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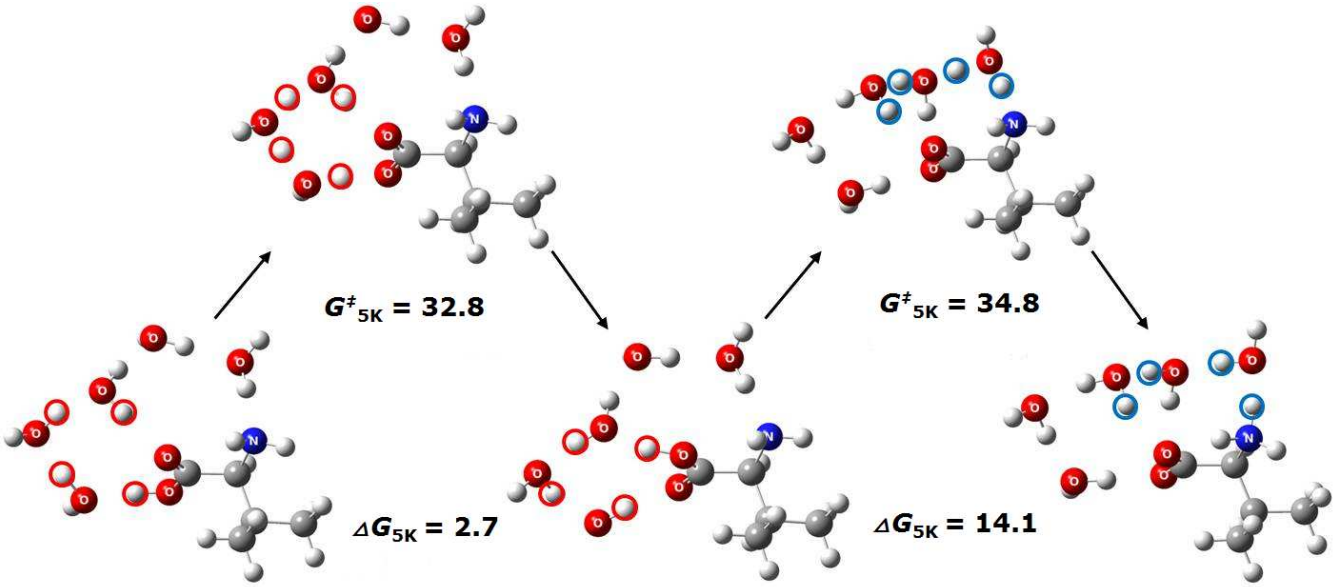
TOC Keyword: gas phase hydration, water, amino acid, dipeptide, zwitterion

Ju-Young Kim, Doo-Sik Ahn, Sung-Woo Park, and Sungyul Lee



Gas phase hydration of amino acids and dipeptides: Effects on the relative stability of zwitterion vs. canonical conformers

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<Invited Review>

Gas phase hydration of amino acids and dipeptides: Effects on the relative stability of zwitterion vs. canonical conformers

Ju-Young Kim, Doo-Sik Ahn,[a] Sung-Woo Park,[b] and Sungyul Lee

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Abstract

We present a brief review for studies of the relative stability of canonical vs. zwitterionic forms of amino acids and dipeptides under the influence of gas phase hydration. Focus is given on how many water molecules are necessary to stabilize the zwitterionic conformer. Experimental and theoretical investigations for this interesting question are discussed. It is illustrated that the hydrating properties of amino acids and dipeptides are strongly dependent on the characteristics (hydrophilicity, basicity etc.) of side chains, and also on the presence of metal cations or an excess electron. Besides the relative Gibbs free energies of various conformers to estimate their relative thermodynamic stability, the activation barriers of proton transfer processes between canonical and zwitterionic forms are emphasized to assess the kinetic stability of thermodynamically less favorable species in low temperature gas phase environment.

TITLE RUNNING HEAD: Gas phase hydration of amino acids and dipeptides

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Introduction

Solvation is one of the most fundamental and interesting phenomena in chemical science. Although gas phase reactions proved to be instrumental for understanding chemical reactions in terms of molecular properties, the effects of solvents must ultimately be elucidated because most organic and biochemical reactions occur in solution phase. The role of solvent in chemical reactions is not limited to dissolving the reacting species. Interactions with solvent molecules influence the physicochemical properties of solutes, even tremendously increasing the rates of chemical reactions.

Biochemical processes in cells, of course, exemplify many instances in which the solvent (water) profoundly affects the molecular structure and reactivity. Biochemical reactions may not be discussed by omitting the role of water, because water exerts such strong influence on the thermodynamics and kinetics of the processes. One prominent example is the structures of amino acids[1-14] and peptides under the influence of water molecules. This interesting subject has been under intensive study both theoretically and experimentally, because the structures and the stability of canonical[15-18] and zwitterionic[16, 19-25] forms are profoundly affected by solvent. Amino acids exist in canonical form in gas phase, whereas zwitterionic (charge-separated) conformer is predominant in aqueous solution.[24-27] One of the central questions concerning the structures and biochemical properties of amino acids is: How many water molecules are required to stabilize the zwitterionic form? This question has been addressed by examining the relative stability of these two forms as a function of the number of interacting water molecules. Thus far, the experimental structural information on multiply hydrated amino acids is limited, and few of the previous studies has provided conclusive evidence as to how the structure of an amino acid changes upon solvation and where the transition from canonical structure to zwitterion occurs.

In this brief review, we discuss recent experimental and theoretical investigations for the role of water in determining the effects of gas phase hydration on relative stability of canonical (non-ionic) vs. zwitterionic forms of amino acids and dipeptides. We illustrate that both the thermodynamic and kinetic aspects of the chemistry of these biomolecules should be taken into account. The relevant parameters to

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be considered are the relative Gibbs free energies of various conformers, and the activation barriers for transformations between them. Emphasis is placed on the latter property (Gibbs free energies of activation) to estimate the kinetic stabilities of biomolecules.

We illustrate that the role of water is profound: the interacting water molecules may either influence the structures of the conformers, or take part in the transformation thereof directly (mediating the movement of the proton). We discuss the thermodynamic and kinetic stability of zwitterionic amino acids and dipeptides relative to canonical forms as a function of the number of water molecules, thereby elucidating how many molecules are necessary to stabilize the zwitterion. It turns out that amino acids with different kinds of side chains (hydrophobic, acidic, basic, etc.) exhibit very different behavior toward the influence of water. We also describe the effects of water on the canonical ←→ zwitterion transformation, especially its participation in multiple proton transfer processes. Our present review of amino acids and dipeptides is not exhaustive, limited to those for which attempts were made to unravel the influence of solvent on the stability of zwitterionic conformers. We present the case by classifying them based on the properties of their side chains. Amino acids and dipeptides with extra charges (with an extra electron, or metal cations) are also discussed. Studies of protonated amino acids would need separate discussion, and are excluded from this brief review.

