Density Functional Studies on Conformational Behaviors of Glycinamide in Solution

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Conformational behaviors and relative stabilities for four glycinamide conformers in aqueous solution have been investigated at the B3LYP/6-311++G** level of theory employing the self-consistent isodensity polarized continuum (SCIPCM) model within the framework of the self-consistent reaction field (SCRF) theory. Overall, the peptide bond (C1−N4) in all of the conformers is strengthened while the C1═O5 bond is weakened upon solvation though the structural parameters have no significant changes except for the dihedral angles in conformer **IIA**. The relative stabilities among glycinamide conformers still remain as that in the gas phase except that two minor conformers reverse their order. The characteristic frequencies of amide I, primarily involving the C1═O5 stretching mode, are red-shifted in all conformers, and IR intensities of mostly absorption bands are calculated to become more intense in going from the gas phase to solution. The microscopic model, which is simulated by studying the interactions of four glycinamide conformers with one water molecule in the gas phase, has also been performed to explore the microhydrated effects. All of the results, which are based on the SCIPCM model, microscopic model, and combination of them as well, are in agreement with one another, especially for the prediction of the relative stabilities among all of the glycinamide conformers. Comparison of the SCIPCM model employed in the present study and Onsager model used previously indicates that the latter may be used to study larger analogous systems that are too expensive to treat with the SCIPCM model computationally. Additionally, the tautomeric equilibria between glycinamide and glycinamidic acid have been assessed with and without the participation of one water molecule. Calculated results show that the presence of solvent disfavors the tautomeric process, whereas the water-assisted proton transfer plays a positive role in the tautomeric process.

1. Introductions

The importance of the amide functional group is demonstrated by the fact that the amide peptide bond is the basic linkage in peptides and proteins. Glycinamide ($H_2NCH_2CONH_2$), which is a simple derivative of glycine and is of great importance in interstellar studies and biochemistry, should serve as a simple and appropriate model compound for N-terminal amino acids in peptides. In past years, some related studies had been reported theoretically and experimentally.[1−10] For example, the formations of the peptide bond in glycinamide uncatalyzed or catalyzed by the metal cations or ammonia had been extensively studied.[1−4] Klassen et al. reported the collision-induced dissociation threshold energies of protonated glycinamide determined with a modified triple quadrupole mass spectrometer.[5] The unimolecular chemistry of protonated glycinamide and its proton affinity determined by mass spectrometric experiments and theoretical model had been reported by Kinser et al.[6] The interrelationship between conformations and theoretical chemical shift had been investigated by Sulzbach et al.,[7] in which some useful conformational information had been mentioned using the restricted Hartree−Fock (RHF) theory and 6-31G* basis set. Ramek et al. discussed the basis-set influence on the nature of the conformations of glycinamide (minimum or saddle point) in ab initio self-consistent field (SCF) calculations.[8] Recently, the possible conformers of glycinamide in the gas phase had been systematically explored by us, in which three pairs of mirror-image conformers and one C_s conformer had been found on the global potential energy surface (PES) of glycinamide at the B3LYP/6-311++G** level of theory.[9] The calculated proton affinity for the global minimum, 216.81 kcal/mol, is well consistent with the experimental value 217.23 kcal/mol.[6] Additionally, the ionization potentials and electron affinities of glycinamide in the gas phase and in solution had also been predicted theoretically.[10] In those studies,[9,10] the reliability of the B3LYP/6-311++G** level of theory had been verified through comparisons with higher-level calculations including MP2, MP3, MP4(SDQ), and CCSD(T) levels. As a tentative and primary study, the conformational behaviors of glycinamide in aqueous solution had been explored using the simple Onsager model within the self-consistent reaction field (SCRF) theory.[11−14] As we all know, the solvent effects often play an important role in determining the conformational preferences, equilibrium constants, vibrational spectra, and other chemical or biochemical quantities. However, to our best knowledge, the systematic studies about glycinamide in solution have never been reported to date despite its importance in biochemistry, which mostly exists in solution. Thus, it is necessary to systematically explore its conformational behaviors in solution to gain more insights into the realistic nature of glycinamide.

Generally speaking, there are three usual approaches widely used to deal with the questions of a molecule in solution: (1) adding discrete solvent molecules around the subsystem of interest (microhydrated model); (2) placing the molecule in a cavity surrounded by a continuum characterized by some macroscopic properties such as dielectric constants (macroscopic model); (3) combinations of the two approaches mentioned

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TABLE 1: Selected Structural Parameters for Glycinamide Conformers in the Gas Phase and in Aqueous Solution Employing the SCIPCM Model within SCRF Theory[a]

