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ORIGINAL ARTICLE

The influences of water solvent on the structures and stabilities of Na^+–AD conformers

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Abstract The influences of water solvent on the structures and stabilities of the complex ion conformers formed by the coordination of alanine dipeptide (AD) and Na^+ have been investigated using supramolecular and polarizable continuum solvation models at the level of B3LYP/6-311++G**, respectively; 12 monohydrated and 12 dihydrated structures of Na^+–AD complex ion were obtained after full geometrical optimization. The results showed that H_2O molecules easily bind with Na^+ of Na^+–AD complex ion, forming an ion-lone pair interaction with the Na–O bond length of 2.1–2.3 Å. Besides, H_2O molecules also can form hydrogen bonds $O_W–H_W\cdots O(1)$, $O_W–H_W\cdots O(2)$, $N(1)–H(1)\cdots O_W$ or $N(2)–H(2)\cdots O_W$ with O or N groups of the Na^+–AD backbone. The most stable gaseous bidentate conformer C7AB of Na^+–AD is still the most stable one in the solvent of water. However, the structure of the most unstable gaseous conformer α'B of Na^+–AD collapses under the attack of H_2O molecules and changes into C7AB conformation. Computations with IEFPCM solvation model of self-consistent reaction field theory give that aqueous C5A is more stable than $C7_{eq}$B and that the stabilization energies of water solvent on monodentate conformers of Na^+–AD complex ion (about 272–294 kJ/mol) are more than those on bidentate ones (about 243 kJ/mol).

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Introduction

Proteins are polymers formed by many amino acids through peptide bonds. Exploring the influencing factors on protein folding is of great significance in various fields, such as agriculture, medicine and drug design (Branden and Tooz 1998). More than 70 years ago, Pauling et al., were the first to ponder the influences of water on protein folding (Mirsky and Pauling 1936). The folding of natural proteins in a dilute solution can be studied by investigating the influences of water molecules on the structures and stabilities of the constructing peptides (Thirumoorthy and Nandi 2007; Perczel et al. 1995). As a protonic solvent, water molecules can form hydrogen bonds with peptides, producing notable solute–solvent interactions. Many experimental (Godfrey and Brown 1995; Godfrey et al. 1993) and theoretical studies (Hu et al. 1993; Frey et al. 1992; Jensen and Gordon 1991) have demonstrated that these hydrogen bond interactions can significantly affect the structures and stabilities of peptides.

As the simplest peptide molecule, alanine dipeptide (AD) possesses many common structural characteristics of amino acids, and is always used as a modeling system for studying peptides' structures and hydrations (Scarsdale et al. 1983; Boehm and Brode 1991; Gould and Kollman 1992; Gould et al. 1994; Kaschner and Hohl 1998; Beachy et al. 1997). Six gaseous stable conformers ($C7_{eq}$, C5, $C7_{ax}$, β_2, α_L and α') of AD have been reported, and they are stabilized by the intramolecular hydrogen bond interactions between amino and carbonyl groups (Vargas et al. 2002). These groups can also form intermolecular H-bonds with a protonic solvent. Wang and Duan (2004) reported the three-dimensional potential energy surfaces of AD in gas phase, as well as in a non-polar solvent studied with PCM solvation model at the MP2/cc-pVTZ//MP2/6-31G** level. Additionally, conformational transformations of AD conformers were probed by investigating AD–$4H_2O$ clusters.

Metal ion proteins have important biological functions. As a common ionizing reagent for protein sequencing (Selvarengan and Kolandaivel 2005), Na^+ extensively exists in biological systems. Studies of the interactions between Na^+ and aspartic acid (Asp) or glutamic acid (Glu) show that the most stable structures of Na^+–Asp and Na^+–Glu are always tridentate (Heaton et al. 2008). Our previous work (Qiao et al. 2007) showed that the most stable conformer of Na^+–AD complex is bidentate, owing to the fact that the AD molecule only has two C=O groups, while aspartic and glutamic acids have a CO_2 acid group plus the C=O forming the backbone. We have gained the six stable gaseous conformers of Na^+–AD complex ion including two bidentate conformers (C7AB and C7′AB) with seven-membered ring structures and four monodentate ones ($C7_{eq}B$, C5A, $C7_{ax}B$ and $\alpha'B$) with intramolecular hydrogen bondings (shown in supplementary Figure S1).

Solvation effects have an important impact on the conformational stabilities, vibrational frequencies, chemical properties and bioactivities of proteins (Li et al. 2004). To the best of our knowledge, the solvation effects on Na^+–AD complex ion have not been reported. The Na^+ of the Na^+–AD complex ion is easily hydrated. Besides, carbonyl and amino groups of the backbone of Na^+–AD easily form intermolecular hydrogen bonds with the surrounding water molecules. It can be speculated that there are various solute–solvent interactions between Na^+–AD and the solvent water. In this work, the influences of the incorporation of one or two explicit H_2O molecules into the six conformers of Na^+–AD were studied with supramolecular model at the B3LYP/6-311++G** level. Also, the polarizable continuum solvation models of self-consistent reaction field (SCRF) theory (Tomasi et al. 2005) including PCM (Miertug et al. 1981), IPCM (Foresman et al. 1996) and IEFPCM (Mennucci et al. 1997) were utilized to mimic the bulk solvent polarization effects of Na^+–AD in water. The present study may provide some fundamental information for probing the folding processes of metal ion proteins in diluted solutions.

Computational model and method

The molecular structure and atomic numberings of alanine dipeptide (AD) are depicted in Fig. 1. Note that AD is terminated by CH_3 groups to avoid end effects. The backbone structure was defined by the dihedral angles ϕ (C(3)–N(2)–C(1)–C(2)) and ψ(N(2)–C(1)–C(2)–N(1)). Previous studies (Wang and Duan 2004; Qiao et al. 2007; Vargas et al. 2002) showed that the gaseous AD molecule possesses six stable conformations, i.e., $C7_{eq}$, C5, $C7_{ax}$, β_2, α_L and α'. Study of the coordination of Na^+ and AD molecule showed that there are six stable conformers (shown in supplementary Figure S1) of Na^+–AD complex ion (Qiao et al. 2007). The relative stabilities of these conformers are in the sequence as: $C7AB > C7'AB > C7_{eq}B > C5A > C7_{ax}B > \alpha'B$. Here, marks “A” and “B” are used for donating the coordination modes of Na^+ with O(2) and O(1) of AD backbone, respectively. Therefore, C7AB and C7′AB are the bidentate structures of Na^+–AD, while the other four ($C7_{eq}B$, C5A, $C7_{ax}B$ and $\alpha'B$) are the monodentate ones. The Ramachandran angles for the six conformers C7AB, C7′AB, $C7_{eq}B$, C5A, $C7_{ax}B$ and $\alpha'B$ are $(\phi, \psi) = (-82.6, -99.1)$, (71.4, 105.7), (−82.0, 66.2), (−158.3, 165.3), (71.5, −52.1) and (−169.0, −38.6), respectively. The relative energies corresponding to these conformers are 0.0, 7.4, 56.3, 56.6, 60.0 and 92.5 kJ/mol, respectively. Obviously, the two bidentate structures are largely energetically favored to the four monodentate ones.