Glycine, Alanine, Valine: Hydrophobic side chains

Effects of gas phase hydration on the structure of glycine[28, 29] (Gly) has been investigated by a number of experimentalists. Nonose et al.[30] used electrospray ionization to study the structures and incremental binding energies of Gly. Kresin et al.[31] investigated the hydroxyl loss fractions for Gly and tryptophane (Trp) molecules picked up by water clusters $(H_2O)_n$ or $(D_2O)_n$ ($n \leq 15$) in a supersonic expansion and analyzed by electron bombardment mass spectrometry. Balabin[32] reported the jet-cooled spontaneous Raman spectrum of a glycine – water complex ($Gly(H_2O)$). The low-frequency vibrational spectrum (below 500 cm^{-1}) of the solvated molecule is recorded and assigned using ab initio (MP2) and DFT

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(B3LYP, BLYP, PBE0 = PBE1PBE) methods. Experimental study of the onset of the stabilized Gly zwittierion by explicit water molecules has been rare. Alonso et al.[33] determined the structures of Gly(H_2O) with canonical Gly core by molecular-beam Fourier transform microwave spectroscopy. Bowen and co-workers[8] studied hydrated Gly anions by mass spectrometric and size-selected photoelectron spectroscopy, finding that at five water molecules are needed to transform Gly anion into its zwitterion. Considering that an extra electron attached to an amino acid usually favors the formation of zwitterionic amino acids with less number of water molecules than neutral amino acid, they concluded that at least five water molecules would be required to transform neutral Gly into its zwitterion. So far, the number of water molecules at the threshold of canonical → neutral transformation of Gly is not known by experiments.

Aiken and Gordon's computational work[9] on Gly$(H_2O)_n$ (n = 0 – 8) is so far the most comprehensive theoretical study of gas phase hydration of Gly – water clusters. Employing a variety of quantum chemical methods, they suggested that Gly$(H_2O)_7$ with zwitterionic Gly core is the global minimum energy structure, lying ~ 1.3 kJ/mol below the lowest energy canonical conformer.

Thus, whereas the theoretical studies indicate that seven water molecules[9] are required to stabilize the zwitterion on thermodynamic grounds, experimental observations[8] for Gly – water clusters are not conclusive yet, only suggesting that at least five water molecules are necessary. Although the Gly$(H_2O)_{5-6}$ clusters with zwitterionic Gly core are less stable (that is, with higher Gibbs free energies) than those with canonical Gly core, the activation barriers of zwitterionic → canonical Gly$(H_2O)_{5-6}$ transformation may be of considerable interest. This is because the thermodynamically less favorable zwitterion may be kinetically stable (that is, they may exist during a period of time enough to be observed experimentally at low temperature (~ 5 K) gas phase environment), if the barrier is sufficiently high. This may be the basis of Blom et al.'s[7] experimental observation of zwitterionic Trp$(H_2O)_5$ whose Gibbs free energy was calculated to be 12.1 kJ/mol higher than the canonical counterpart, as discussed below.

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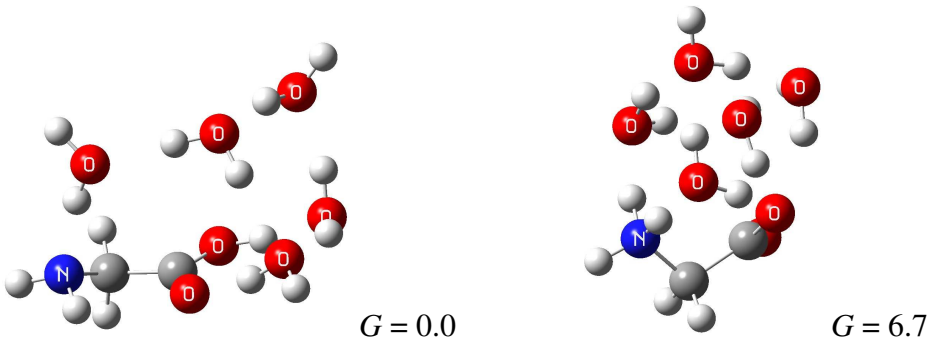
Because the Gibbs free energy of $Gly(H_2O)_5$ with zwitterionic Gly core presented in Figure 1 is 6.7 kJ/mol higher than the canonical $Gly(H_2O)_5$,[14(c)] the formation of the former conformer is clearly less favorable. The zwitterion → canonical isomerization exhibit, on the other hand, a substantial barrier (36.8 kJ/mol).[14(c)] This fairly large barrier to may kinetically separate the zwitterionic and the canonical $Gly(H_2O)_5$, rendering them observable at least in the gas phase at low temperature.

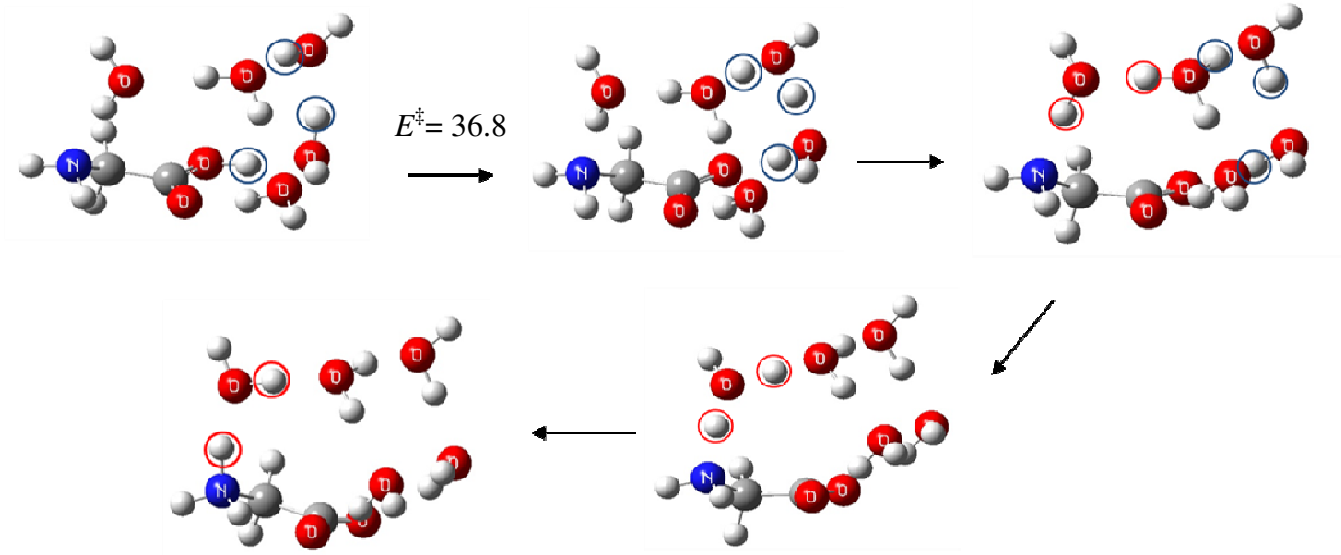
Figure 1. (1) Structures of the lowest energy conformers of canonical $Gly(H_2O)_5$ (relative Gibbs free energies in kJ/mol, ZPE included; MP2/aug-cc-pvdz). (2) Dynamic pathway of zwitterion → canonical isomerization (reaction barrier in kJ/mol, ZPE included; B3LYP/6-311++G(d,p)).

