. In the cluster of the NE1 species, five water molecules were directly attached to the NE1 and the remaining three water molecules formed a hydrogen-bond bridge to the water molecules directly attached to the NE1. In contrast, in the cluster of the ZW, six water molecules were directly attached to the ZW and the remaining two water molecules were involved in the hydrogen-bond bridge. Anyway, the optimized structure in aqueous solution is not much different from that in the gas phase. As a result, the relaxation energies, which required to transfer the structure from gas phase to aqueous solution, ΔE_{Rex} [= $E(\text{gas}) - E(\text{gas, geometry optimized in aqueous solution})$], were small. For example, the ΔE_{Rex} values were only 1.9 and 3.5 kcal mol⁻¹ for the NE1 and the ZW cluster, respectively, at the MP2/6-311+G(d,p) level. This indicates that the use of the cluster geometries optimized in the gas phase could give a reliable result for the study in aqueous solution.

Table 4 shows that the E_{el} values for the ZW cluster in the gas phase were more favorable than that of the NE1 cluster. For example, the former was more stable than the latter by 8.0 kcal mol⁻¹. However the G values for the ZW cluster in the gas phase became slightly lower than those for the NE1 cluster at the B3LYP and MP2 levels with the 6-311+G(d,p) basis set, and the NE1 cluster was still more favorable at the B3LYP/6-311+G(3df,2p) level. Consequently, the ΔG_{Z-N} values were very small (-2.2 kcal mol⁻¹) compared to the

experimental values even at the MP2 level. This indicates that the cluster model in the gas phase is still insufficient to reproduce the experimental findings.^{2,5} However, when the ΔG_{Z-N} values were calculated by use of CPCM method in aqueous solution, the agreement between two values were good, even if the ΔG_{Z-N} value at CPCM-B3LYP/6-311+G(d,p) level was somewhat underestimated. Therefore the combined discrete/continuum solvation model could be one of the appropriate approaches to explore the glycine chemistry in theoretical studies.

Conclusions

The ZW form of glycine in aqueous solution could be located as a stable species in aqueous solution in all cavity models considered in this work, even if the ZW in the gas phase was not stable. However, it was found that the relative stabilities of the ZW compared to the NE form in aqueous solution are considerably underestimated by use of the united atom topological models with implicit hydrogens of the UA0, UAHF and UAKS cavity models.^{72,73} On the contrary, the ΔG_{Z-N} values agreed well with the experimental findings for the calculations adopting the PAULING⁷⁴ and BONDI⁷⁵ cavity models. This shows that the united atom topological cavity models are inadequate and the cavity models with explicit hydrogens should be used to obtain a reliable result in glycine chemistry by using the continuum model. For solvent effects on the relative stabilities of the NE conformers, the NE3 form was the global minimum in the gas phase at all levels of theory, but the NE1 became more stable than the NE3 in aqueous solution. This shows the importance of solvent effects in determining the relative stabilities of the conformers. When microsolvation model was combined with the continuum model (CPCM method), the ΔG_{Z-N} values in aqueous solution agreed well with the experimental findings.^{2,5} However, microsolvation model in the gas phase was insufficient to reproduce the experimental results. Therefore, the combined discrete/continuum solvation model could be the best approach to explore the structures and energetics in glycine chemistry.

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