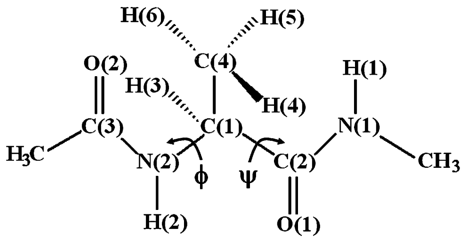


Fig. 1 Molecular structure and atomic numberings of alanine dipeptide (AD). The backbone structure was defined by the dihedral angles ϕ(C(3)–N(2)–C(1)–C(2)) and ψ(N(2)–C(1)–C(2)–N(1))

The influences of H_2O solvent on the structures of Na^+–AD conformers were theoretically studied by the polarized continuum solvation model and supramolecular one with one or two explicit H_2O molecules, respectively. As we know, Na^+ is prone to hydrate. Besides, amino and carbonyl groups of AD backbone easily form intermolecular hydrogen bonds with the added water molecules, respectively. Thus, a single H_2O molecule was introduced to each conformer of Na^+–AD complex ion in the following two ways. (1) Incorporation of a H_2O molecule from the near side of Na^+. The resultant complexes were classified into H_2O–Na^+–AD. (2) Adding a H_2O molecule nearby the O(1), O(2), N(1) or N(2) atoms, which can potentially form intermolecular hydrogen bonds with the added water molecule. Different locations were attempted, mostly for anticipated hydrogen bondings. The resultant complexes were classified into Na^+–AD–H_2O. The H_2O molecule was placed about 3.0 Å away from the conformers in order to avoid forced interactions. The intermolecular structures were optimized at the level of B3LYP/6-311++G**. The results suggested that one H_2O molecule more easily combines with Na^+ than with the backbone structure of AD.

The second H_2O molecule was incorporated into the monohydrated conformers of H_2O–Na^+–AD from the near side of Na^+ or O(1), O(2), N(1), N(2) atoms of AD backbone. The resultant complexes were classified into $2H_2O$–Na^+–AD and H_2O–Na^+–AD–H_2O, representing the coordination between the added H_2O and Na^+ and the H-bond interaction between H_2O and AD backbone, respectively. Also, various possible locations for H_2O molecules were attempted in order to examine all possible stable configurations. To avoid oversimplification in the further introduction of the second H_2O molecule, the six original conformers of Na^+–AD were also used for the simultaneous addition of two H_2O molecules.

Density functional theory (DFT) included in Gaussian 98 suite package (Frisch et al. 1998) has been applied to study the influences of solvent water on the structures and stabilities of Na^+–AD complex ion conformers. The DFT calculations have been performed with Becke's three-parameter hybrid density functional using the Lee, Yang and Parr correlation functional (B3LYP) (Becke 1993; Lee et al. 1988). Supramolecules formed by Na^+–AD and one or two explicit H_2O molecules were fully optimized at the level of B3LYP/6-311++G**. Totally, 24 optimized hydrated configurations of Na^+–AD containing one or two H_2O molecules have been obtained. Vibration frequency computation was carried out at the same level for each optimized structure. The lack of any imaginary frequencies ensured that each structure corresponds to a minimum of the potential energy surface.

Except for the supramolecular method with explicit H_2O molecules, PCM (Miertug et al. 1981), IPCM (Foresman et al. 1996) and IEFPCM (Mennucci et al. 1997) solvation models of SCRF theory, included in the Gaussian 98 suite package (Frisch et al. 1998), have been applied to investigate the macroscopic interactions between Na^+–AD complex ion and water solvent with the optimized gaseous and hydrated structures of Na^+–AD complex ion. Water solvent's dielectric constant was taken as 78.39.

Results and discussions

Incorporation of a single H_2O molecule to Na^+–AD complex ion

Six conformers of H_2O–Na^+–AD

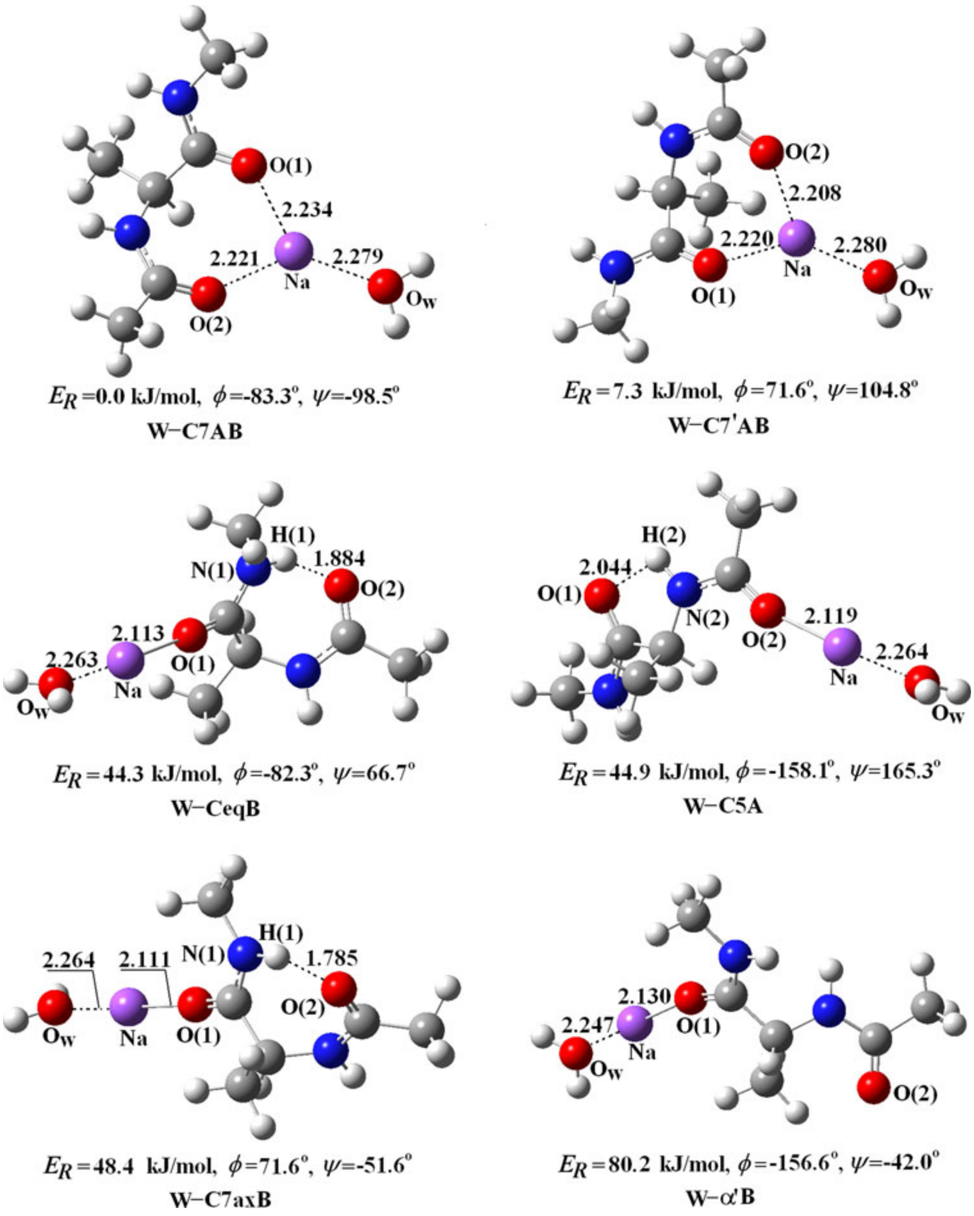
Considering that Na^+ is prone to hydrate, a single H_2O molecule was firstly introduced into six conformers of Na^+–AD from the near side of Na^+. The resultant structures were fully optimized at the B3LYP/6-311++G** level. Six stable conformers labeled as W–C7AB, W–C7′AB, W–C7_{eq}B, W–C5A, W–C7_{ax}B and W–α'B were obtained and are shown in Fig. 2. Their relative energies are 0.0, 7.3, 44.3, 44.9, 48.4 and 80.2 kJ/mol, respectively. It can be seen that C7AB and C7′AB are still the two most stable structures in the presence of one explicit water molecule, and they are largely energetically favored to the four monohydrated conformers of Na^+–AD. The energies of monohydrated C7_{eq}B, C5A and C7_{ax}B are close to each other. W–α'B can stably exist but is still the most unstable one.

