Density functional theory (DFT) calculations are reported for the structures of neutral and zwitterionic glycine-(CH_{2}OH)$_{n}$ where $n=1$-$6$. Initial geometries of the clusters of neutral and zwitterionic glycine with 1$-$6 methanol molecules are fully optimized at B3LYP/6-31+G* level of theory. The lowest energy configurations are located and their hydrogen bond structures are analyzed. Theoretical prediction reveals that the methanol prefer to locate near the carboxylic acid group for the small clusters ($n\leq3$) with the neutral form while the configurations with the methanol bridging the acid and the amino group are favorite in the zwitterionic form clusters. When the number of the methanol molecules in the clusters reaches five and six, the two forms tend to be isoenergetic.

Key words: Microsolvation, Amino acid, Methanol, DFT, Hydrogen bond cluster

I. INTRODUCTION

It is well known that neutral amino acids exist predominantly in their neutral (nonionized) form (N-form)) in the gas phase, while in solution or in crystals they occur in the zwitterionic form (Z-form) [1,2]. As the simplest amino acid, the glycine literature is vast. There are a huge amount reports on the microsolvation of the glycine with water molecules [3-$8$]. In 1996, using both MP2 and HF theoretical methods with the base sets up to 6-31++G**, the 1:1 glycine-water complex was studied by Ding and Krogh-Jespersen [9]. In their report, the single water molecule was found to bridge the carboxylic acid and the amino groups, and amino acid neutral was 26.75 kJ/mol lower in energy at the HF/6-31++G** level of theory. Recently, DFT method has been employed to study the large clusters of the glycine and waters [10]. With the B3LYP/6-31+G* theoretical method, the structures of glycine with 3, 4, 11, or 17 explicit water molecules were optimized. The 11 water-glycine complex was found to exist in a zwitterionic state. Study with the more extensive 6-311++G** basis set and the B3LYP method found that three water molecules in the glycine-(H$_2$O)$_3$ complex were concentrated near the carboxylic acid group of the neutral glycine [6]. Aikens and Gordon examined the structures and relative energies of neutral and zwitterionic glycine-(H$_2$O)$_n$ clusters where $n=1$-$8$ [11]. Bridging structures were predicted to be the global minima after 3-$5$ discrete water molecules are included in the calculations. It was also found that calculations incorporating electron correlation stabilize the zwitterionic structures by about 29.26$-$37.62 kJ/mol relative to the N structures regardless of the number of discrete water molecules considered. More recently, structural properties, energetics and vibrational frequencies for the optimized stable structures of glycine-(H$_2$O)$_3$ complex were analyzed at the correlated ab initio (MP2) and density functional methods (B3LYP, PW91, MPW1PW91, and PBE) using 6-311++G** basis set [8]. In this study, both (−NH$_3^+$) as proton donor and (CO$_2^-$) as proton accepter have been considered for the effect of the microsolvation on zwitterionic glycine. The other DFT method (PBE1PBE) has also been used to explore the microsolvation of neutral and zwitterionic glycine and the results showed that neutral glycine was favored when it associated with zero to six water molecules. However, with seven water molecules, the two structures were isoenergetic [12]. Alanine is another “hot” amino acid molecule [13-$17$]. Recently, the structures of neutral and zwitterionic alanine-(H$_2$O)$_n$ clusters ($n=2$-$10$) were calculated at the level of B3LYP/6-31+G* and MP2/6-31++G**/B3LYP/6-31+G**. With six or seven water molecules, the calculated energies indicated that the two forms may coexist. Eight water molecules were sufficient to computationally guarantee the reported experimental observation of zwitterionic dominance in solution [18]. Regardless that methanol is an important organic solvent, reports on the solvation dynamics of amino acid with methanol are very few. Recently, Paizs et al. presented experimental and theoretical studies for tryptophan-methanol complexes [19]. The tryptophan-methanol complexes showed convincing evidence that a minimum of five solvent molecules were necessary to observe a zwitterionic structure.