(1)



canonical zwitterion

(2)



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This aspect of the gas phase hydration of amino acids (zwitterionic ←→ canonical proton transfer processes of amino acid – water clusters) has been rarely investigated compared to the corresponding thermodynamic studies. To our best knowledge, Yamabe et al.'s[34] theoretical investigation of isomerization of Gly under the influence of up to eleven water molecules seems to be the only study other than our work. They found that a water molecules may act as a catalyst in proton transfer of $Gly(H_2O)_4$.

A lot of investigations were also carried out for Gly – water *anions* with an excess electron. Diken et al.[35] found that Gly^- and $Gly^-(H_2O)_{1-2}$ has canonical Gly core by photoelectron spectroscopy. Xu et al.[8] observed that a zwitterionic species is formed for $[Gly(H_2O)_n]^-$ with $n \geq 5$ based on mass spectrometry and photoelectron spectroscopy. Complexation with metal cations is also found to favor the formation of zwitterionic amino acids, decreasing the number of water molecules required. Williams and co-workers[36] assessed the interactions between divalent metal ions and Gly. They found that except for beryllium, metal ions render the Gly zwitterions more stable by 21 ~ 50 kJ/mol than Gly in its canonical form.

The situation for alanine (Ala) is similar to Gly in that the experimental observations on the Ala – water clusters are not conclusive, but theoretical studies clearly suggest that seven water molecules are required to stabilize the cluster with zwitterionic Ala core. By examining the $Ala(H_2O)_{1-8}$ clusters employing a systematic approach (the EFP discrete solvation model with a Monte Carlo algorithm to sample the configuration space) to find the global minimum, Gordon and co-workers[37] found that canonical and zwitterionic $Ala(H_2O)_7$ (Figure 2) are quasidegenerate, either from being calculated to be the global minimum energy structure, depending on the theoretical methods.

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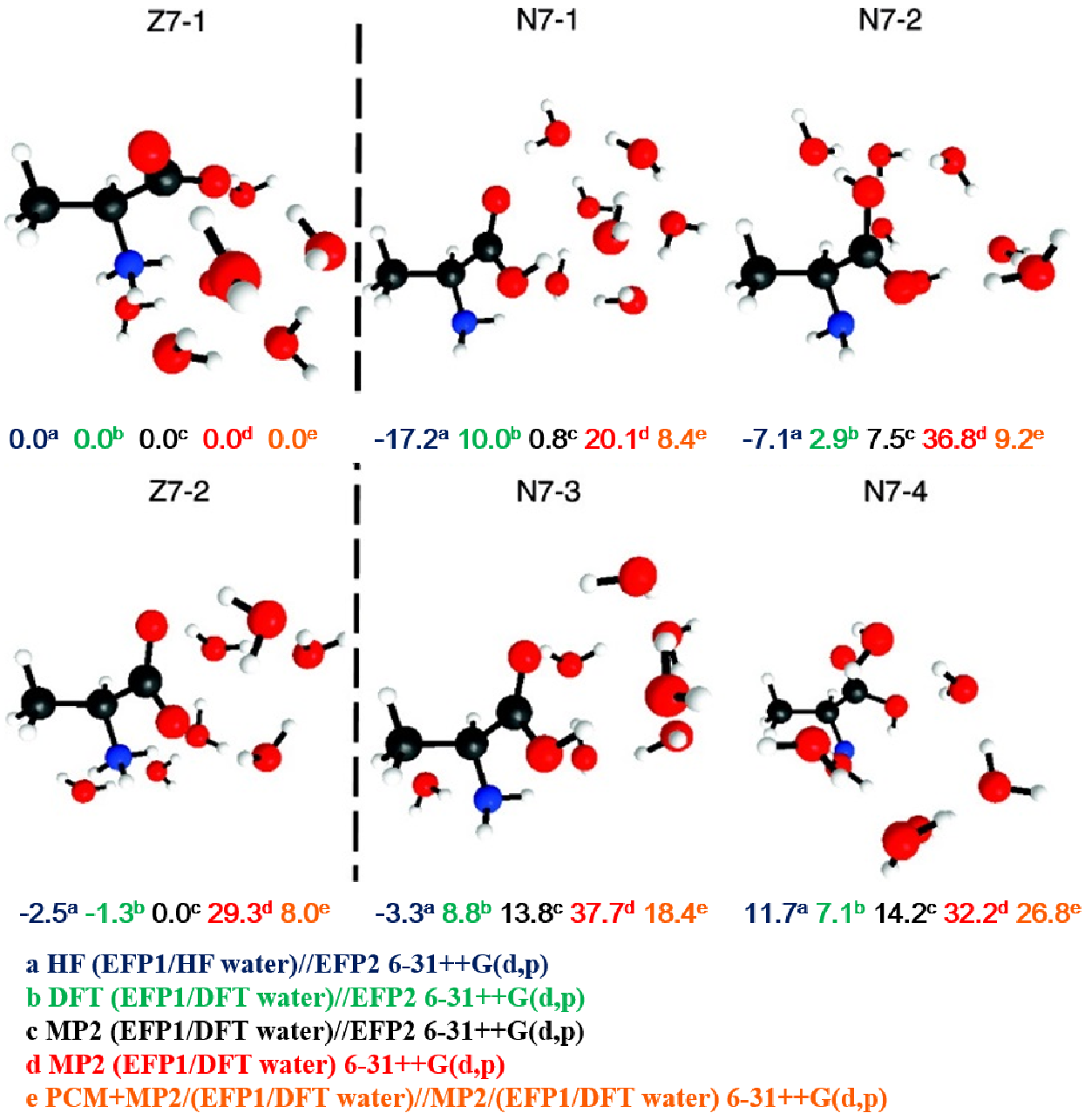
Figure 2. Structures of the lowest energy conformers of Ala$(H_2O)_7$ (relative energies in kJ/mol). From Ref. [37]



The proton transfer process between zwitterionic and canonical Ala – water system has been studied only for Ala$(H_2O)_2$.[15] Figure 3 shows that isomerization proceeds by concerted double proton transfer mediated by two water molecules. The barriers are, however, very small (< 8.2 kJ/mol), indicating the zwitterionic Ala$(H_2O)_2$, whose Gibbs free energies are higher than the canonical structures by > 21 kJ/mol, are not kinetically stable either.