Comparison of the Ramachandran angles in each of the six conformers of H_2O–Na^+–AD complex ion with those in the corresponding gaseous Na^+–AD conformers (Qiao et al. 2007; see also the supplementary Figure S1) shows that the incorporation of a single H_2O molecule from the side of Na^+ does not change the backbone of Na^+–AD much. The alterations of dihedral angles of ϕ and ψ are only within 1.0° except in the case of the least stable conformer α'B, in which the incorporation of a single H_2O molecule results in the changes of ϕ and ψ by 12.4° and 3.4°, respectively.

In all the six conformers of H_2O–Na^+–AD complex ion, the bond lengths of newly formed Na–O_W bonds are 2.1–2.3 Å. The incorporation of a single H_2O molecule results that the original Na–O bonds increase slightly by about 0.1 Å. The Na, O(1), O(2) and O_W in bidentate structures are nearly coplanar. The dihedral angles of O(1)–Na–O(2)–O_W in W–C7AB and W–C7′AB are 179.1° and −178.9°, respectively. The Na, O_W and O(2) or O(1) in monodentate structures are almost in a line. As a whole, the incorporation of a single H_2O molecule in such way only affects the local region around Na^+ and does not pose an obvious effect to the backbone of AD.

Six conformers of Na^+–AD–H_2O

Taking into account the fact that potential hydrogen bonds can be formed between amino or carbonyl groups with the added H_2O molecules. A single H_2O molecule was introduced to the backbone of Na^+–AD to form potential hydrogen bond interactions of N(2)–H(2)···O_W, N(1)–H(1)···O_W, O_W–H_W···O(2) and O_W–H_W···O(1). Various possible locations for the added H_2O molecule relative to the O and N atoms of Na^+–AD are attempted in order to form the above possible hydrogen bond interactions. The resultant structures were fully optimized at the B3LYP/6-311++G** level. Six optimized conformers of Na^+–AD–H_2O labeled as C7AB–W, C7′AB_N(1)–W, C7′AB_N(2)–W, C7_{eq}B–W, C5A–W and C7_{ax}B–W were obtained and are illustrated in Fig. 3. Their relative



E_R=0.0 kJ/mol, ϕ=-83.3°, ψ=-98.5°
W–C7AB

E_R=7.3 kJ/mol, ϕ=71.6°, ψ=104.8°
W–C7′AB

E_R=44.3 kJ/mol, ϕ=-82.3°, ψ=66.7°
W–CeqB

E_R=44.9 kJ/mol, ϕ=-158.1°, ψ=165.3°
W–C5A

E_R=48.4 kJ/mol, ϕ=71.6°, ψ=-51.6°
W–C7axB

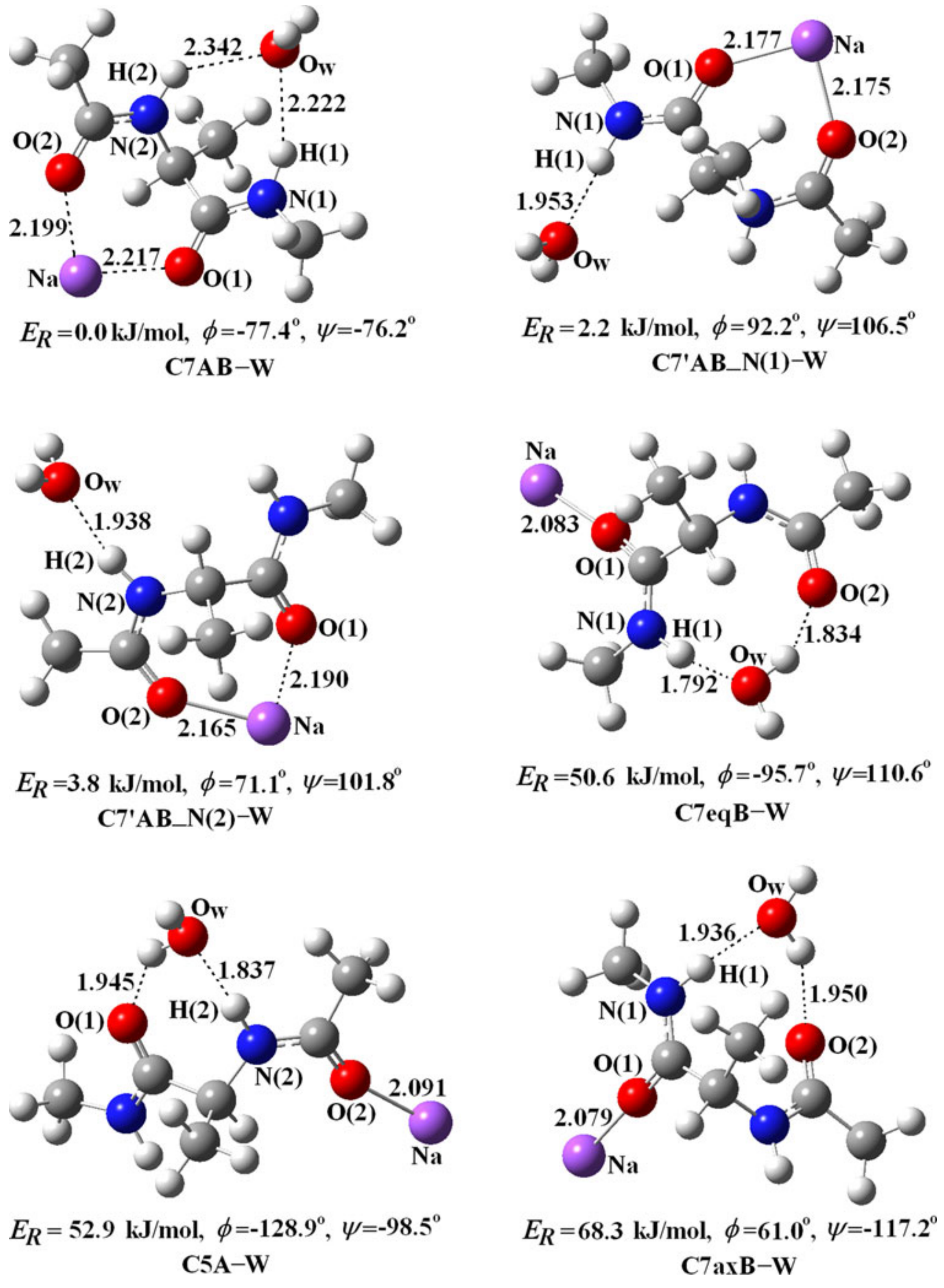
E_R=80.2 kJ/mol, ϕ=-156.6°, ψ=-42.0°
W–α′B

Fig. 2 Six stable conformers of H_2O–Na^+–AD obtained at the B3LYP/6-311++G** level. E_R is the relative energy computed at this level. ϕ and ψ represent the molecular backbone structure shown in Fig. 1. The data in the figure stand for the bond lengths in unit of Å

energies are 0.0, 2.3, 3.8, 50.6, 52.9 and 68.3 kJ/mol, respectively. Obviously, it can be seen that C7AB and C7′AB are still the two most stable structures in the presence of one explicit water molecule near the AD backbone. And they are largely energetically favored to the four monohydrated conformers of Na^+–AD. The stabilities of monohydrated $C7_{eq}B$ and C5A are close to each other. $C7_{ax}B$ becomes the most unstable one.