In this work, we determine the equilibrium structures...
for the glycine with one to six methanol clusters in either neutral (N) or zwitterionic (Z) form. It is important to determine which conformers dominate as the size of the clusters increase. The present work will explore how many methanol molecules are required to make the two forms isoenergetic.

II. COMPUTATIONAL METHODS

Recent reports indicated that the DFT methods could provide a relatively inexpensive but accurate means for calculations of amino acids and waters clusters system [18,20,21]. We employed the DFT in this work on the clusters of the glycine with one to six methanol molecules, including both the N and Z form. Initial geometries of the clusters were built using GaussView software, methanol molecules were placed in a variety of locations of the glycine. The initial configurations were fully optimized at B3LYP/6-31+G* level of theory. The B3LYP/6-31+G* energies of the structures were corrected with zero point vibrational energy. Harmonic frequency calculations were used to verify the stationary states resulting from the optimizations and to obtain zero point vibrational energy corrections (ZPVE). We did not employ the counterpoise correction for basis set superposition error (BSSE), because (i) the intramolecule hydrogen-bond has been formed in the glycine of the clusters, which makes it overestimated [22], (ii) the large number of configurations examined make this calculation prohibitively time-consuming. All calculations in this report were performed with the Gaussian 03 set of programs [23]. The energies we report are the thermal correction to enthalpy unless otherwise noted.

III. RESULTS AND DISCUSSION

A. Glycine-CH$_3$OH

At B3LYP/6-31+G* level of theory, at least 17 optimized structures which include the neutral glycine with one methanol have been found. Seven lowest energy structures are within 16.72 kJ/mol of the minimum energy [12,24]. Six of the lowest energy configurations within 10.45 kJ/mol of the minimum energy are shown in Fig.1, along with their relative enthalpy and Gibbs free energies, the latter are shown in the parenthesis. The energy of the seventh is higher 16.31 kJ/mol than the lowest energy of the structure. That configuration is thus not shown in the figure.

In the six lowest energy structures of glycine-CH$_3$OH (N1), the methanol molecules prefer a location near the carboxylic acid group, which is very similar to the glycine-H$_2$O clusters [11,12]. Methanol offers a hydrogen atom to the carboxylic oxygen and accepts a hydrogen from the hydroxyl group of the glycine. The hydroxyl group of the methanol interacts with the carboxylic acid group and an O–H···O–C–O–H ring-like plane is formed where two hydrogen bonds are involved. The structures differ in the conformation of the glycine [11] and the methyl group of the methanol relative to the side of the ring-like plane (see Fig.1). Thus, their relative energies are just within 10.45 kJ/mol.

With B3LYP/6-31+G*, only two optimized structures are located which involves the zwitterionic glycine with one methanol molecule, which is different from the glycine-H$_2$O. Recent report showed five structures could be found for the zwitterionic glycine-H$_2$O at the level of HF/6-31++G(d,p) [11]. The energies of both Z-form glycine-CH$_3$OH are within 12.54 kJ/mol of the minimum energy structure. In these two configurations, two hydrogen bonds bridge the methanol and the glycine. The difference between those two configurations is the intramolecular hydrogen bonds. In Z1-1, both the intramolecular and the intermolecular hydrogen bonds share the same carboxylic oxygen while in Z-2, two hydrogen bonds include the different carboxylic oxygen, respectively.

The calculation results indicated that the neutral glycine is more stable in glycine-methanol clusters. The
FIG. 2 Lowest energy optimized structures of N2 and Z2. See Fig.1 for details.

The lowest energy of the neutral form structure is lower than that of the Z-form as much as 61.74 kJ/mol with the enthalpy and 63.70 kJ/mol with Gibbs free energy, respectively.