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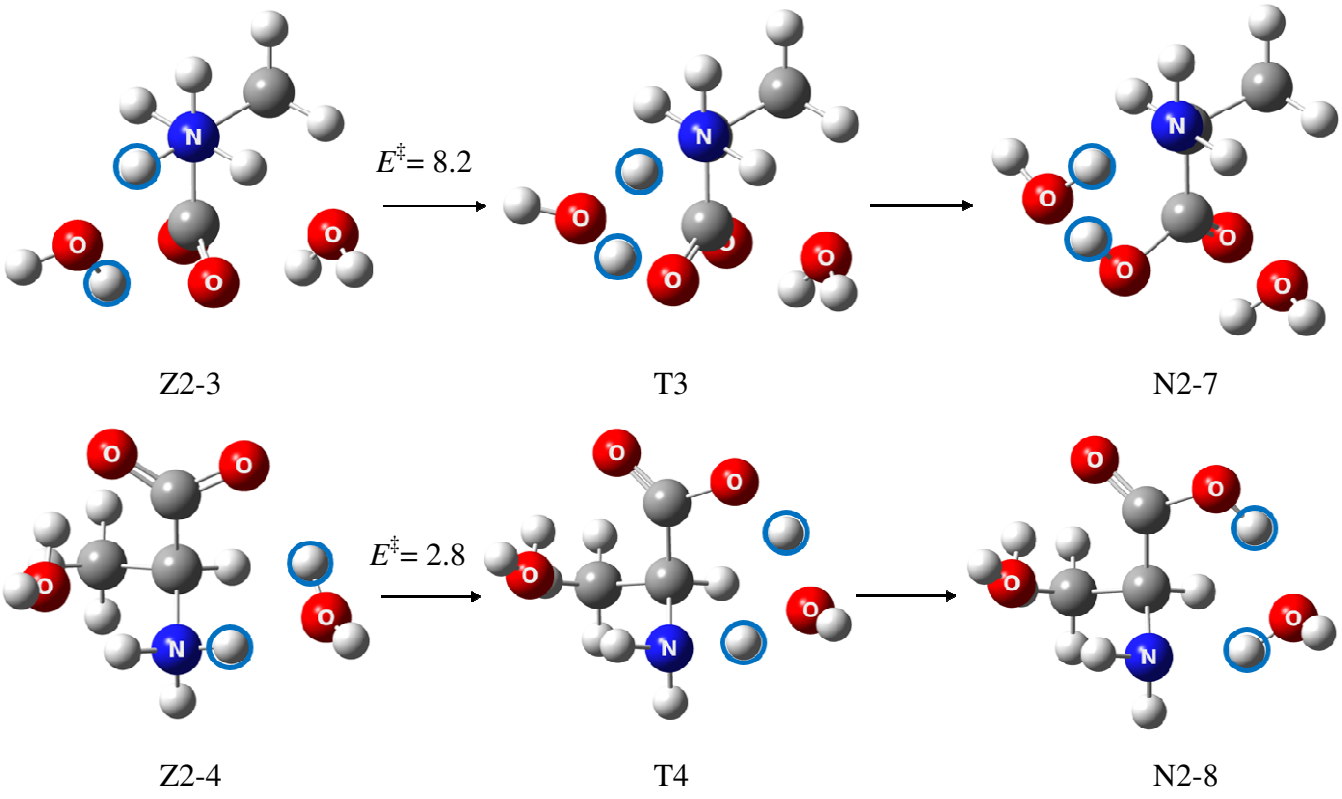
Figure 3. Concerted double proton transfer pathway from the Ala zwitterion-$(H_2O)_2$ clusters to the canonical clusters (reaction barriers in kJ/mol).



Calculations for valine(Val)$(H_2O)_n$ (n = 0 – 5) system by B3LYP/6-311++G(d,p), wB97XD/6-311++G(d,p) and MP2/aug-cc-pvdz level of theory revealed that five water molecules are necessary to stabilize the zwitterionic form of Val.[38] Figure 4 shows that the lowest energy canonical and zwitterionic Val$(H_2O)_5$. Because the two forms are essentially quasidegenerate and the barrier of the canonical → zwitterionic pathway is appreciable, it seems that both forms of Val$(H_2O)_5$ may be observed in low temperature gas phase.[38]

Figure 4. (1) Lowest-lying conformers of canonical Val$(H_2O)_5$ (relative Gibbs free energies in kJ/mol, ZPE included; (a) wB97XD/6-311++G(d,p), (b) MP2/aug-cc-pvdz) (2) Transformation from the lowest energy zwitterionic (zw-5-1) and canonical (ca-5-1) conformer of Val$(H_2O)_5$ (relative Gibbs free energies and reaction barriers in kJ/mol, ZPE included; wB97XD/6-311++G(d,p)).

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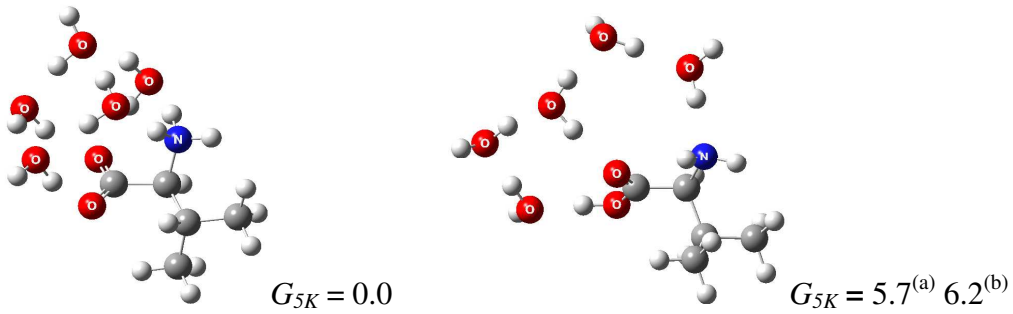
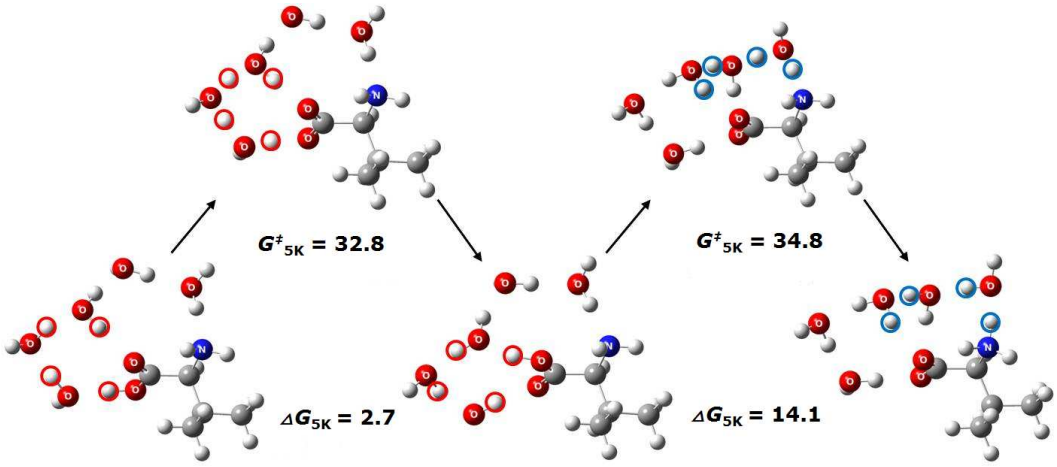
(1)



zwitterion canonical

(2)



(ca-5-1) (ca-5-3) (zw-5-5)

The effects of hydration of Val – alkali metal ion complexes, Val·$M^+(H_2O)_n$, (n = 2 – 6, M = Li, Na, and K), were probed by Williams and co-workers[39] using both theory and blackbody infrared radiative dissociation experiments. They showed that Val·$Li^+(H_2O)_3$ and Val·$Na^+(H_2O)_2$ complexes were zwitterionic, indicating that the size of the metal cation may give different influence on the gas phase hydration of Val.