param	IA	IIA	IIIA	IV
R(1,2)	1.534 (0.003) [0.004]	1.540 (0.0002) [0.003]	1.528 (0.002) [0.003]	1.538 (0.001) [0.003]
R(1,4)	1.357 (0.010) [0.012]	1.366 (0.011) [0.012]	1.364 (0.012) [0.013]	1.363 (0.013) [0.013]
R(1,5)	1.220 (−0.011) [−0.013]	1.218 (−0.010) [−0.012]	1.218 (−0.011) [−0.012]	1.219 (−0.012) [−0.013]
R(2,3)	1.467 (0.003) [0.002]	1.450 (−0.003) [−0.0004]	1.456 (−0.006) [−0.001]	1.454 (0.0001) [0.002]
A(2,1,4)	114.70 (−0.39) [−1.03]	114.97 (0.14) [−1.08]	115.47 (−0.22) [−1.03]	116.71 (−0.47) [−0.96]
A(2,1,5)	120.94 (0.22) [1.11]	122.42 (0.02) [1.29]	121.77 (0.33) [1.18]	120.44 (0.63) [1.16]
A(1,2,3)	113.67 (−0.05) [0.18]	115.39 (−0.49) [−0.19]	109.74 (−0.53) [−0.16]	120.63 (0.24) [0.26]
A(2,3,9)	111.52 (0.24) [−0.19]	110.19 (0.19) [−0.14]	111.55 (1.45) [0.18]	114.39 (1.13) [−0.12]
A(2,3,10)	111.57 (0.49) [−0.15]	109.72 (−0.28) [0.09]	109.00 (0.16) [−0.08]	114.39 (1.13) [−0.13]
A(9,3,10)	107.44 (0.13) [−0.16]	105.77 (−0.26) [−0.21]	108.63 (1.11) [0.05]	110.79 (1.14) [−0.05]
A(1,4,6)	119.00 (0.54) [0.87]	122.35 (0.26) [0.96]	122.02 (−0.16) [0.63]	121.97 (0.09) [1.06]
A(1,4,11)	119.28 (−1.30) [0.01]	118.83 (−0.83) [−0.02]	118.33 (−1.12) [−0.28]	118.61 (−1.05) [−0.07]
A(6,4,11)	121.58 (0.63) [−0.94]	118.72 (0.48) [−0.92]	118.73 (0.42) [−1.23]	119.42 (0.96) [−0.96]
D(4,1,2,3)	−13.93 (−2.82) [−1.45]	−170.26 (9.43) [−4.73]	−153.14 (−0.56) [−2.76]	0.0 (0.0) [−0.43]
D(4,1,2,7)	105.57 (−3.23) [−1.68]	67.93 (10.38) [−5.09]	83.39 (−0.51) [−2.69]	124.14 (0.14) [−0.40]
D(4,1,2,8)	−141.17 (−3.25) [−1.58]	−46.79 (10.06) [−5.18]	−31.60 (−0.44) [−2.64]	−124.14 (−0.14) [−0.43]
D(5,1,2,3)	167.15 (−2.75) [−1.35]	10.49 (10.17) [−5.23]	29.83 (0.32) [−2.26]	180.0 (0.0) [359.74]
D(2,1,4,6)	−1.01 (−1.20) [−0.10]	−0.16 (−0.16) [−0.39]	11.64 (8.80) [5.62]	0.0 (0.0) [1.49]
D(2,1,4,11)	−176.72 (1.72) [0.95]	−176.51 (3.36) [−0.70]	−179.50 (−5.05) [−2.93]	180.0 (0.0) [359.40]
D(5,1,4,6)	177.87 (−1.28) [−0.20]	179.09 (−0.90) [0.13]	−171.36 (7.92) [5.16]	180.0 (0.0) [1.32]
D(5,1,4,11)	2.16 (1.64) [0.85]	2.74 (2.62) [−0.18]	−2.50 (−5.92) [−3.39]	0.0 (0.0) [−0.77]

[a] The data in parentheses refer to the results in aqueous solution relative to those in the gas phase. The data in brackets refer to the geometric changes of glycinamide conformers upon monohydration. The bond lengths (*R*) are in Å; bond angles (*A*) and dihedral angles (*D*) are in deg. Atomic numbering used for glycinamide is displayed in Figure 1.

above. In the present study, the self-consistent isodensity polarized continuum (SCIPCM) model within the framework of the SCRF theory, which has been quite successful in describing the solvent effects on the molecules,[15−23] has been used to model the continuum or nonspecific solvent effects on the conformational behaviors for glycinamide. The specific solvent effects in aqueous solution have been discussed qualitatively by exploring the interaction of glycinamide with one single water molecule. Especially, for conformer **IA**, its interactions with two and three water molecules have been investigated. Moreover, the combination of SCIPCM model and monohydrated glycinamide has been studied to further determinate the relative stabilities among the available glycinamide conformers. As an important supplement, the tautomeric equilibria between glycinamide and glycinamidic acid with and without the participation of one water molecule have also been assessed.

2. Computational Details

Using those optimized structures in the gas phase as starting points,[9] we fully reoptimized all of the geometries at the B3LYP/6-311++G** level of theory without any symmetry constraints employing the SCIPCM model within the framework of SCRF theory. Every conformer is further characterized by the harmonic vibrational frequencies. Additionally, calculations of intrinsic reaction coordinate (IRC)[24,25] have been performed to confirm the validity of the transition states connecting glycinamide and glycinamidic acid.

As mentioned above, the density functional method adopted here is B3LYP,[26,27] that is, Becke's three-parameter hybrid functional using the Lee−Yang−Parr correlation function. The 6-311++G**, which is a triple-ζ basis set including diffuse and polarization functions on both heavy and hydrogen atoms, is used throughout the calculations.

To explore the conformational behaviors in solution qualitatively, the SCIPCM model has been used throughout the calculations.[28] In the Onsager model, the solute occupies a spherical cavity inside the solvent. The permanent dipole moment of the solute induces a dipole moment (reaction field) in the surrounding medium, which in turn will interact with the dipole moment of the solute. This solute−solvent interaction is updated until self-consistency is achieved. Compared with the Onsager model, the SCIPCM model uses the improved cavity defined by an isodensity surface coupled with the electron density of the molecules and would be appropriate for the reasonable estimation for solvation energy. In the present paper, the results obtained at two models have been compared aimed to determine an appropriate method for the further study of larger analogous compounds to glycinamide, where only the data in aqueous solution are given because all of the parameters obtained in other solvents show the same change tendencies as those in aqueous solution. The dielectric constants for the various solvents applied in the SCIPCM model calculations are ϵ = 10.36, 20.7, 38.2, and 78.39 for dichloroethane, acetone, nitromethane, and water, respectively. The isodensity value of 0.0004 for SCIPCM model is used throughout as recommended by Wiberg and Rablen.[29]

To eliminate the basis set superposition errors (BSSE) produced in the calculations of interaction energy between glycinamide or glycinamidic acid and one water molecule, the Boys−Bernardi counterpoise technique has been employed.[30]

All computations were performed using the Gaussian 98 program with tight SCF convergence criteria.[31]

3. Results and Discussions

Table 1 lists the selected geometric parameters of the four glycinamide conformers under study in the gas phase, together with the structural changes of glycinamide upon solvation or monohydration. The relative energies, zero-point vibrational energies (ZPVEs), and solvation energies in solution are summarized in Table 2. The corresponding energy quantities for the complexes of glycinamide and glycinamidic acid with one water molecule are given in Table 3. Calculated changes in dipole moments and rotational constants in going from the gas phase to solution have been presented in Table 4. Table 5 presents the calculated tautomeric energy and activation energy in the tautomeric process. Figure 1 shows the optimized structures for glycinamide, glycinamidic acid, and the corre-