B. Glycine-(CH$_3$OH)$_2$

Fifteen configurations of the neutral glycine-(CH$_3$OH)$_2$ (in N2) can be obtained at the level of B3LYP/6-31+G*. Within 16.72 kJ/mol of the minimum energy structure, only four structures can be identified. Furthermore, their relative energies are less than 10.45 kJ/mol. Their structures and relative energies are shown in Fig.2.

For the configurations N2-1 and N2-2, a methanol-methanol hydrogen bond bridge is formed, which located near the carboxylic acid group. This result consists with the glycine-H$_2$O system [12]. In both configurations, one of the methanol molecules donates a hydrogen to the carboxylic group, while another one accepts one hydrogen atom from the hydroxyl group of the glycine. In N2-1, two hydrogens of the amino group point toward the carboxylic oxygen. While in N2-2, those two hydrogen atoms point toward the hydroxyl oxygen. N2-1 has lower energy than that of N2-2 for the glycine adopts a more stable conformer in N2-1 [11]. For N2-3 and N2-4, only one hydrogen of the amino group interacts with the oxygen of the acid group. Their energies are higher 4.18 kJ/mol than those of the N2-1 and the N2-2, respectively.

There are ten lowest-energy configurations found which involve the zwitterionic glycine with two methanol molecules at the level of B3LYP/6-31+G*. Within 16.72 kJ/mol of the minimum energy structure, five of them can be found and their relative energies are 6.27 kJ/mol. Z2-1 and Z2-2 have the lowest energy, a methanol-methanol hydrogen bond bridge is formed in these two configurations. The bridge offers one hydrogen to the CO$_2^-$ group and accepts one hydrogen from the ammonium group. In addition, one hydrogen of the ammonium group interacts with the oxygen of the CO$_2^-$ group to form an intramolecular hydrogen bond. The difference between those two configurations is that the same oxygen is involved in the hydrogen bonds in Z2-1 while in Z2-2, two oxygen atoms are involved in two different hydrogen bonds, respectively. Z2-4 has the similar structure with Z2-2. The difference between them is that the ring-like plane including multi-hydrogen-bond is located at the different sides of the amino acid molecule plane. Z2-3 and Z2-5 have higher energies among five configurations. Two ring-like planes that include two hydrogen bonds which bridge the carboxylic acid and ammonium groups are located at two sides of the amino acid molecule plane, respectively. In Z2-3, only one oxygen of the carboxylic acid group involves in the hydrogen bond bridges. In Z2-5, two oxygen atoms involve two different hydrogen bond bridges, respectively.

Calculation results indicate that the difference of the enthalpy and Gibbs free energies of N2-1 and Z2-1 is 45.69 and 47.03 kJ/mol respectively, which is comparable with the glycine-water system [12].

C. Glycine-(CH$_3$OH)$_3$

At B3LYP/6-31+G* level of theory, we optimized seventeen neutral configurations of glycine-(CH$_3$OH)$_3$ clusters. Five lowest energy configurations within 16.72 kJ/mol of the minimum energy structures are shown in Fig.3.

In N3-1 and N3-2, a long-chain including multi hydrogen bonds is formed by three methanol molecules which are near the carboxylic acid group. Those two structures have the lowest energies. In this long-chain, the hydroxyl of the glycine donates the hydrogen and the carboxylic oxygen acts as the hydrogen acceptor.
FIG. 3 Lowest energy optimized structures of N3 and Z3. See Fig.1 for details.

In N3-1, the two amino hydrogen atoms point to the carbonyl group. In N3-2, they point to the hydroxyl of the glycine. In N3-5, the long-chain only includes two methanol molecules, and the third methanol molecule just interacts with amino groups. The energy of N3-5 is higher 15.05 kJ/mol than the lowest structure (i.e. N3-1).

In N3-3 and N3-4, one hydrogen bond long-chain bridges the carboxylic acid and the amino group. The carboxylic acid group acts as the hydrogen donor while the amino groups act as the acceptor. The hydrogen of the amino group points to the carbonylic oxygen in N3-3 while in N3-4, that does to the hydroxy oxygen.