Serine: Hydrophilic side chain

Serine[40] (Ser) is the smallest amino acid with a hydrophilic side chain. The hydroxyl group may participate in proton transfer in the neutral/zwitterions isomerization processes as an "intramolecular solvent" The hydrophilic side chain –OH may also form hydrogen bond with water molecules. Thus,

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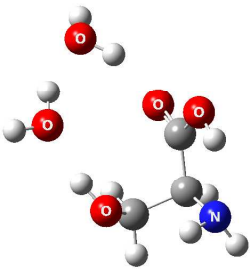
assuming that proton transfer from the carboxyl to the amino group in Ser may involve as many water molecules as in the amino acids with hydrophobic side chains, it may be presumed that more water molecules would be necessary to stabilize the zwitterionic Ser. So far, gas phase hydration of Ser was investigated only up to $Ser(H_2O)_2$.[41] Since the energies of $Ser(H_2O)_2$ with zwitterionic Ser are at least 25 kJ/mol higher than the lowest energy canonical conformer (C3-2-a) given in Figure 5, they are considered to be unstable thermodynamically. Most of the zwitterionic $Ser(H_2O)_2$ isomerize to canonical forms without significant barriers, making them also kinetically unstable. Some may, however, isomerize to the canonical form via considerable barriers. For example, the zwitterionic (Z2-6) conformer transforms via a fairly large barrier (26.0 kJ/mol).

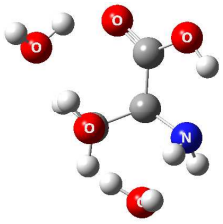
Figure 5. (1) Lowest-lying conformers of canonical $Ser(H_2O)_2$ (relative energies in kJ/mol, ZPE included; B3LYP/6-31++G(d,p), (a) MP2/6-31++G(d,p)) (2) Mechanism of canonical ↔ zwitterion isomerization of $Ser(H_2O)_2$ (reaction barrier in kJ/mol, ZPE included; B3LYP/6-31++G(d,p)).

(1)



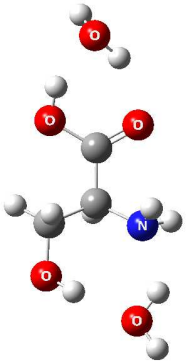
E = 0.0, 5.4[(a)]

C2-2-a



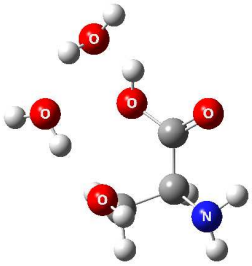
E = 6.2

C2-2-b



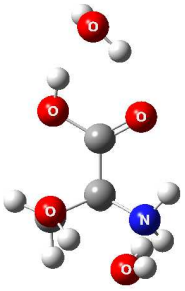
E = 11.3

C1-2



E = 1.0, 0.0[(a)]

C3-2-a



E = 13.1

C3-2-b

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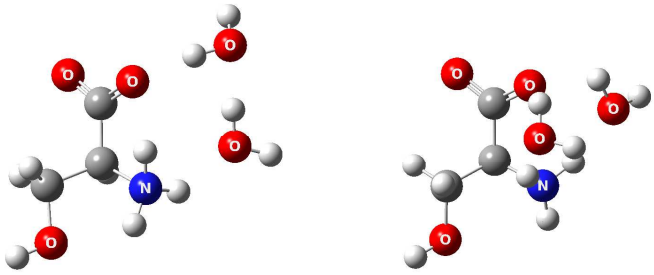
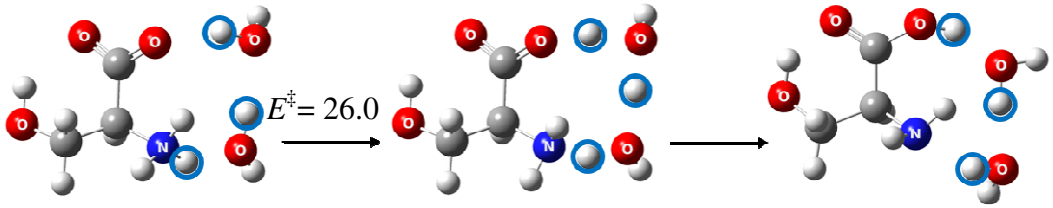


Z2-1 Z2-2

(2)



Z2-6

Arginine, Lysine, Histidine: Basic side chains

Saykally and co-workers[42] were the first to examine the relative stability of zwitterionic/canonical arginine[43-48] (Arg) in the gas phase. By employing the infrared cavity ringdown laser absorption spectroscopy, they clearly observed that gas phase Arg is a canonical conformer. Although Arg is similar to other amino acids in that the canonical form is only observed in the gas phase, the presence of the strongly basic guanidine side chain in Arg may give properties that are distinct from the other amino acids. For example, the strongly basic guanidine side chain may render the proton transfer from the carboxyl group more facile under the influence of solvent. So far, however, experimental study of Arg – water system concerning the relative stability of zwitterionic/canonical Arg has not been reported yet.

Figure 6 presents the calculated structures and relative energy of the zwitterionic and canonical conformers of Arg(H_2O).[49] The energy of the conformer (Z22-1) with the zwitterionic Arg core is lower than those of the lowest energy canonical form (C5-1) by ~ 7.0 kJ/mol by B3LYP/6-311++G(d,p) method. This observation is quite striking, considering that the zwitterionic Arg is at least 8 kJ/mol higher in energy than the canonical Arg.[49] It is also remarkable to observe that a single water molecule may stabilize the zwitterionic Arg relative to the canonical form, because it was well agreed that at least

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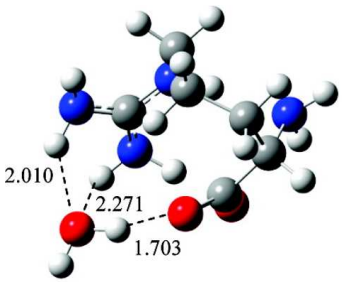
five molecules of water are necessitated to make the zwitterionic form energetically competitive with the canonical conformer. It must be noted that a proton is transferred from the carboxyl to the sidechain guanidine group in Arg, in contrast with other amino acids. The two zwitterionic conformers (Z22-1) and (Z21-2) depicted in Figure 6 are almost of the same energy (within 2.4 kJ/mol).

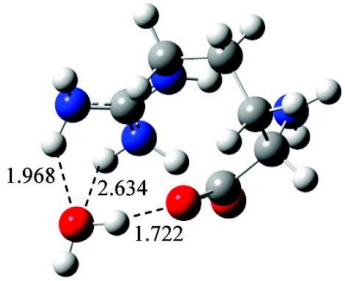
Figure 6. Structures of the lowest energy conformers of (1) zwitterionic and (2) canonical Arg(H_2O) (relative energies with respect to (Z22-1) in kJ/mol, ZPE included; (a) B3LYP/6-31++G(d,p) (b) MP2/aug-cc-pvdz and bond lengths in Å).