Among these structures, C7′AB_N(1)–W and C7′AB_N(2)–W are the two resultant structures of the incorporation of a single H_2O molecule into C7′AB, distinguished from the binding sites of the H_2O molecule. Besides, it should be noted that in the presence of a single H_2O molecule near the backbone, α′B conformer of Na^+–AD complex ion is very unstable and collapses to the relatively stable C7AB–W structure.

Two new hydrogen bonds of N(1)–H(1)···O_W and N(2)–H(2)···O_W were simultaneously formed with the incorporation of a single H_2O molecule into the most stable bidentate complex C7AB, resulting in the most stable structure of Na^+–AD–H_2O. The bond lengths of the newly formed hydrogen bonds H(1)···O_W and H(2)···O_W were 2.222 and 2.342 Å, respectively. The incorporation of a single H_2O molecule into the bidentate C7′AB probably produces a new hydrogen bond N(1)–H(1)···O_W or N(2)–H(2)···O_W, resulting in the structure of C7′AB_N(1)–W or C7′AB_N(2)–W. The newly formed hydrogen bond lengths in these two structures were 1.953 and 1.938 Å,



E_R=0.0 kJ/mol, ϕ=-77.4°, ψ=-76.2°
C7AB–W

E_R=2.2 kJ/mol, ϕ=92.2°, ψ=106.5°
C7'AB_N(1)–W

E_R=3.8 kJ/mol, ϕ=71.1°, ψ=101.8°
C7'AB_N(2)–W

E_R=50.6 kJ/mol, ϕ=-95.7°, ψ=110.6°
C7eqB–W

E_R= 52.9 kJ/mol, ϕ=-128.9°, ψ=-98.5°
C5A–W

E_R=68.3 kJ/mol, ϕ=61.0°, ψ=-117.2°
C7axB–W

Fig. 3 Six stable conformers of Na^+–AD–H_2O obtained at the B3LYP/6-311++G** level. E_R is the relative energy computed at this level. ϕ and ψ represent the molecular backbone structure shown in Fig. 1. The data in the figure stand for the bond lengths in unit of Å

respectively. The energy difference between these two structures is very small, only 1.5 kJ/mol.

The incorporation of a single H_2O molecule entirely breaks down the originally existing N(1)–H(1)···O(2), N(2)–H(2)···O(1) or N(2)–H(2)···N(1) hydrogen bond interactions in the four monodentate conformers of Na$^+$–AD complex ion. Meanwhile, new hydrogen bonds such as O···H–O_W and N–H···O_W were formed. For example, with the introduction of a H_2O molecule into the structure of C7$_{eq}$B, a stronger O(2)···H–O_W hydrogen bond with the bond length of O(2)···H as 1.792 Å was formed. In the structures of C5A and C7$_{ax}$B, incorporation of a single H_2O molecule produces N–H···O_W and O···H–O_W hydrogen bonds simultaneously, with the bond lengths of 1.8–1.9 Å. These newly formed hydrogen bonds are important for the stabilization of Na$^+$–AD–H_2O complexes.

Comparison of the six optimized conformers of Na$^+$–AD–H_2O complex ion with the corresponding gaseous structures (Qiao et al. 2007; see also the supplementary Figure S1) shows that the formations of the new hydrogen bonds between the backbone of Na$^+$–AD and the added H_2O molecule result in a large torsion of AD backbone with large changes of Ramachandran angles (ϕ and ψ). The alternations of the dihedral angles ϕ and ψ are 0.3–29.4° and 0.8–65.1°, respectively. The Ramachandran angles of C7′AB_N(2)–W change least, 0.3° and 3.9°, respectively, while those of $C7_{ax}B$–W change largest, 10.5° and 65.1°, respectively. With regard to the most stable C7AB conformer, its ϕ and ψ change by 5.2° and 22.9°, respectively. Obviously, the new formation of hydrogen bond interactions, resulting from the incorporation of an H_2O molecule into the backbone of Na^+–AD complex ion, has a tremendous impact on the backbone structure of Na^+–AD.

Summary of the stabilities of 12 monohydrated Na^+–AD conformers

The above two different ways of the incorporation of a single H_2O molecule result in a total of 12 conformers of monohydrated Na^+–AD complex ion. The relative stability order is as following: W–C7AB > W–C7′AB > C7AB–W > C7′AB_N(1)–W > C7′AB_N(2)–W > W–$C7_{eq}B$ > W–C5A > W–$C7_{ax}B$ > W–α′B > $C7_{eq}B$–W > C5A–W > $C7_{ax}B$–W. Obviously, for any conformer of Na^+–AD complex ion, the resulting structure formed by the incorporation of a single H_2O molecule from the near side of Na^+ is more stable than the one formed from adding the H_2O molecule to the backbone of Na^+–AD to form the potential hydrogen bonds. It can be inferred that the Na–O ion-lone pair interaction is stronger than the intermolecular hydrogen bond interactions and the near side of Na^+ is favorable to the backbone of AD for the incorporation of H_2O molecule.

Incorporation of two H_2O molecules into Na^+–AD complex ion

Five conformers of $2H_2O$–Na^+–AD

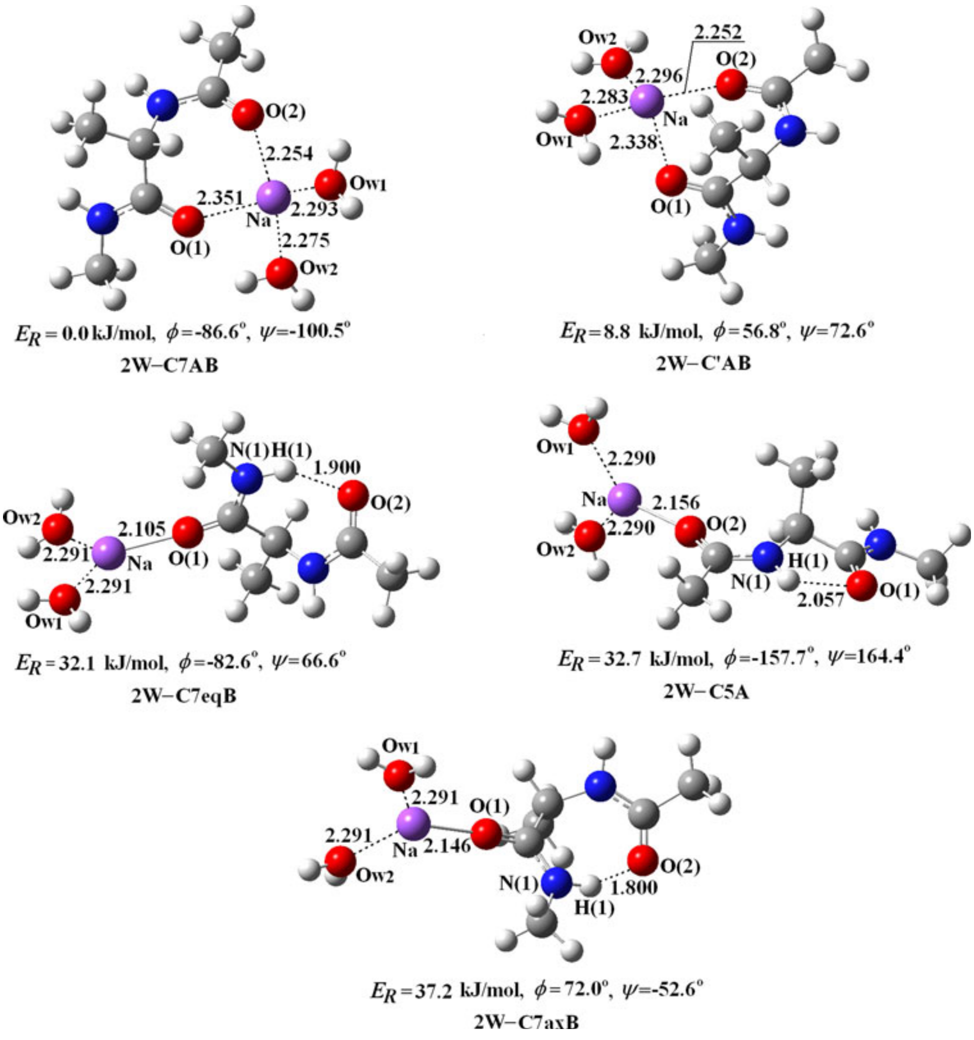
The above study has shown that the near side of Na^+ of Na^+–AD complex ion is favorable for the incorporation of H_2O molecule. In this section, the simultaneous incorporation of two H_2O molecules from the near side of Na^+ into the six conformers of Na^+–AD complex ion were investigated. Five optimized conformers of $2H_2O$–Na^+–AD labeled as 2W–C7AB, 2W–C7′AB, 2W–$C7_{eq}B$, 2W–C5A and 2W–$C7_{ax}B$ were obtained and are illustrated in Fig. 4. It is noteworthy to point out that the structure of the least stable conformer α′B breaks down and changes to the most stable 2W–C7AB after the incorporation of two H_2O molecules. Simultaneous introduction of two H_2O molecules from the near side of Na^+ only causes little effect on the backbones of the conformers (except α′B) of Na^+–AD complex ion. With the exception of C7′AB, the dihedral angles ϕ and ψ change only by 0.6–4° and 0.4–1.4°, respectively. With respect to the conformer C7′AB, ϕ and ψ angles change largely, by 14.6° and 33.1°, respectively. It can be found that the O(1)–Na–O(2) angle and the coplanarity of the 7-membered ring O(1)–Na–O(2)–C(3)–N(2)–C(1)–C(2) of C7′AB decrease remarkably after the incorporation of two H_2O molecules.