As many as twenty Z-form cluster structures are located at the level of B3LYP/6-31+G* which involve one glycine and three methanols. Ten lowest energy configurations within 16.72 kJ/mol of the minimum energy structures are found (see Supplementary material, Fig.S1). The lowest six configurations within 4.18 kJ/mol are shown in Fig.3. Among these six configurations, Z3-5 and Z3-6 have similar shapes and higher energies. In both configurations, three methanol molecules form a methanol-methanol hydrogen bond long-chain and bridge the carboxylic acid and the ammonium group, where the CO$_2^-_{}$ group acts as the hydrogen acceptor while the ammonium group as the donor. For the other four configurations, i.e. Z3-1, Z3-2, Z3-3 and Z3-4, methanol molecules are involved in two bridges between the ammonium and the carboxylic acid group. One bridge includes two methanol molecules, while the third methanol is involved in another bridge. Those four configurations have the similar energies, and are of the lowest energy structures. Z3-1 has the lowest enthalpy while Z3-4 has the lowest Gibbs free energies (see Fig.3)

The difference of the lowest enthalpy and Gibbs free energies of two forms (N and Z) was estimated as 30.22 and 38.46 kJ/mol respectively, which become smaller than that for glycine-(CH$_3$OH)$_2$.

D. Glycine-(CH$_3$OH)$_4$

At B3LYP/6-31+G* level of theory, at least 16 lowest energy configurations are located. Ten lowest energy structures are within 16.72 kJ/mol of the minimum energy [12,24], which are shown in Fig.S2 in the Supplementary material. The lowest six configurations are shown in Fig.4.

For the glycine-(H$_2$O)$_4$ system, in the four lowest energy configurations located at the level of B3LYP and PBE1PBE [12], four waters form a ring and interact each other through four hydrogen bonds. This ring is then hydrogen bonded to the acid group. Furthermore, similar structures could be found for all the larger clusters ($n>4$) [12]. However, the glycine-methanol system is different. In the lowest configuration (N4-1), a hydrogen bond long-chain including four methanol molecules bridges the amino and the carboxylic acid group. The
carboxylic acid group acts as the hydrogen donor while the amino group does as the acceptor. N4-3 and N4-6 have similar configuration, but have higher energy 2.51 and 8.78 kJ/mol than N4-1, respectively. Noting that it is different for the smaller clusters glycine-(CH$_3$OH)$_n$ ($n \leq 3$). In those lowest energy configurations, all the methanols are located near the carboxylic acid group. However, the glycine-(CH$_3$OH)$_4$ (i.e. N4-2, N4-4, and N4-5) with the similar configurations are less stable. Based on the Gibbs free energies, however, N4-5 would be the most stable structure, where four methanols are near to the acid group (see Fig.4).

Fourteen lowest energy configurations including the zwitterionic glycine with four methanols have been optimized at B3LYP/6-31+G* level of theory. Eleven lowest energy structures are within 16.72 kJ/mol of the minimum energy, which are shown in Fig.S2 in the Supplementary material. Six configurations within 10.45 kJ/mol of the minimum energy structure are shown in Fig.4. In Z4-1, as the lowest energy configuration, there are two methanol-methanol hydrogen bond chains to bridge the CO$_2^-$ and the ammonium group. Only one carbonyl oxygen is involved in the hydrogen bond. However, two bridges between the CO$_2^-$ and

FIG. 4 Lowest energy optimized structures of N4 and Z4. See Fig.1 for details.
the ammonium group in Z4-2 and Z4-3 are different. In
those two configurations, one bridge consists of three
methanols while only one methanol is included in an-
other bridge. Their enthalpy energies are also higher
less than 4.18 kJ/mol than that of Z4-1. In Z4-2, two
oxygen atoms of the CO$^2^-$ group are involved in the hy-
drogen bond while only one oxygen is included in Z4-3.
In Z4-4 and Z4-5, which is similar to Z4-1, two oxygen
atoms of the CO$^2^-$ group are involved in two differ-
ent rings, however. For Z4-6, all the four methanols
are involved in a single chain-like hydrogen bond bridge
between the CO$^2^-$ and the ammonium group.