(1)



$E = 0^{(a)}\ 0^{(b)}$

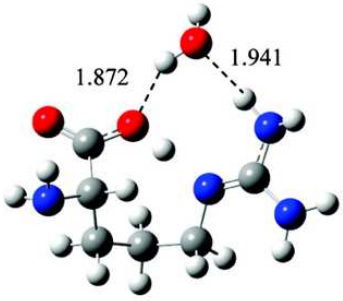
(Z22-1)



$E = 2.4^{(a)}\ 2.6^{(b)}$

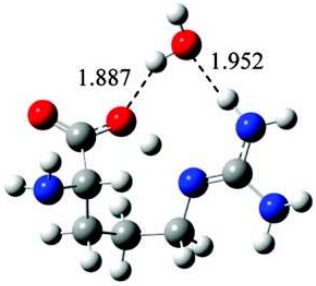
(Z21-2)

(2)



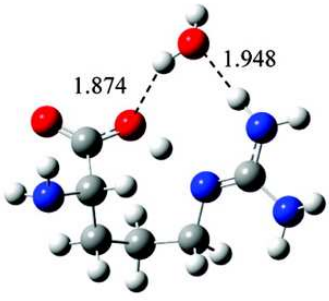
$E = 7.0^{(a)}\ 21.8^{(b)}$

(C5-1)



$E = 7.9^{(a)}\ 22.1^{(b)}$

(C4-7)



$E = 8.2^{(a)}\ 22.2^{(b)}$

(C4-1)

One important issue would be the mechanism and the barrier of formation of the zwitterionic Arg(H_2O) from canonical conformer. If the Arg(H_2O) complex initially produced with canonical Arg core is kinetically very stable (that it, if the barrier to zwitterionic Arg(H_2O) is high), the latter form of

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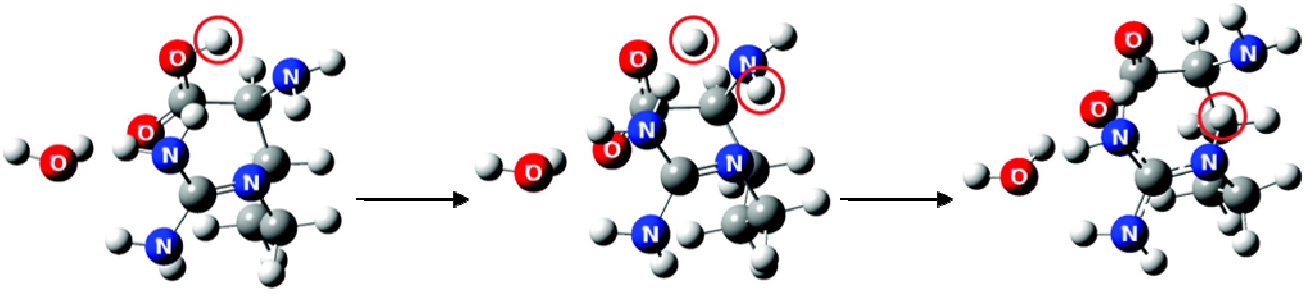
Arg(H_2O) could hardly be formed. The barrier from the canonical form to zwitterion is ~ 18.7 kJ/mol (Figure 7), indicating that the canonical conformer of Arg(H_2O), once formed, may easily transform to zwitterion. Figure 7 also shows that the lowest energy zwitterionic form (Z22-1) connects via a double proton transfer process to canonical form.

Figure 7. Isomerization from the canonical form of Arg(H_2O) to the zwitterionic form (relative energies, relative Gibbs free energies and reaction barrier in kJ/mol, ZPE included; (a) B3LYP/6-311++G(d,p) (b) MP2/6-311+G(d)).



E = 28.7[(a)] 35.4[(b)]
G = 26.3[(a)] 31.7[(b)]
(C22-1)

$E^{‡}$= 18.7[(a)] 19.3[(b)]
$G^{‡}$= 9.6[(a)] 9.2[(b)]
(Ts22-1)

E = 0
G = 0
(Z22-1)

Effects of metal cations on the relative stability of zwitterionic/canonical Arg were studied extensively by Williams and co-workers.[45, 50, 51] They observed that cationized Arg[45, 52] (Arg•M^+, M = H. Li, Na, K, Rb, Cs) is in zwitterionic form, and that one water molecule stabilizes the cationized Arg.[50] An excess electron tends to stabilize the zwitterionic conformer relative to the canonical forms. For example, Gutowski and co-workers[52] reported that Arg solvated by an excess electron renders the zwitterionic and canonical Arg quasidegenerate. The effects of anions on the structure of Arg have been treated very recently by Milner et al.[53] These authors found that fragmentation of X^-·Arg (X^- = F^-, Cl^-, Br^-, I^-, NO_3^-, ClO_3^-) gives Arg zwitterion.

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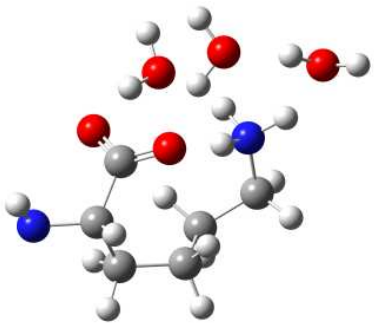
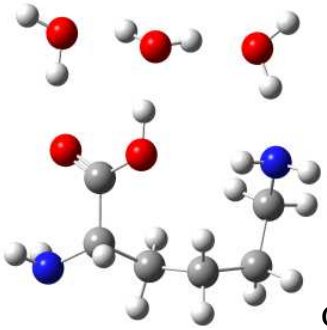
Lysine (Lys) is the amino acid with a very basic side chain, only second to Arg. Theoretical work carried out in our lab[54] examined Lys$(H_2O)_n$ (n = 2, 3), predicting that the zwitterionic Lys becomes quasidegenerate with the canonical forms due to the solvating effects of three water molecules. This smaller number of water molecules to stabilize the Lys zwitterion than that (> 5 water molecules) for the amino acids with hydrophobic side chains described above seems to be the effects of the strongly basic side chain in Lys. Figure 8 depicts the structures of Lys$(H_2O)_3$ with zwitterionic and canonical Lys core, in which the Gibbs free energy of the zwitterionic conformer is shown to be lower than the canonical form.

Figure 8. Structures of lowest energy canonical and zwitterionic forms of Lys$(H_2O)_3$ (relative Gibbs free energies in kJ/mol, ZPE included; (a) MP2/aug-cc-pvdz (b) wB97XD/6-311++G(d,p)).