The bond lengths of Na–O in the six $2H_2O$–Na^+–AD conformers are about 2.15–2.35 Å. In the two bidentate structures 2W–C7AB and 2W–C7′AB, the added H_2O molecules deviate from the plane of O(2), O(1) and Na. The dihedral angles of O_{W1}–Na–O(1)–O(2) are 101.3° and −142.7°, respectively. Those of O_{W2}–Na–O(1)–O(2) are −144.7° and 61.6°, respectively. In the three dihydrated monodentate conformers 2W–$C7_{eq}$, 2W–5A and 2W–$C7_{ax}B$, O_{W1}, O_{W2}, Na and O(1) or O(2) are nearly coplanar. The results indicate that Na^+ bonded to two, three and four atoms is prone to adopt linear, planar and tetrahedral conformations, respectively. The incorporation of two H_2O molecules does not change the original hydrogen bond interactions in Na^+–AD complex ion, which indicates that the introduction of water molecules only has a local influence on the chemical bonds around Na^+, but little effect on the backbones of Na^+–AD conformers except α′B.

Seven conformers of H_2O–Na^+–AD–H_2O

As the above analysis shows, one H_2O molecule is prior to combine with Na^+ and form H_2O–Na^+–AD structures. So the following is the second incorporation mode of the two explicit H_2O molecules, one from the near side of Na^+, and the other one to the backbone of Na^+–AD to form potential hydrogen bond interactions, where hydrogen bonds N(1)–H(1)···O_W, N(2)–H(2)···O_W, O(2)···H–O_W and O(1)···H–O_W were attempted. Two incorporation modes were tried. One is the simultaneous addition of the two H_2O molecules. Another is the addition of the second H_2O molecule to the monohydrated H_2O–Na^+–AD. These two ways of incorporation gave the same results, both resulting in seven structures of H_2O–Na^+–AD–H_2O labeled as W–C7AB_N(2)–W, W–C7AB_N(1)–W, W–C7′AB_N(2)–W, W–C7′AB_N(1)–W, W–C5A–W, W–$C7_{eq}B$–W and W–$C7_{ax}B$–W. Their optimized structures are shown in Fig. 5. It should be noted that hydrogen bonds N(2)–H···O_{W2} and N(1)–H···O_{W2} are both possible for the introduction of one of the two H_2O molecules to the backbone of C7AB and C7′AB. Therefore, two optimized structures are the result, respectively. Besides, the introduction of the two H_2O molecules collapses the structure of α′B and changes it to the most stable structure W–C7AB_N(2)–W.

The incorporation of the two H_2O molecules into the structure of C7AB results in two conformers



$E_R = 0.0$ kJ/mol, $\phi = -86.6°$, $\psi = -100.5°$
2W–C7AB

$E_R = 8.8$ kJ/mol, $\phi = 56.8°$, $\psi = 72.6°$
2W–C'AB

$E_R = 32.1$ kJ/mol, $\phi = -82.6°$, $\psi = 66.6°$
2W–C7eqB

$E_R = 32.7$ kJ/mol, $\phi = -157.7°$, $\psi = 164.4°$
2W–C5A

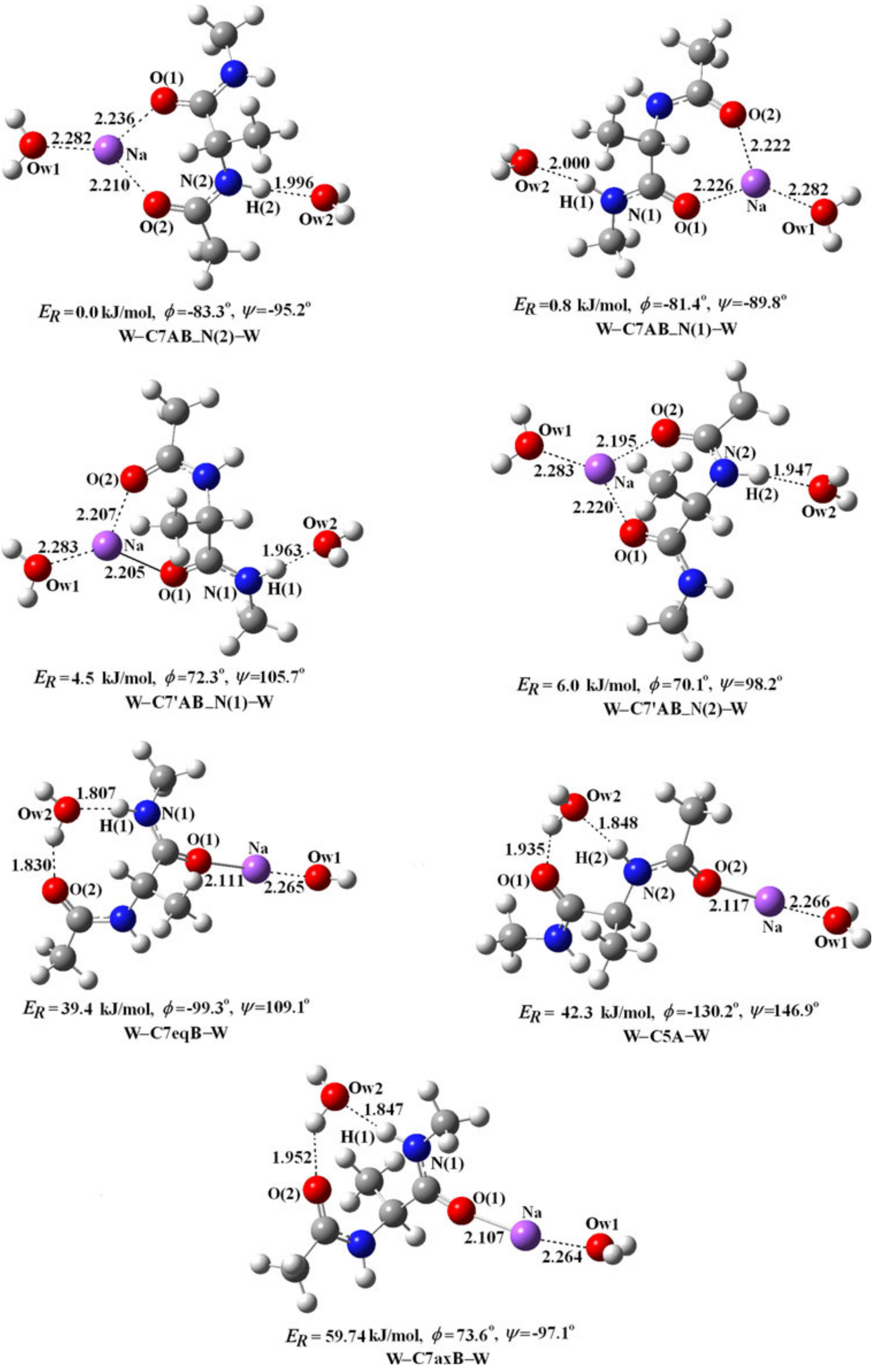
$E_R = 37.2$ kJ/mol, $\phi = 72.0°$, $\psi = -52.6°$
2W–C7axB