TABLE 2: Relative Energies (in kcal/mol) and ZPVEs (in kcal/mol) of Glycinamide and Glycinamidic Acid Conformers in the Gas Phase and in Aqueous Solution[a]

	$\epsilon = 1.0$				$\epsilon = 78.39$			
conformer	**IA (IA′)**	**IIA (IIA′)**	**IIIA (IIIA′)**	**IV (IV′)**	**IA (IA′)**	**IIA (IIA′)**	**IIIA (IIIA′)**	**IV (IV′)**
$\Delta E_{\text{relative}}$[b]	0.0 (0.0)	2.07 (1.87)	3.06 (3.03)	3.40 (0.79)	0.0 (0.0)	1.55 (1.22)	2.45 (2.94)	2.00 (0.51)
$\Delta E_{\text{relative}}$[c]	0.0 (0.0)	1.50 (1.92)	2.62 (2.99)	2.96 (0.66)	0.0 (0.0)[f]	1.21 (1.60)[f]	2.26 (2.62)[f]	1.84 (2.05)[f]
$\Delta E_{\text{solvation}}$[b]	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	−7.73 (−5.88)	−8.25 (−6.53)	−8.33 (−5.97)	−9.14 (−6.16)
$\Delta E_{\text{solvation}}$[c]	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	−7.87 (−7.54)[f]	−8.18 (−8.0)[f]	−8.24 (−7.96)[f]	−8.94 (−8.89)[f]
ΔG	0.0 (0.0)	0.69 (1.70)	2.42 (2.89)	2.65 (0.68)	0.0	0.49	2.05	1.70
DE[d]	0.0	0.0	0.0	0.0	0.20	0.16	0.40	0.25
ZPVE	57.64	57.09	57.22	57.15	57.50	57.16	57.31	57.35
population[e]	75.02	23.28	1.27	0.43	66.91	29.10	2.09	1.90

[a] The data in parentheses refer to the glycinamidic acid conformers. In aqueous solution, the data are obtained from the single-point calculations employing the SCIPCM model. [b] The relative energies without including ZPVE corrections. [c] The relative energies including ZPVE corrections. [d] Deformation energy derived from the energy difference between the neutral conformer at the geometry in solution and its corresponding equilibrium structure in the gas phase. [e] Boltzmann populations including its corresponding mirror-image conformers. [f] The data obtained from single-point calculations for glycinamide employing the SCIPCM model.

TABLE 3: Calculated Relative Energies (in kcal/mol), Interaction Energies (in kcal/mol), and ZPVEs (in kcal/mol) of Monohydrated Glycinamide and Monohydrated Glycinamidic Acid Conformers

	IA + $1H_2O$ (**IA′** + $1H_2O$)	**IIA** + $1H_2O$ (**IIA′** + $1H_2O$)	**IIIA** + $1H_2O$ (**IIIA′** + $1H_2O$)	**IV** + $1H_2O$ (**IV′** + $1H_2O$)
$\Delta E_{\text{relative}}$[a]	0.0 (0.0)	2.27 (2.15)	3.19 (3.19)	3.16 (1.21)
$\Delta E_{\text{relative}}$[b]	0.0 (0.0)	1.86 (2.13)	2.87 (3.12)	2.77 (1.05)
$\Delta E_{\text{relative}}$[c]	0.0 (0.0)	1.77 (2.01)	2.78 (3.07)	1.94 (0.66)
$\Delta E_{\text{solvation}}$	−8.32 (−6.87)	−8.81 (−7.01)	−8.72 (−7.0)	−9.54 (−7.42)
ΔG	0.0 (0.0)	1.28 (1.85)	2.75 (2.99)	2.63 (1.07)
ZPVE	73.38 (73.76)	72.97 (73.74)	73.06 (73.69)	72.99 (73.60)
$\Delta E_{\text{interaction}}$[d]	−6.72 (−8.39)	−6.33 (−8.16)	−6.41 (−8.25)	−6.83 (−8.00)
BSSE	0.58 (0.86)	0.63 (0.88)	0.65 (0.88)	0.61 (0.87)
DE_1[e]	0.26 (0.57)	0.26 (0.63)	0.28 (0.63)	0.26 (0.57)
DE_2[e]	0.22 (0.39)	0.19 (0.37)	0.18 (0.36)	0.22 (0.35)

[a] The relative energies without including ZPVE corrections. [b] The relative energies including ZPVE corrections. [c] The relative energies refer to those obtained from single-point calculations in aqueous solution employing the SCIPCM model. [d] The data in parentheses refer to those of the monohydrated glycinamidic acid. [e] DE_1 and DE_2 refer to the deformation energies of glycinamide and glycinamidic acid and those of the water molecules in monohydrated glycinamide and glycinamidic acid, respectively.

TABLE 4: Calculated Dipole Moments (in D) and Rotational Constants (in GHz) for Glycinamide Conformers in the Gas Phase and in Aqueous Solutions[a]

Dipole Moments

ϵ	**IA**	**IIA**	**IIIA**	**IV**
1.0[b]	4.07 (2.74)	3.44 (0.34)	3.73 (2.21)	4.18 (0.76)
78.39	1.06	1.00	1.53	1.31

Rotational Constants

ϵ	constant	**IA**	**IIA**	**IIIA**	**IV**
1.0	A	9.630	10.027	9.945	9.502
	B	3.964	3.825	3.928	3.880
	C	2.916	2.867	2.939	2.846
78.39	A	0.063	−0.015	−0.027	0.017
	B	−0.007	0.001	−0.012	0.007
	C	−0.004	−0.009	−0.012	0.005

[a] The data in aqueous solution refer to the differences between the results in aqueous solution and in the gas phase. [b] The data in parentheses refer to those of the glycinamidic acid.