The calculation results indicated the most stable
zwiterions cluster (Z4-1) lies 17.43 kJ/mol with the en-
thalpy and 23.94 kJ/mol with Gibbs free energy above
the most stable neutral form (N4-1). This value be-
comes smaller than that of the small clusters (n<3).

E. Glycine-(CH$_3$OH)$_5$

At B3LYP/6-31+G* level of theory, there are at least 13
optimized configurations for the neutral glycine-
(CH$_3$OH)$_5$ clusters. Eleven lowest energy structures are
within 16.72 kJ/mol of the minimum energy (see them
in Fig.S3 in the Supplementary material). Six configu-
urations within 8.36 kJ/mol of the minimum energy are
shown in Fig.5.

When n=4, the N-form configuration with the
methanols bridging the acid and amino group (i.e.
N4-1) has started to be the most stable structure. In
N5-1, the lowest energy structure, a long-chain includ-
ing four methanol molecules bridges the carboxylic acid
and the amino group. Another methanol (the fifth methanol)
forms another bridge in the cluster to link
two groups. And N5-3 has the similar structure to
N5-1. N5-2 has the higher enthalpy energy 1.46 kJ/mol
than N5-1 does. However, its Gibbs free energy is
lower than that of N5-1. In the configuration N5-2
and N5-5, all five methanol molecules form a hydro-
gen bond long-chain and interact with the carboxylic acid
group. The difference between these two configu-
trations is the orientation of the hydrogen atoms of the
amino group. In N5-2, two hydrogen atoms point to
the carbonyl group while in N5-5, two hydrogens point
to the hydroxyl group of the glycine. Thus, N5-5 has
higher energy 2.93 kJ/mol than N5-2 does. In N5-4
and N5-6, a hydrogen bond long-chain consisting of five
methanol molecules bridges between the amino and the
acid group.

For Z-form of the glycine-(CH$_3$OH)$_5$ cluster, we
found at least 15 configuration at B3LYP/6-31+G*
level of theory. Ten lowest energy structures are within
16.72 kJ/mol of the minimum energy, shown in Fig.S3
in the Supplementary material. Six of them within
9.61 kJ/mol of the minimum energy are shown in Fig.5.
Two hydrogen-bond bridges between the carboxylic acid
and the ammonium group are formed in all four
lowest energy configurations. Two bridges include two
and three methanol molecules, respectively. In Z5-1,
there are an intermolecular hydrogen bond formed be-
tween the CO$^2^-$ and the ammonium group and an in-
tramolecular hydrogen bond in the glycine. However,
no intramolecular hydrogen bond is formed in the other
three configurations. In Z5-2 and Z5-4, two oxygen
atoms of the CO$^2^-$ group are involved in the two dif-
ferent bridges while just one oxygen is involved in Z5-3.
Both Z5-5 and Z5-6 have two rings which bridge the
ammonium and the carboxylic acid group. Only one
methanol is involved in one ring while in another one,
four methanol molecules are involved. Those two struc-
tures have higher energies at least 4.18 kJ/mol than the
former four.

For the glycine-(CH$_3$OH)$_5$ clusters, the difference of
the lowest energies of the zwiterionic and the neutral
structures has decreased to 2.26 kJ/mol with the en-
thalpy and 12.21 kJ/mol with Gibbs free energy, and
the neutral form has lower energy.

F. Glycine-(CH$_3$OH)$_6$

At B3LYP/6-31+G* level of theory, thirteen lowest
energy configurations for the Z-form glycine-(CH$_3$OH)$_6$
are found. Six lowest energy configurations within
16.72 kJ/mol of the minimum energy are shown in
Fig.6.