$G_{5K} = 0$



$G_{5K} = 0.98^{(a)}\ 1.30^{(b)}$

zwitterion canonical

Effects of metal cations on the stability of zwitterionic Lys were studied by Williams group.[55-57] By using density functional theory and blackbody infrared radiative dissociation experiments, they found that lowest-energy structure of lithiated Lys without a water molecule is nonzwitterionic; Adding a water molecule to lithiated Lys did not stabilize the zwitterionic form of Lys. The Lys·Na^+ and Lys·K^+ complexes determined by infrared multiple photon dissociation spectroscopy were also reported to be nonzwitterionic.[56] The related amino acid α-*N*-methyllysine and ϵ-N,N-dimethyllysine, however, were zwitterionic[57] under complexation by Na^+, K^+, and by Li^+, Na^+, K^+, respectively, illustrating that side

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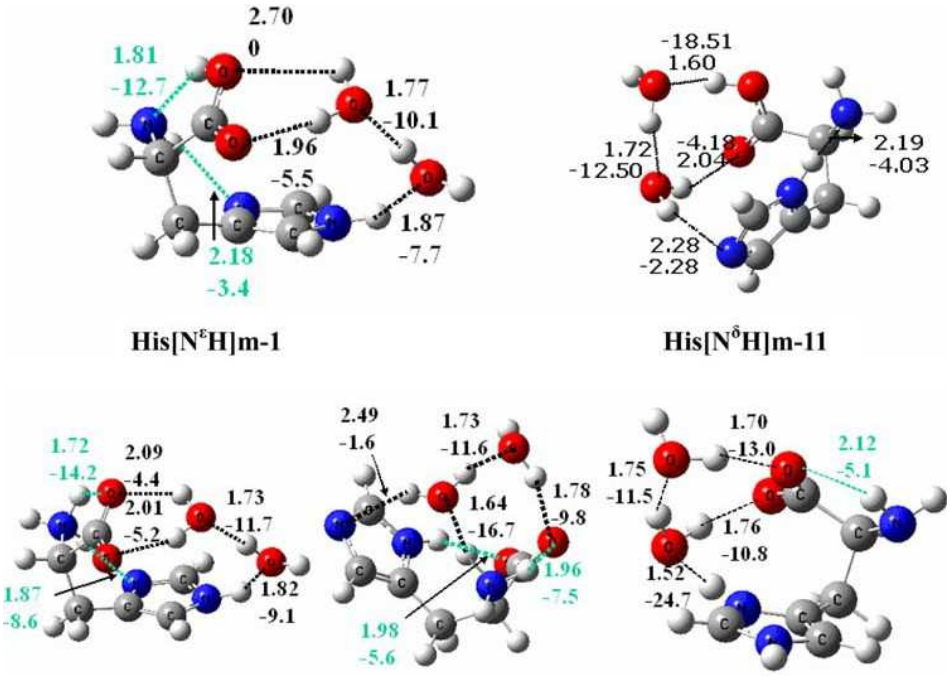
chains can have very different effects on the stability of different conformers in the metal cationized amino acids.

Gas phase hydration of histidine (His) was treated by Lin and co-workers.[58] Their calculations showed that for $His(H_2O)_{1-2}$ the canonical forms are clearly more stable than the zwitterion (Figure 9). Effects of metal cations on the conformation of His was studied by Armentrout and co-workers.[59]

Figure 9. Structures of lowest energy conformers of $His(H_2O)_2$ (bond lengths in Å). From Ref. [59].



Proline: Cyclic amino acid

Proline[60,61] (Pro) is somewhat different in the structure from other amino acids. Due to the pyrrolidine ring embedded, Pro plays an important role in determining the *β*–turn structure in polypeptides and proteins.[62] Pro is also unique among the amino acids in that the N-terminus is a secondary amine. Because it is well known that secondary amines exhibit larger basicity (in aqueous solution) and larger proton affinity (in gas phase),[63] this structural feature of Pro may show the effects of gas phase hydration

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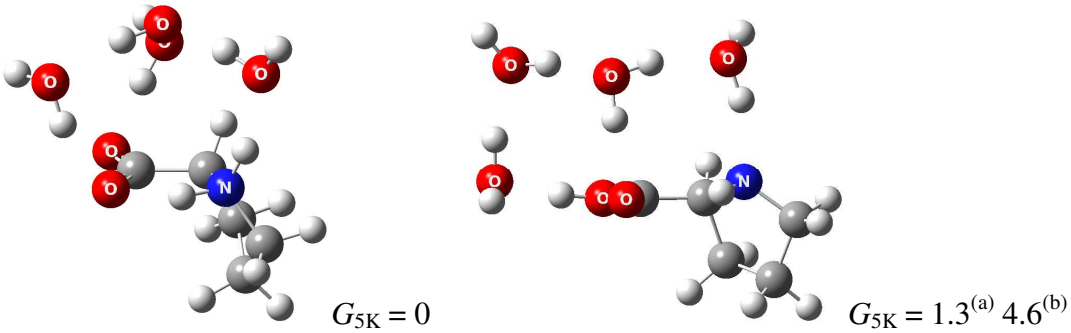
that are different from other amino acids with primary amine groups. The observation of sodiated Pro zwitterion by Ohanessian and co-workers[64] in gas phase seems to be the result of this.

Figure 10 depicts the structures of $Pro(H_2O)_4$ optimized by wB97XD/6-311++G(d,p) and MP2/aug-cc-pvdz methods.[65] Because the relative Gibbs free energy G_{5K} of $Pro(H_2O)_4$ with canonical Pro core is higher than that with zwitterionic Pro by 1.3 (4.6) kJ/mol at wB97XD/6-311++G(d,p) (MP2/aug-cc-pvdz) level of theory, four water molecules seem to be enough to stabilize the Pro zwitterion.

Figure 10. Structures of lowest energy canonical and zwitterionic forms of $Pro(H_2O)_4$ (relative Gibbs free energies in kJ/mol, ZPE included; (a) wB97XD/6-311++G(d,p) (b) MP2/aug-cc-pvdz)



Tryptophan, Phenylalanine: Aromatic side chain

Because of the presence of the aromatic rings, gas phase hydration of Trp and phenylalanine (Phe) are more amenable to studies by ultraviolet(UV) spectroscopy than other amino acids lacking the proper chromophore. The early pioneering UV spectroscopic work on singly hydrated neutral tryptophan was carried out using resonance-enhanced two-photon ionization and laser-induced fluorescence spectroscopy. Peteanu and Levy[66] investigated resonant two-photon ionization spectrum of singly hydrated Trp. Sulkes et al.[67] used laser-induced fluorescence to examine the excitation spectrum of the Trp - single water complex. Simons and co-workers[68] investigated the hydrated complexes of Trp by a combination of calculations, ion dip infrared spectroscopy, UV hole burning, and resonant two-photon ionization. Bowen and co-workers' experiments[8] on the anions of Trp set four water molecules as lower

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limits for the number of water molecules needed to induce zwitterion formation in these amino acids. It was Paizs, Oomens and co-workers[7] that unambiguously determined the onset of Trp zwitterion under the influence of water molecules. By means of the IR spectroscopy and DFT calculations for $Trp(H_2O)_{1-6}$ complexes, they observed that the zwitterionic Trp may be stabilized by four water molecules. These authors obtained the IR spectra to assign the bands in 1300-1850 cm^{-1} to either canonical or zwitterionic Trp conformers. They also observed weak absorption by zwitterionic $Trp(H_2O)_5$ and $Trp(H_2O)_6$. It would be interesting to interpret these results in terms of thermodynamic and kinetic stability of the zwitterionic vs. canonical Trp as dictated by the relative Gibbs free energy and the activation barrier of zwitterion → canonical transformation process, respectively. Because the calculated energy of zwitterionic $Trp(H_2O)_5$ is higher by 12.1 kJ/mol than the canonical form, the weak absorption by zwitterionic $Trp(H_2O)_5$ may not be explained by the energy gap, as the authors pointed out. Thus, it may be that a modest barrier for zwitterion → canonical change renders a zwitterionic $Trp(H_2O)_5$ to be kinetically stable at low temperature gas phase. For $Trp(H_2O)_6$, the energy gap narrows down to ~4 kJ/mol (canonical form still more stable), so that the minor absorption may readily be assigned as that of zwitterionic $Trp(H_2O)_6$.