TABLE 5: Calculated Tautomeric Energy, Activation Energy, and ZPVE Corrections in the Tautomeric Process from Glycinamide to Glycinamidic Acid[a]

	IA	**IIA**	**IIIA**	**IV**
$\Delta E_{\text{tautomerism}}$[b]	14.44	14.84	14.81	12.20
	(15.98)	(15.60)	(16.29)	(14.44)
	12.49	12.76	12.74	10.77
	(13.55)	(13.79)	(13.84)	(12.27)
$\Delta E^*_{\text{forward}}$[b]	45.37	44.62	44.59	43.19
	(50.64)	(49.97)	(50.02)	(48.79)
	19.05	19.27	19.17	17.94
	(23.33)	(23.58)	(23.67)	(22.49)
$\Delta E^*_{\text{reverse}}$[b]	30.93	29.77	29.79	30.99
	(34.66)	(34.37)	(33.73)	(34.35)
	6.56	6.51	6.43	7.17
	(9.78)	(9.79)	(9.83)	(10.22)
ΔE_{zpve}[c]	−3.39	−2.91	−3.09	−3.03
	(−3.51)	(−3.63)	(−3.59)	(−3.52)
	−3.51	−3.20	−3.32	−3.34
	(−3.89)	(−3.97)	(−3.94)	(−3.95)

[a] All of the units are in kcal/mol. [b] The data in parentheses refer to those in aqueous solution. The upper data in every row refer to the tautomeric case without water-assisted, and the lower data refer to those with the water-assisted case. [c] The ZPVE corrections refer to those in the determination of the forward and reverse activation energies in the gas phase and corresponding values in the water-assisted tautomerization.

sponding transition state connecting them, together with the atomic numbering used in the calculations. The optimized structures for the monohydrated glycinamide, glycinamidic acid, and corresponding transition state connecting them in the gas phase are displayed in Figure 2. Finally, Figure 3 displays the optimized glycinamide **IA** complexes with two and three water molecules.

For simplicity, we only take **IA**, **IIA**, **IIIA**, and **IV** for examples since the mirror-image conformers are identical to each other in energy and in structural parameters except for the dihedral angles.

3.1. Geometries. Full geometry optimizations at the B3LYP/6-311++G** level of theory reveal that all seven glycinamide conformers in the gas-phase still exist and possess the mirror-image features in various solutions with dielectric constants from 10.36 to 78.39. The relative changes observed in bond lengths, bond angles, and dihedral angles in going from the gas phase

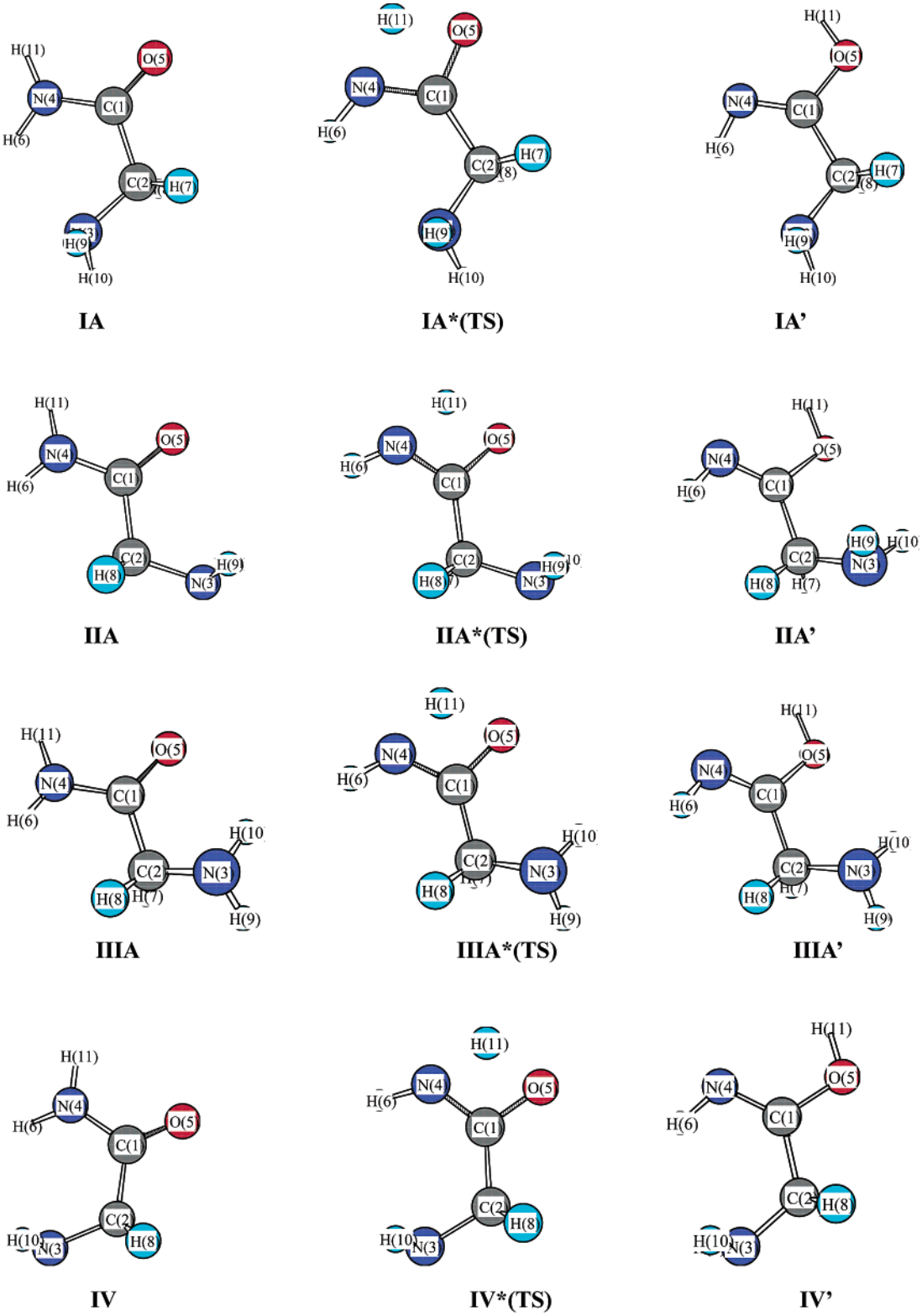

Figure 1. Optimized glycinamide and glycinamidic acid conformers and their corresponding transition states (TS) connecting them in the gas phase.

to solution are presented in Table 1. On the whole, the solvent effects have no substantial influences on the geometrical structures except for the dihedral angles in conformer **IIA**, which can be further reflected from the calculated deformation energies as presented in Table 2.