For the N-form glycine-(CH$_3$OH)$_6$, the configuration
including two bridges between the carboxylic acid and
the amino group has the lowest energy (i.e. N6-1).
The energy of N6-1 is lower 4.81 kJ/mol than that of
N6-2, where all the methanols are located near the car-
boxylic acid group and form a single hydrogen bond
long-chain. However, N6-2 has the lowest Gibbs free
energy among six configurations. In N6-3, N6-4, N6-5
and N6-6, their energies are higher at least 4.18 kJ/mol
than the two lowest configurations. In the configura-
tion N6-3 and N6-6, two hydrogen bond bridges link the
carboxylic acid and the amino group. Three methanol
molecules are involved in each bridge in N6-3. In N6-6,
one bridge includes only one methanol molecule and an-
other one includes five methanol molecules. In N6-4, a
long ring-like bridge includes five methanol molecules
near the carboxylic acid group and another methanol
molecule suspends to the carbonyl group. In N6-5, four
methanol molecules form a long ring-like bridge near
the carboxylic acid group, and another two methanol
molecules bridge the carbonyl and the amino group in
the clusters.

At B3LYP/6-31+G* level of theory, we can ob-
tain at least thirteen structures with the Z-form con-
former. At least nine lowest energy structures are within
16.72 kJ/mol of the minimum energy (see them
in Fig.S4 in the Supplementary material). Six configu-
trations within 8.36 kJ/mol of the minimum energy of
the structure are shown in Fig.6. Except Z6-3, which
has the lowest Gibbs free energy, the other five configu-
trations are similar. All of them have two bridges,
and each bridge includes three methanols. Furthermore, in Z6-1 and Z6-2, there is an intramolecular hydrogen bond between the CO$_2^-$ and the ammonium group. In Z6-1, two oxygen atoms of the CO$_2^-$ group are involved in the hydrogen bonds. However, in Z6-2, only one oxygen of the CO$_2^-$ group is hydrogen bonded. Z6-1 is thus the lowest energy structure. In Z6-5, one of the oxygen atoms is involved in the two bridges while another one is just involved in the intramolecular hydrogen bond. In Z6-4, three hydrogen atoms of the ammonium group are bonded to the methanols which have been involved in the long-chain bridge. In Z6-6, one hydrogen of the ammonium group is not bonded. Z6-6 has higher energy 8.36 kJ/mol than Z6-1. Z6-3 is a different configuration. There are two rings in this cluster, one includes two methanol molecules while another one includes four solvent molecules.

It is astonishing that the lowest energy of the Z-form glycine-(CH$_3$OH)$_6$ lies 9.86 kJ/mol with the enthalpy and ca. 11.24 kJ/mol with Gibbs free energy below the corresponding neutral structures. In other words, when n=5 and 6, the Z-form and the N-form for the clusters

FIG. 5 Lowest energy optimized structures of N5 and Z5. See Fig.1 for details.
Glycine-(CH$_3$OH)$_n$ has been isoenergetic.

IV. DISCUSSION

Theoretical prediction reveals some trends concerning the geometries of the glycine-methanol clusters. For the neutral form (N-form), the first three methanols prefer to locate near the carboxylic acid group. When $n=4$, the configuration with four methanols bridging the carboxylic acid and the amino group has the lowest energy. When the number of the solvents (methanols) reaches six, the configuration with the multi-methanol bridge between the carboxylic acid and the amino group are the lowest energy structure. This configuration could potentially allow the hydrogen of the carboxylic acid group transferring to the amino group and forming a zwitterionic structure. When $n \leq 4$, the lowest structures have only one ring formed by the hydrogen bonds,

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the number of solvents in the clusters reaches five and Z-form as the methanol increased from 1 to 6. When difference of the lowest energies between the N-form and ble I and Fig.7, the trend shows a decrease of the dif-
ference (kJ/mol) between the lowest energy Z- and N- forms. For $n=5$, and 6, there is another intermolecular hydrogen bond formed which makes the structure more stable. For the glycine-(H$_2$O)$_n$ clusters ($n>3$), in the lowest energy configurations, waters form a ring interacting with each other through multiple hydrogen bonds, and this ring is then hydrogen bonded to the amino acid molecule [12]. The report indicates that the larger clusters tend to form cage-like structures by waters [18]. However, the similar cage-like structure for the glycine-methanol system is not found. It can be explained that the water molecule could provide two hydrogen atoms for the formation of hydrogen bonds while the methanol can only supply one.