As for Phe, Bowen and co-workers[8] suggested that the zwitterionic form of Phe may be stabilized by four water molecules.

Diglycine, Dialanine, Diproline: Dipeptides

Considering that diglycine $(Gly)_2$ is the simplest dipeptide, it is surprising to see that its gas phase hydration has not been studied. To our best knowledge, $(Gly)_2$ – water system has not been examined experimentally yet. There exist several reports for protonated[69, 70] and cationized $(Gly)_2$.[71] Using infrared multiple photon dissociation (IRMPD) spectroscopy and MP2(full)/6-311++G(2d,2p)//B3LYP/6-311+G(d,p) level of theory, Wu and McMahon[69] observed that the most stable $(Gly)_2H^+$ is canonical (Figure 11). Figure 12 compares the Gibbs free energies of $(Gly)_2(H_2O)_3$ with canonical and zwitterionic

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$(Gly)_2$ core recently obtained in a computational study in our lab.[72] Because the Gibbs energy of zwitterionic $(Gly)_2(H_2O)_3$ is 31.6 kJ/mol higher than canonical $(Gly)_2(H_2O)_3$, it is predicted that hydration by up to three water molecules does not give thermodynamic stability of the zwitterion relative to the canonical forms. Our calculations also suggest that zwitterionic $(Gly)_2(H_2O)_3$ is not stable kinetically.

Figure 11. Structures and IRMPD spectra of lowest energy conformers of (1) $(Gly)_2H^+$ and (2) $(Pro)_2H^+$. From Ref. [69]

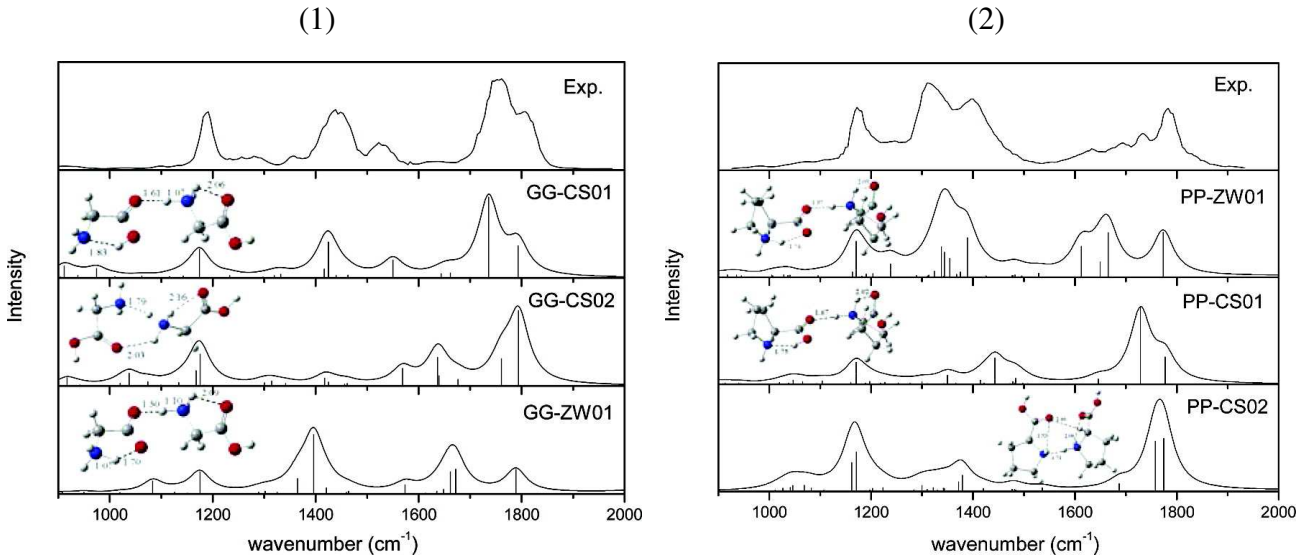
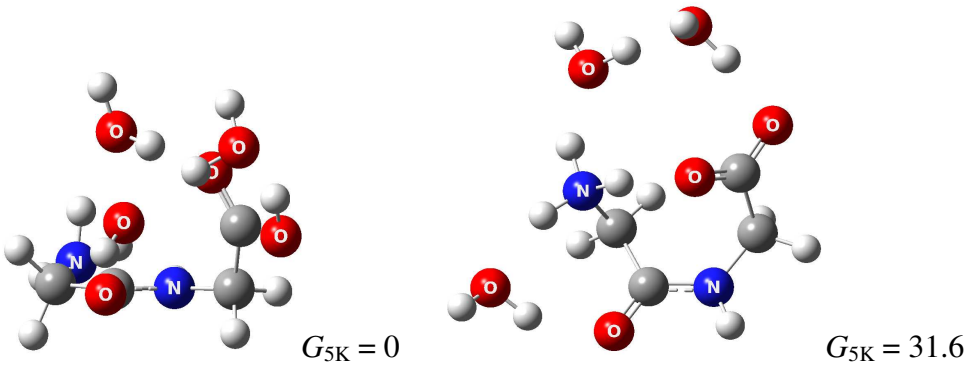


Figure 12. Structures of lowest energy canonical and zwitterionic forms of $(Gly)_2(H_2O)_3$ (relative Gibbs free energies in kJ/mol, ZPE included; wB97XD/6-311++G(d,p)).



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Although conformers of dialanine $(Ala)_2$ in water were studied by several groups using various theoretical methods,[73-75] to our best knowledge none was reported for its gas phase hydration yet. For the protonated diproline $(Pro)_2H^+$, Wu and McMahon[69] reported that the lowest energy structure of $(Pro)_2H^+$ is zwitterionic, although both canonical and zwitterionic forms were detected in their infrared multiple photon dissociation experiments (Figure 11).

Conclusions

In the present review, we discussed the important role water takes in affecting the structures of amino acids and dipeptides. We showed that the solvent water may not only serve as electrostatic continuum, but it may also act as a direct participant in proton transfer, mediating and/or promoting the process. Further experimental studies for this extremely interesting system will be highly desirable.

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