Analyses of the bond lengths indicate an increase in the double-bond character of the peptide bond (C1−N4) since its bond length is shortened by about 0.01 Å with the increase of dielectric constants. In contrast, the double-bond character of C1═O5 bond is reduced accompanying the elongation of its bond length by about 0.01 Å in various solutions. These above changes in bond lengths should be reflected from their corresponding frequency shifts. Unfortunately, to our best knowledge, there are no experimental frequencies in solution available to date. However, the calculated frequencies (e.g., conformer **IA**) are in good agreement with those in the solid state,[32] in which

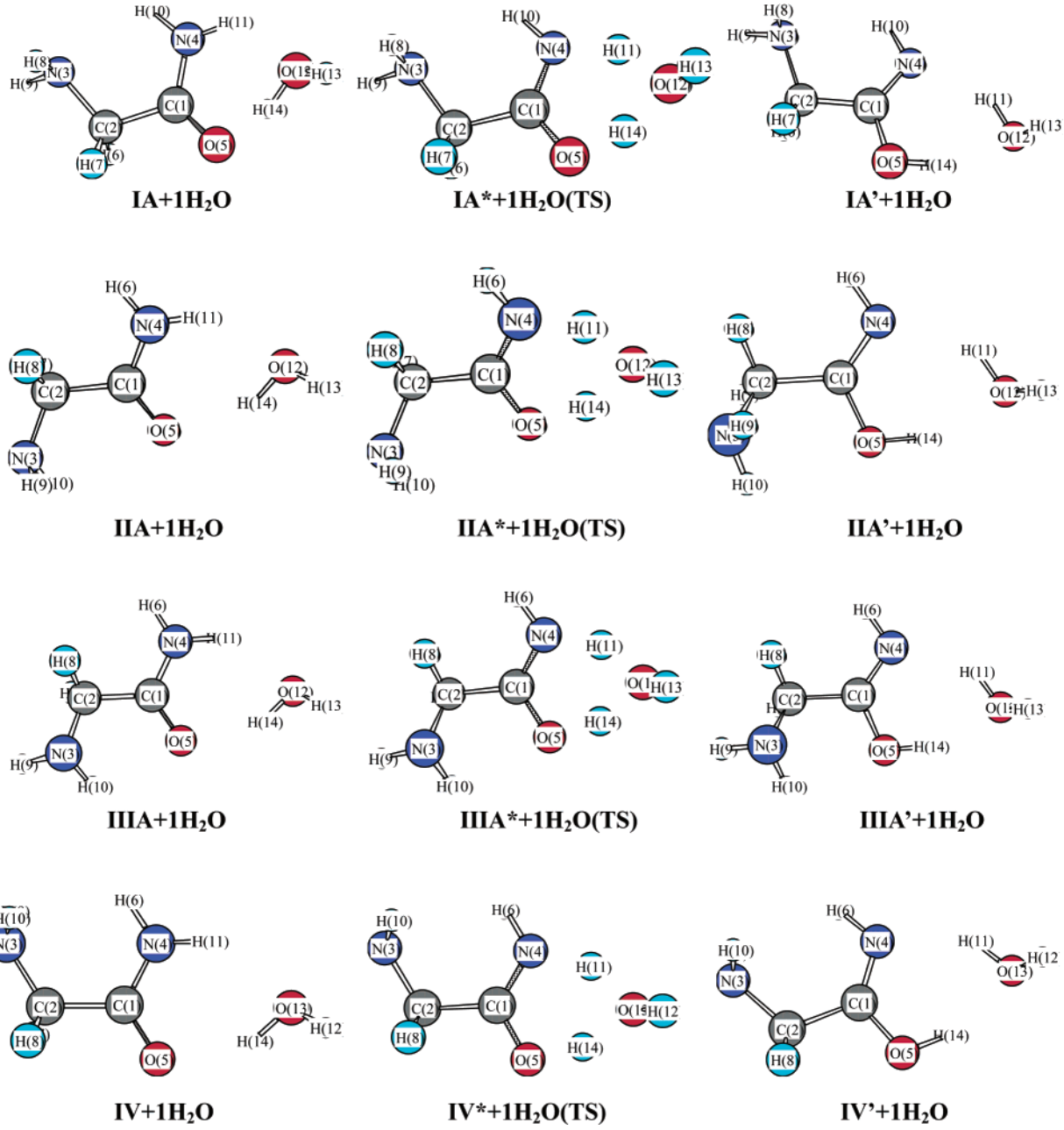

Figure 2. Optimized monohydrated glycinamide and glycinamidic acid conformers and their corresponding transition states (TS) connecting them in the gas phase.

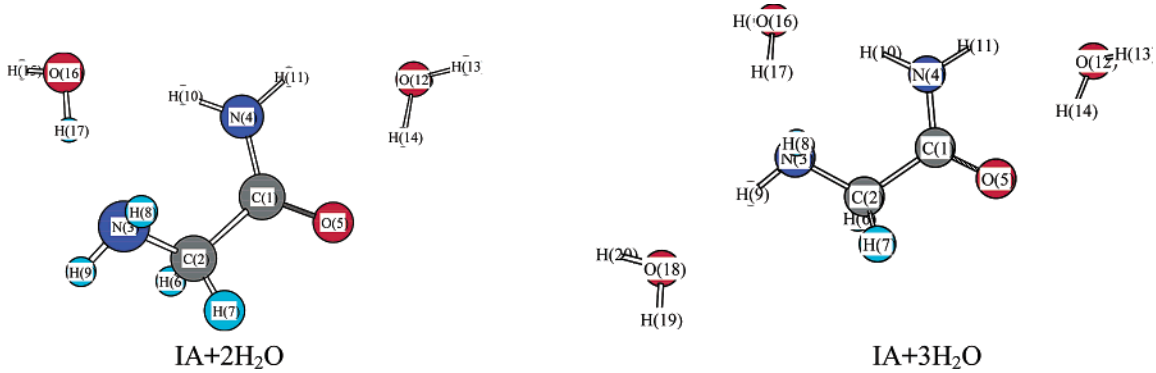

Figure 3. The complexes of glycinamide conformer **IA** with two and three water molecules obtained at the B3LYP/6-311++G** level of theory.