Fig. 4 Five stable conformers of $2H_2O$–Na^+–AD obtained at the B3LYP/6-311++G** level. E_R is the relative energy computed at this level. ϕ and ψ represent the molecular backbone structure shown in Fig. 1. The data in the figure stand for the bond lengths in unit of Å

W–C7AB_N(2)–W and W–C7AB_N(1)–W, with newly formed strong hydrogen bonds of N(2)–H(2)···O_W and N(1)–H(1)···O_W, respectively. Their H···O_W hydrogen bond lengths are 1.996 and 2.000 Å, respectively. The energy difference between the two structures is very small, only 0.8 kJ/mol. A similar situation occurs for C7′AB. Hydrogen bonds of N(1)–H(1)···O_W or N(2)–H(2)···O_W are possible with the introduction of two H_2O molecules. Thus, there are also two resultant conformers labeled as W–C7′AB_N(1)–W and W–C7′AB_N(2)–W, with the H···O_W hydrogen bond lengths of 1.963 and 1.947 Å, respectively. Their stabilities were also similar, with the energy difference only of 1.5 kJ/mol. The incorporation of the second H_2O molecule into the structure of W–$C7_{eq}$ results in the simultaneous formation of the new strong hydrogen bonds O(2)···H_W–O_W and N(1)–H(1)···O_W with the H···O bond lengths of 1.830 and 1.807 Å, respectively. The new strong hydrogen bonds O(1)···H_W–O_W and N(2)–H(2)···O_W with the H···O bond lengths of 1.935 and 1.848 Å were formed when the second H_2O molecule is introduced into W–C5A. The incorporation of the second H_2O molecule into W–$C7_{ax}$B also results in two new strong hydrogen bonds O(2)···H_W–O_W and N(1)–H···O_W, with the H···O bond lengths of 1.952 and 1.847 Å. In short, incorporations of the second H_2O molecule into the bidentate structures W–C7AB and W–C7′AB result in new strong hydrogen bonds N(2)–H···O_W or N(1)–H···O_W. Nevertheless, two new strong hydrogen bonds are formed when the second H_2O molecule was introduced into the monodentate structures W–$C7_{eq}$, W–C5A and W–$C7_{ax}$B, respectively.

Comparison of the structures of H_2O–Na^+–AD–H_2O (in Fig. 5) with those of the corresponding gaseous ones (Qiao et al. 2007; see also supplementary Figure S1) shows that the introduction of two H_2O molecules into the bidentate structures C7AB and C7′AB results in small torsion of the framework. The changes of the Ramachandran angles (ϕ and ψ) are within 1.3° and 9.3°, respectively. The reason is that the circular structures of the bidentate complexes C7AB and C7′AB are relatively stable and less affected by the new formation of the linear hydrogen bond N–H···O_W.

Fig. 5 Seven stable conformers of H_2O–Na^+–AD–H_2O obtained at the B3LYP/6-311++G** level. E_R is the relative energy computed at this level. ϕ and ψ represent the molecular backbone structure shown in Fig. 1. The data in the figure stand for the bond lengths in unit of Å



E_R=0.0 kJ/mol, ϕ=-83.3°, ψ=-95.2°
W–C7AB_N(2)–W

E_R=0.8 kJ/mol, ϕ=-81.4°, ψ=-89.8°
W–C7AB_N(1)–W

E_R=4.5 kJ/mol, ϕ=72.3°, ψ=105.7°
W–C7′AB_N(1)–W

E_R= 6.0 kJ/mol, ϕ=70.1°, ψ=98.2°
W–C7′AB_N(2)–W

E_R=39.4 kJ/mol, ϕ=-99.3°, ψ=109.1°
W–C7eqB–W

E_R= 42.3 kJ/mol, ϕ=-130.2°, ψ=146.9°
W–C5A–W

E_R= 59.74 kJ/mol, ϕ=73.6°, ψ=-97.1°
W–C7axB–W

However, large torsions of the framework were found for the cases of monodentate structures of $C7_{eq}$, C5A and $C7_{ax}$B. The changes of the ϕ and ψ are 2.1–28.1° and 18.4–45.5°, respectively. It can be found that the torsion of the backbone is mainly contributed by the introduction of H_2O molecule to the AD backbone of the structures. Introduction of the second H_2O molecule to the conformers of the monodentate H_2O–Na^+–AD complex ion results in the simultaneous formation of hydrogen bonds N–H···O_W and O···H_W–O_W. These hydrogen bond interactions deduce a larger circular structure, resulting in a large torsion of molecular backbone.

Figure 3 shows that the introduction of a single H_2O molecule to the framework of C7AB results in the simultaneous formation of hydrogen bonds of N(1)–H(1)···O_W and N(2)–H(2)···O_W. However, adding the second H_2O molecule to the backbone of W–C7AB (where one H_2O molecule already binds with Na^+) produces only one hydrogen bond N(1)–H···O_{W2} or N(2)–H···O_{W2}. This result means that the presence of the first H_2O molecule bonded with Na^+ results in a faint change of molecular backbone, which further influences the intervention of the second H_2O molecule added to the backbone.

Summary of the stabilities of 12 conformers of the dihydrated Na^+–AD

Totally, 12 conformers of the dihydrated complex ion including five $2H_2O$–Na^+–AD and seven H_2O–Na^+–AD–H_2O structures were obtained. The order of their relative stabilities is as following: 2W–C7AB > 2W–C7′AB > W–C7AB_N(2)–W > W–C7AB_N(1)–W > W–C7′AB_N(1)–W > W–C7′AB_N(2)–W > 2W–$C7_{eq}$B > 2W–C5A > 2W–$C7_{ax}$B > W–$C7_{eq}$B–W > W–C5A–W > W–$C7_{ax}$B–W. Clearly, for any conformer of Na^+–AD, $2H_2O$–Na^+–AD formed by adding the two H_2O molecules at the near side of Na^+ is more stable than the one formed by adding the two H_2O molecules to the backbone and the nearby of Na^+, respectively. It can be inferred that two H_2O molecules would be prone to preferentially bind with Na^+ to form $2H_2O$–Na^+–AD complex structures.