Table I summarize the absolute enthalpy and Gibbs free energies in Hartree for the lowest energy zwitterion and neutral glycine-methanol cluster.

<table>
<thead>
<tr>
<th>H (kJ/mol)</th>
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but two rings can be found when $n=5$.

In the clusters including the zwitterionic glycine, the configurations with the methanols bridging the acid and ammonium group are the favorite. Previous studies have indicated that optimization of an initial zwitterionic structure leads to proton transfer from the ammonium group to the carboxylic acid group [12]. However, our calculations reveal that even one methanol is sufficient to keep the “extra” proton bonded to nitrogen at the level of B3LYP/6-31+G*. Higher level computations being engaged in our group will make this point certain or not. For $n≥2$, in the lowest energy Z-form configurations, the methanol prefers to bridge the ammonium to the carboxylic acid group by forming one or two long hydrogen bonds chain. For $n=5$ and 6, there is another intermolecular hydrogen bond formed which makes the structure more stable. For the glycine-(H$_2$O)$_n$ clusters ($n>3$), in the lowest energy configurations, waters form a ring interacting with each other through multiple hydrogen bonds, and this ring is then hydrogen bonded to the amino acid molecule [12]. The report indicates that the larger clusters tend to form cage-like structures by waters [18]. However, the similar cage-like structure for the glycine-methanol system is not found. It can be explained that the water molecule could provide two hydrogen atoms for the formation of hydrogen bonds while the methanol can only supply one.

Table I summarize the absolute enthalpy and Gibbs free energies in Hartree for the lowest energy zwitterion and neutral glycine-methanol cluster.

<table>
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<th>Neutral</th>
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six, the two forms (Z-form and N-form) are isoenergetic. This result agrees with the experimental study of tryptophan-methanol complexes that a minimum of five solvent molecules are necessary to observe a zwitterionic structure [19]. Extending this trend (in Fig.7), the lowest Gibbs free energy difference between two forms has decreased to 33.86 kJ/mol when $n=8$, and the enthalpy difference is 53.09 kJ/mol when $n=9$, which is comparable with the experimental results that Gibbs free energy and the enthalpy for the process Z(aq)→N(aq) are 30.51 and 43.05 kJ/mol, respectively [11,25]. Thus, a tentative estimate may obtain that eight or nine methanol molecules are needed to fully solvate a glycine molecule. This estimate consists with the previous reports that eight water molecules could not fully solvate glycine [11] and the 11 water-glycine complex was found to exist in a zwitterionic state [10]. Higher level and extensional calculations presently undertaken in our group are designed to address these estimates.

V. CONCLUSION

In this study, we explored the microsolvation of the glycine with the methanols by the use of the DFT calculations. We found that one methanol molecule can stabilize the zwitterionic form (Z-form) in the clus-
ter glycine-CH$_3$OH at B3LYP/6-31+G* level of theory. For the clusters Gly-(CH$_3$OH)$_n$ with $n \leq 3$, the methanols prefer to locate near the carboxylic acid group of the N-form glycine while the configurations with the methanols bridging the acid and the amino group are the favorite for the clusters with the zwitterionic form (Z-form) glycine. When $n=5$ and 6, the clusters of two forms (Z- and N-form) tend to be isoen-

ergetic. Furthermore, a tentative estimate suggests that at least eight and nine solvent molecules are needed to fully solvate a glycine molecule.

**Supplementary materials:** Supplementary materials are available at the CJCP website alongside the main article.

VI. ACKNOWLEDGMENTS

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