the highest intensity infrared bands occur at about 1660 versus 1703 cm^{-1} in our present studies. The N−H stretching vibrations, from about 3520 to 3690 cm^{-1}, should be well consistent with the second infrared band occurring at about 3350 cm^{-1} in the solid state if one considers the computational errors implied in the method and basis set used here. Comparisons with those

obtained from Onsager model indicate that both models can yield well-consistent results regarding bond lengths.[9] In fact, analogous compounds, such as formamide and *N*-methylacetamide, also undergo those changes mentioned above in going from the gas phase to solution.[14,33,34] Additionally, the intramolecular H-bond formed from the amide to the amine in conformer **IA** slightly decreases by about 0.02 Å with respect to that in the gas phase, indicating the slight strengthening of the H-bond in various solutions. For the similar intramolecular H-bond formed in conformer **IV**, its H-bond length also decreases by 0.003 Å though its strength is still very weak (the H-bond length is about 2.5 Å). Moreover, the strengthening of the intramolecular H-bond can be further confirmed by the electron distributions on those atoms associated with the H-bonds, where the atomic charges on N3 and H6 increase about 0.06 in absolute value except for the H6 with an increment about 0.02 in conformer **IA**.

As for the bond angles, the changes in going from the gas phase to solution vary not more than ±1.5°. Especially, analyses of those angles formed by heavy atoms (N and O atom) indicate that the whole molecule is loosened for conformers **IIA** and **IIIA** to make them better solvated by solvents, while it is tightened for conformers **IA** and **IV** because of the existences of the intramolecular H-bonds mentioned above. At the same time, the deviations of the predicted bond angle changes in aqueous solution vary about 2° between SCIPCM model and Onsager model.[9]

Among the geometrical parameters, the changes in dihedral angles upon solvation are relatively larger, which can be understandable since the dihedral angles are more flexible with respect to those bond lengths and angles. All of the mirror-image features between conformers still exist as can be seen from their equal negative and positive dihedral angles. For conformer **IV**, the C_s symmetry is kept. More importantly, the planarity of the peptide bond in every conformer is much clearer than that in the gas phase. There are relatively larger differences in dihedral angles between SCIPCM model and Onsager model with the exception of the C_s symmetry conformer **IV**. For example, in aqueous solution, the main skeleton angle *D*(4,1,2,3) for **IA** is −11.11° (−9.07°), for **IIA** is −179.69° (−159.56°), and for **IIIA** is −152.58° (−159.67°), where the data in parentheses refer to those obtained from the Onsager model. Obviously, there is a larger difference in the calculated parameters of **IIA**. Considering the improvement of SCIPCM model mentioned above, we take the results of SCIPCM model as benchmarks in this study.

As mentioned above, conformer **IIA** undergoes a larger deviation for its main skeleton angle (∼9.0°). Considering the computational errors implied in the method and basis set used here, one may think that conformer **IIA** should be C_s symmetry in various solutions. In fact, the structure of **IIA** in solution corresponds to a transition state with an imaginary frequency (∼30.1 cm^{-1}) in the gas phase. Similarly, the complete C_s symmetry for **IIA** also corresponds to a transition state connecting the **IIA** and its mirror-image conformer (with an imaginary frequency 60.7 cm^{-1}) in solution, where the energy barrier height is about 0.13 kcal/mol including ZPVE corrections. This means that the potential energy surface (PES) near conformer **IIA** is very shallow. Of course, this question should remain open to the further higher-level calculations.

To better understand the interaction of glycinamide with one explicit water molecule, it is necessary to analyze their geometrical structures upon complexation. As displayed in Figure 2, all of the complexes possess a cyclic double hydrogen-bonded structure. Of course, many monohydrated glycinamide complexes can be formed through single intermolecular H-bond as reported for the analogous compounds such as alaninamide and formamide.[35−37] However, the selected complexes in the present study are representative because they all have the same interaction pattern, namely, every conformer has a network of intermolecular hydrogen bonds from the amide to water and from water to the carbonyl oxygen, which is well consistent with the analogous complexes of alaninamide and formamide with one water molecule.[35−37] Thus, they stand in the same situation and have comparability in relative stability among them. Note also that these complexes should be the most favorable forms in all possible interaction patterns. One may question that another double H-bonded complex may be formed between the water molecule and two terminal N atoms in conformer **IA**. Actually, this complex (not shown) is 2.62 kcal/mol higher in energy than **IA** + $1H_2O$ considering ZPVE corrections. As shown in Figure 2, the intermolecular H-bond distances of O5H14 are 1.865 (2.103), 1.893 (2.060), 1.897 (2.059), and 1.876 Å (2.056 Å), respectively, where the data in parentheses refer to those of the H-bonds formed between O12 of water and H11 of amide (i.e., O12H11). Obviously, the strength of the former should be larger than that of the latter since the former has a shorter distance and NH_2 is a good proton acceptor but a less effective proton donor.[38−40] As listed in Table 1, the changes in structure upon monohydration are almost similar to those obtained from the SCIPCM model, which can be further confirmed by their similar deformation energies (DE) as listed in Tables 2 and 3. On the other hand, the obvious changes for the geometry of water molecule in all complexes can also be observed. For example, the OH bond length (O12−H14) is elongated by about 0.017, 0.015, 0.015, and 0.017 Å in the four complexes because of the formations of the intermolecular H-bond with the carbonyl O atom in glycinamide, while another OH bond length (O12−H13) is slightly shortened by about 0.001 Å on average. The bond angle HOH is widened by about 1.6° to better form a double intermolecular H-bond with glycinamide. In fact, the distortion of a single water molecule from its equilibrium geometry to its geometry in complexes would require about 0.22, 0.19, 0.18, and 0.22 kcal/mol in energy, respectively (see DE in Table 3). All of these changes in geometry and the formations of the monohydrated complexes are fundamental in better understanding the water-assisted proton transfer between H11 and O5.