The influences of H_2O molecules on Na^+–AD complex ion

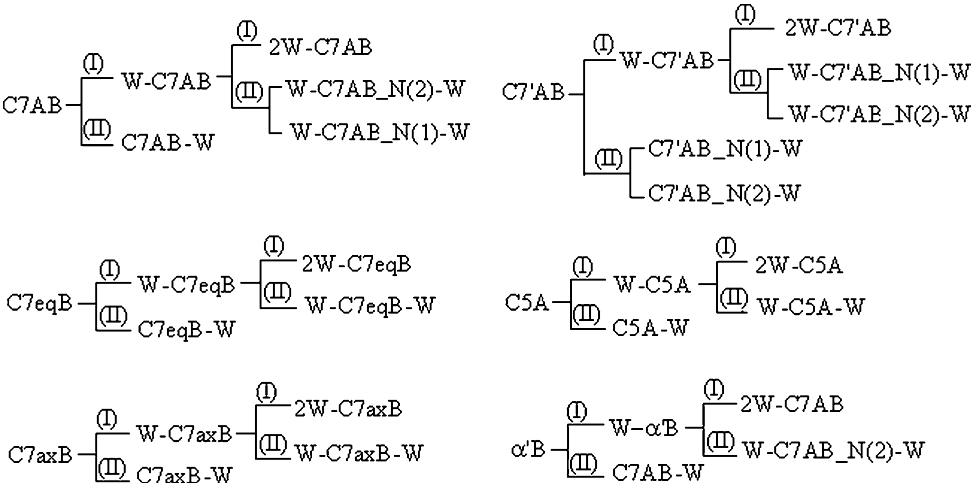
Comprehensive study of the influences of one and two explicit H_2O molecules on the six conformers of Na^+–AD gives a total of 12 monohydrated and 12 dihydrated conformers of Na^+–AD. These hydrated complex ion conformers are summarized in Scheme 1. Whether in gaseous phase or at the presence of one or two H_2O molecules, the bidentate structures are far more stable than the monodentate ones, and C7AB is always the most stable conformer.

Incorporation of one H_2O molecule from the near side of Na^+ into the conformer α'B only induces local effect near the Na^+. Thus the conformer W–α'B can be stably present. However, the incorporations of one H_2O molecule to the AD backbones of α'B and W–α'B both break down the structures and result the most stable structures C7AB–W and W–C7AN_N(2)–W, respectively. Scheme 2 illustrates α'B–H_2O cluster collapsed to C7AB–W. Adding one H_2O molecule to the backbone of α'B makes the hydrogen bond interactions between O_w of H_2O and N(1)–H(1) or N(2)–H(2) possible. However, poor planarity of the two amidos in original structure of α'B with the dihedral angle up to 60° and not enough space between H(1) and H(2) atoms are the two holdbacks. Thus, the right moiety of the backbone of α'B shown in Scheme 2 rotates forward and clockwise in order to increase the coplanarity of the two amidos and the space between H(1) and H(2) atoms for the formation of the hydrogen bonds N(1)–H(1)···O_W and N(2)–H(2)···O_W. Such torsion of the backbone decreases the distance between Na^+ and O(2), and results that Na^+ can simultaneously coordinate with O(1) and O(2) atoms, forming the structure of C7AB–W.

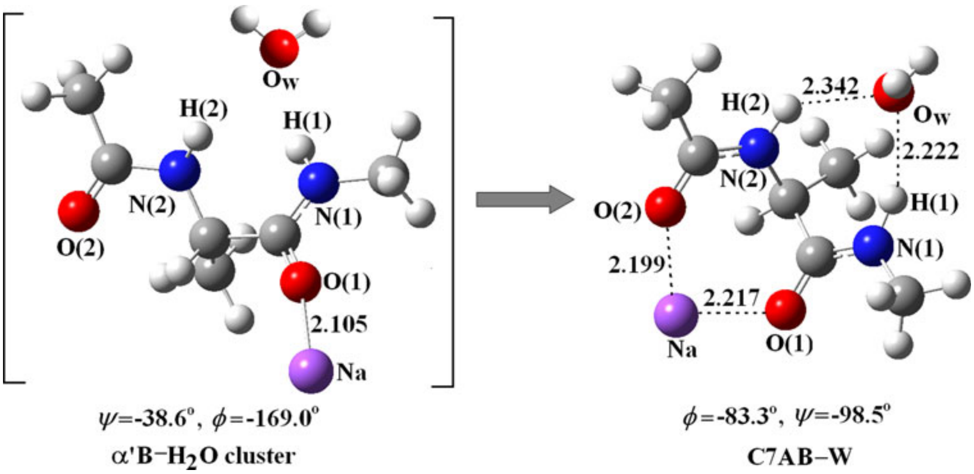
The simultaneous incorporations of the two H_2O molecules from the near side of Na^+ into the conformer α'B also induce a large geometric change and entirely break down the backbone, resulting the structure of 2W–C7AB. Scheme 3 shows H_2O–W–α'B cluster collapsed to 2W–C7AB. It can be found that the two added H_2O molecules bind with Na^+ quickly, and then the right moiety of the AD backbone rotates clockwise. Meanwhile, one of the two added H_2O molecules moves towards O(2) of the backbone, finally resulting the formations of the hydrogen bonds O_{W1}–H_{W1}···O(2) and C(1)–H(3)···O_{W1}. These hydrogen bond interactions greatly decrease the distance between Na^+ and O(2). As we know, the stabilization energy forming Na–O ion-lone pair interaction is larger than those of the hydrogen bond interactions, which results the further movement of O(2) towards Na^+ and the breakdown of the hydrogen bonding between O(2) and the H_2O molecule. Finally, the structure of 2W–C7AB was formed. This is a good example that water molecule possessing its unique capability of forming potential H-bond interactions acts as a triggering factor for the geometrical transformation.

Influences of water on Na^+–AD studied by the polarizable continuum solvation models

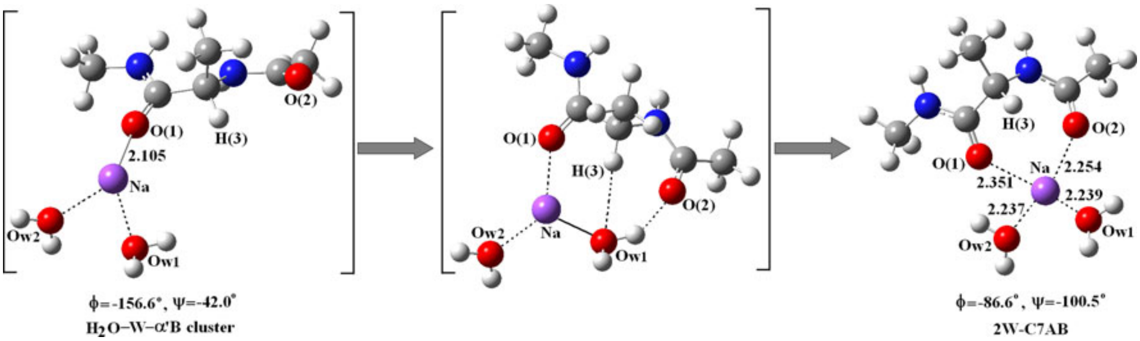
Incorporations of one or two explicit H_2O molecules into Na^+–AD conformers give the fine descriptions of the interactions between H_2O molecules and Na^+–AD, in particular, the micro-interaction mechanism between H_2O and Na^+ or the backbone structure. Nevertheless, the incorporation of two H_2O molecules can not sufficiently describe the solvation effects of H_2O. Therefore, the polarizable continuum solvation models including PCM (Miertug et al. 1981), IPCM (Foresman et al. 1996) and IEFPCM (Mennucci et al. 1997) of SCRF theory (Tomasi J et al. 2005) were employed to further study the solvation effects of H_2O on Na^+–AD.