Additionally, for glycinamide **IA**, its interactions with two and three water molecules have been considered for further investigations on explicit interactions. As displayed in Figure 3, another double intermolecular H-bond formed from the amide to water and from water to the amino has been found, where the distances for O6−H10 and N3−H17 are 1.98 and 1.91 Å, respectively. When another water molecule is added, only a single intermolecular H-bond has been formed between O18 and H9 (2.09 Å). Interestingly, the peptide bond (C1−N4) and C1═O5 bond are strengthened and weakened, respectively, where the increments for these two bonds are almost the same as those of the monohydrated glycinamide mentioned above. As expected, the main skeleton angle *D*(4,1,2,3) has been changed about 13° relative to that in neutral state because of the existence of local interactions (e.g., two intermolecular H-bonds). The calculated deformation energies for glycinamide in **IA** + $2H_2O$ and **IA** + $3H_2O$ relative to that in **IA** + $1H_2O$ are 1.99 and 1.83 kcal/mol, respectively. Actually, the interaction energies between **IA** and two or three water molecules are −9.97 and −13.03 kcal/mol, respectively, where both of them are

slightly greater than that in **IA** + $1H_2O$ (−6.72 kcal/mol) as mentioned above. Thus, it seems that the monohydrated glycinamide may reflect the microhydrated effects on conformational behaviors qualitatively though the number of one water molecule is too small to fully represent a hydration shell. Of course, the more extensive studies on the glycinamide−water clusters should be further explored employing more efficient methods, such as the QM/MM/PCM approach proposed by Cui.[41] On the other hand, to further confirm the reliability of the B3LYP in the study of the H-bonded systems, MP2/6-311++G** level of theory has been employed to reoptimize the hydrated glycinamide conformers with one, two, and three water molecules. Computational results indicate that the geometries, especially for the intermolecular H-bond distances mentioned above, are well consistent with those obtained at the B3LYP/6-311++G** level of theory, where the deviations between two levels are not more than 0.02 Å for the H-bond distances. Thus, the B3LYP method should be preferable relative to MP2 method because of the highly cost for the latter computationally.

3.2. Relative Stabilities. Table 2 summarizes the relative stabilities, ZPVEs, and solvation energies for the four glycinamide conformers in aqueous solution, together with the corresponding results in the gas phase for comparison. Table 3 gives the calculated results for monohydrated glycinamide. Obviously, the relatively larger interaction energies between glycinamide and one water molecule indicate that the existences of explicit water molecules may produce larger impacts on the geometric structures for glycinamide in realistic aqueous solution. The calculated BSSEs, varying from 0.58 to 0.65 kcal/mol, suggest that the 6-311++G** basis set is appropriate for the study of interactions between glycinamide and water molecules.

As expected, all conformers are further stabilized when the solvent dielectric constants increase. In solution, the calculated relative energy order among all of the conformers is well consistent with those of the relative Gibbs free energies. Thus, the relative stability order among all of the conformers should be as follows: **IA** > **IIA** > **IV** > **IIIA**, which is identical to that in the gas phase except for the reverse order between conformer **IIIA** and **IV**. The possible reason for this phenomenon should be owed to the larger dipole moment for **IV** (4.18 D) with respect to that of **IIIA** (3.88 D). At the same time, inspection of Table 3 also indicates that the same order in relative stability is true for those complexes of glycinamide with one water molecule. Moreover, the relative energies obtained from single-point B3LYP/6-311++G** calculations employing the SCIPCM model based on these optimized complex structures still give a consistent result. Actually, the relative stability order in solution is still reproduced by the single-point energy calculations using SCIPCM model based on the optimized gas-phase structures without monohydration. For example, the relative energy for conformers **IIA**, **IIIA**, and **IV** relative to **IA** is 1.60, 2.62, and 2.05 kcal/mol, respectively, which is well consistent with that obtained from SCIPCM model in aqueous solution. More importantly, all of these calculated results here are in good agreement with those predicted employing the Onsager model.[9] Thus, the relative stabilities among all of the conformers should be correctly determined in solution. On the other hand, the relative energies in solution for conformers **IIA**, **IIIA**, and **IV** relative to **IA** become smaller than that in the gas phase, implying that the Boltzman populations among the available conformers should be altered in going from the gas phase to solution. As shown in Table 2, the calculated Boltzmann populations estimated from the relative Gibbs free energy decrease for **IA**,[42] while they increase for other conformers upon solvation, though the changes in solution are small. Obviously, **IV** has the largest increments among all of the conformers due to its largest solvation energy in solution.

Comparisons of ZPVEs presented in Table 2 demonstrate that ZPVEs are nearly insensitive to the various solutions for all of the conformers. Obviously, the energy differences for conformers **IIA**, **IIIA**, and **IV** relative to **IA** decrease if ZPVE corrections are taken into account. On the other hand, ZPVE corrections make the solvation energy increase for conformer **IA** while it decreases for other conformers.

As listed in Table 2, all of the solvation energies increase with the increase of dielectric constants. Obviously, the solvation energy for **IV** is the largest among the available conformers because of its larger dipole moment. Judging from the size of the dipole moment only, one may infer that **IIA** should have the smallest solvation energy since it is the least polar conformer whether in the gas phase or in solution. However, **IA** has the smallest solvation energy in various solutions. The possible reason should be attributed to the fact that the contributions of the higher multipole moments to the solvation energy in **IIA** are larger than those of **IA**. Compared with these results here, the Onsager model underestimates the solvation energy by about 4.22, 5.50, 5.80, and 5.87 kcal/mol for conformers **IA**, **IIA**, **IIIA**, and **IV**, respectively.[9] Additionally, since the solvation energies are similar for **IA** and **IIA**, the relative stabilities in solution between them should depend mostly on the gas-phase calculations. In other words, the conformational preferences in solution should be governed by their intrinsic stabilities in the gas phase.

As a result, a conclusion may be drawn that the single-point energy calculation may give reasonable qualitative results of the relative stability for the analogous compounds from the viewpoint of the economical computations, which can be confirmed by comparing the calculated relative stabilities and solvation energies obtained from the different geometries with and without structural relaxation.

3.3. Solvent Effects on Other Relevant Quantities. The changes in dipole moments and rotational constants upon solvation have been summarized in Table 4. As expected, the dipole moments for all of the conformers increase with the increase of dielectric constants despite their different increments. The orders in magnitude (**IV** > **IIIA** > **IA** > **IIA**) remain the same as that in the gas phase (**IV** > **IA** > **IIIA** > **IIA**) except for the reverse order between **IA** and **IIIA**. The larger dipole moment for **IV** should be responsible for its larger solvation energy in solution as mentioned above. Additionally, the order in the size of dipole moments in aqueous solution employing the Onsager model are predicted as follows: **IA** > **IV** > **IIIA** > **IIA**, which is different from those mentioned above except for the least polar conformer **IIA**.

As for the rotational constants, some regularities can be observed, though solvent effects on them are minor. For example, the rotational constant A (B) of conformer **IA** (**IIA**) increases, while B and C (A and C) decrease. For **IIIA**, all of them decrease with the increase of dielectric constants, while the opposite is true for conformer **IV**. These subtle changes should be helpful in the search for them using the rotational spectroscopy.

3.4. Solvent Effects on Tautomeric Equilibria. As an additional supplement for this paper, the tautomeric equilibria between glycinamide and glycinamidic acid have been explored. To our best knowledge, the systematical studies on them have not been carried out to date. The four most related structures

for glycinamidic acid have been selected, which are representative of the studies for tautomerization between glycinamide and glycinamidic acid from the viewpoint of the geometry, though there are other conformers on the PES of glycinamidic acid. Preliminary studies show that the four glycinamidic acid conformers possess smaller dipole moments relative to their corresponding tautomeric forms (glycinamide), that is, 2.74, 0.34, 2.21, and 0.76 D, respectively, indicating that solvent effects should be smaller on glycinamidic acid in geometry and stability. Thus, solvent effects on the tautomeric equilibria are assessed qualitatively through the single-point calculations at the optimized gas-phase geometries employing the SCIPCM model. This approximation should be reasonable as mentioned above and can be further confirmed by the calculated smaller solvation energies relative to those of glycinamide conformers as listed in Tables 2 and 3.

As a notable feature in the water-assisted tautomerization, it should be noted that the strength of the intermolecular H-bonds formed between glycinamidic acid and a single water molecule are enhanced compared with those monohydrated glycinamide conformers, though what we most concern is the tautomeric energy and activation energy as discussed below. First, the calculated intermolecular H-bond distances, 1.89 (1.81), 1.91 (1.79), 1.91 (1.79), and 1.91 Å (1.80 Å), are shorter than those of the corresponding monohydrated glycinamide conformers mentioned above, where the data in parentheses refer to the H-bonds formed between the amide N atom and the H atom in water molecule. Moreover, compared with monohydrated glycinamide, the larger interaction energies between glycinamidic acid and water molecule and larger deformation energies for glycinamidic acid and water also give additional evidence of the formation of the stronger intermolecular H-bonds.

As displayed in Table 5, the tautomeric energies from glycinamide to glycinamidic acid are predicted to be from 12.20 to 14.84 kcal/mol in the gas phase, indicating the stabilization of glycinamide in the gas phase. Furthermore, the energy differences between them increase about 0.7−2.2 kcal/mol if solvent effect in aqueous solution is considered. This means that the tautomerization between glycinamide and glycinamidic acid becomes less favorable in aqueous solution. On the other hand, the energy differences in the water-assisted case are reduced by about 1.4−2.0 kcal/mol. Similarly, the presence of the aqueous solution increases the energy difference by about 1.0−1.5 kcal/mol. Additionally, as shown in Table 2, the relative stabilities among the four glycinamidic acid conformers are different from those of the glycinamide conformers before tautomerization whether in the gas phase or in aqueous solution, namely, **IA′** > **IV′** > **IIA′** > **IIIA′**, indicating that solvent has little effect on glycinamidic acid conformers.

Table 5 also gives the calculated forward and reverse activation energies. The larger energy heights for the forward process (43.19−45.37 kcal/mol) or reverse process (29.77−30.99 kcal/mol) indicate that the tautomerization between glycinamide and glycinamidic acid is difficult to proceed in the gas phase. In aqueous solution, the corresponding energy heights are increased by about 5.4 and 4.0 kcal/mol for the forward and reverse process, respectively. However, the tautomeric process may be greatly improved through the participation of one water molecule. Obviously, in water-assisted tautomerization, all of the energy heights are reduced by about 25.0 kcal/mol, which are consistent with the results of the water-assisted tautomerization between formamide and formamidic acid. Once again, the presence of bulk water increases the energy heights by about 4.0 kcal/mol. Thus, a qualitative conclusion may be drawn that the tautomerization between glycinamide and glycinamidic acid is not facilitated by bulk water whether in the gas phase or in the water-assisted case. At the same time, the participation of one water molecule should play a key role in stimulating the tautomeric process. Additionally, it should be noted that the ZPVE corrections should be important in the determination of the activation energy heights as listed in Table 5.

4. Conclusions

In the present paper, solvent effects on the conformational behaviors and relative stabilities for four glycinamide conformers have been systematically investigated at the B3LYP/6-311++G** level of theory employing SCIPCM model, monohydrated model, and a combination of both of them. On the whole, all of these models give well-consistent results, though the number of one water molecule is too small to fully represent a hydration shell, indicating the validity of them in predicting the solvent effects. Compared with the optimized gas-phase structures, minor changes in geometry occur except for the dihedral angles of **IIA** in solution. Computational results show that the relative stabilities among all of the conformers in solution remain in the same order, that is, **IA** > **IIA** > **IV** > **IIIA**, which is consistent with that in the gas phase except for the reverse order between **IIIA** and **IV** due to the solvent effects. The most notable changes in frequency are the red shifts occurring for the characteristic amide I due to the elongation of the C1═O5 bond. Moreover, the IR intensities are much stronger than those in the gas phase. Additionally, the solvent effects on the dipole moments and rotational constants have also been discussed. As an important supplement for this paper, the tautomeric equilibria between glycinamide and glycinamidic acid have been assessed. Results indicate that the water-assisted tautomerization reduces the activation energy height greatly, though the presence of bulk water tends to increase it. Finally, comparisons between SCIPCM and Onsager model suggest that the latter may be used to study larger analogous compounds, which are too expensive to treat with SCIPCM model computationally.

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