Scheme 1 The structural transformation of Na^+–AD complex ion with the incorporation of one or two explicit H_2O molecules. (I) and (II) stand for the introduction of the H_2O molecule at the nearby of Na^+ and to the backbone of AD, respectively



Scheme 2 The geometrical transformation of the α'B–H_2O cluster to C7AB–W



Scheme 3 The geometrical transformation of the H_2O–W–α'B cluster to 2W–C7AB

Table 1 lists the relative values E_R of the single point energies of the six gaseous conformers of Na^+–AD complex ion in water using PCM, IPCM and IEFPCM solvation models, respectively. Obviously, the different solvation models give the different results of the stability sequences of these Na^+–AD conformers. These results are also different from those in gaseous phase (Qiao et al. 2007).

The IPCM solvation model gives the result that the C7′AB conformer of the Na^+–AD complex ion becomes the most unstable conformer, which entirely conflicts with the supramolecular computational results, where the bidentate conformers of Na^+–AD are always relatively stable in the presence of one or two H_2O molecules. It can be speculated that the IPCM solvation model is quite inapplicable to investigate the solvation effects of water on the Na^+–AD complex ion. For demonstration, we have further investigated the solvation effects of dimethyl ether on the Na^+–AD complex ion using the PCM, IPCM and IEFPCM solvation models, respectively. Calculations of the solvated Na^+–AD were performed using both the gas phase and the SCRF-optimized structures, and the results indicate that the IPCM solvation model also cannot reasonably describe the solvation effects of dimethyl ether on the Na^+–AD complex ion.

The PCM and IEFPCM solvation models give the similar results of the relative stability sequences of six conformers of Na^+–AD complex ion in water. Two bidentate structures are far more stable than the four monodentate ones, which is consistent with the computational results using supramolecular model. Nevertheless, careful comparing of the calculation results of these two solvation models shows two discrepancies including the relative stabilities of two bidentate structures C7AB and C7′AB, and those of C5A and $C7_{eq}B$. Computations using the supramolecular model show that the bidentate C7AB is always the most stable conformer and $C7_{eq}B$ is more stable than C5A whether one or two H_2O molecules were introduced. So at this point, it is difficult to determine whether the PCM or the IEFPCM solvation model is more reasonable to describe the solvation of the Na^+–AD complex ion. Therefore, we further performed PCM and IEFPCM calculations for the monohydrated and dihydrated C5A and $C7_{eq}B$. The results are contained in Table 2. Obviously, the energies of the monohydrated and bihydrated C5A are always lower than those of $C7_{eq}B$, indicating that the aqueous C5A is more stable than $C7_{eq}B$. This result is quite close to those obtained from the computations using IEFPCM solvation model for the gaseous Na^+–AD conformers. Therefore, the IEFPCM solvation model is considered relatively reasonable to describe the solvation effect of Na^+–AD in water. Nevertheless, Wang et al.'s work on the solvation of ether and water on AD suggested that the PCM calculations gave good descriptions for the bulk solvent polarization effect (Wang and Duan 2004).

Table 1 The relative single point energies (kJ/mol) of the six stable conformers of Na^+–AD complex ion in water solvent, computed at the level of B3LYP/6-311++G** using PCM, IPCM and IEFPCM solvent models, respectively

Solvent Model	C7AB	C7′AB	$C7_{eq}B$	C5A	$C7_{ax}B$	$\alpha'B$
PCM	0.0	−1.8	24.3	25.3	30.4	60.7
IPCM	0.0	138.1	61.2	65.5	72.9	45.7
IEFPCM	0.0	4.8	30.7	28.0	37.4	41.4
In gas phase	0.0	7.4	56.3	56.6	60.0	92.5

Those in gas are also included; The energy of C7AB in gas phase was computed as −658.18575 Hartree at the level of B3LYP/6-311++G**. Those in water solvent were computed as −658.27774, −658.31331 and −658.27839 Hartree at the level of B3LYP/6-311++G**, using PCM, IPCM and PEFCM solvent models, respectively

Table 3 contains the relative energy results of all the 12 dihydrates of the six Na^+–AD conformers by using the IEFPCM solvation model. Among the three dihydrated conformers of C7AB, 2W–C7AB is energetically favored and is the most stable structure among all the 12 dihydrated conformers. The energy of 2W–C7′AB is only higher than that of 2W–C7AB and is relatively stable; 2W–C5A is the following. It can be found that the energy of 2W–$C7_{eq}B$ is 9.5 kJ/mol higher than that of 2W–C5A. Among the six dihydrated structures of the monodentate Na^+–AD conformers, 2W–C5A was obviously more stable than 2W–$C7_{eq}B$ and the hydrated $C7_{ax}B$ conformer is relatively unstable. Clearly, the combined application of the supramolecular and IEFPCM solvation models showed that the stability order of six conformers of Na^+–AD in the solvent of water is $C7AB > C7'AB > C5A > C7_{eq}B > C7_{ax}B$. The $\alpha'B$ conformer can only exist in the gas, and the aqueous C5A is more stable than the $C7_{eq}B$. This result is different from that in gaseous state.

The molecular solvation energy (ΔE) can be expressed as following.

$$\Delta E = E_{sol} - -E_{gas}$$

where E_{sol} denotes the free energy of the solute in solvent, and E_{gas} stands for that of the solute in gas phase.

The solvation energies of Na^+–AD complex ion conformers in water obtained with the IEFPCM solvation model are contained in Table 4. Obviously, solvation energies are all negative, which indicate the interaction between the solvent and solute are in favor of the stability of the solute. Besides, the stabilization energies of solvent H_2O on monodentate conformers of Na^+–AD (~273 kJ/mol) are bigger than those of bidentate ones (~241 kJ/mol).

Na^+ is easily hydrated and usually in the form of $[Na(H_2O)_6]^+$ (Glendening and Feller 1995). The ability of AD to displace H_2O from a hexahydrated Na^+ has biologic meaning. The zero-point energies and Gibbs free energies of AD, $[Na(H_2O)_6]^+$, $AD[Na(H_2O)_4]^+$ and H_2O in the solvent of water are listed in Table 5. The change of the Gibbs free energy (corrected by zero-point energy) of the displacement of two H_2O by an AD molecule in $[Na(H_2O)_6]^+$ was computed as −4.5 kJ/mol, showing that the process is thermodynamically admissible.

Conclusions

The supramolecular study of the incorporation of one or two explicit H_2O molecules to the six conformers of

Table 2 The total energies (Hartree) of the monohydrated and dihydrated conformers of $C7_{eq}B$ and C5A in water solvent, computed at the level of B3LYP/6-311++G** using PCM and IEFPCM solvent models, respectively

Species	Total energy at the level of B3LYP/6-311++G** in gas	Total energy at the level of B3LYP/6-311++G** using the PCM solvent model in water	Total energy at the level of B3LYP/6-311++G** using the IEFPCM solvent model in water
W–$C7_{eq}B$	−734.65638	−734.75029	−734.74950
W–C5A	−734.65617	−734.75754	−734.75220
$C7_{eq}B$–W	−734.64098	−734.73579	−734.73685
C5A–W	−734.64010	−734.73728	−734.73825
2W–$C7_{eq}B$	−811.14131	−811.22799	−811.22740
2W–C5A	−811.14107	−811.23552	−811.23101
W–$C7_{eq}B$–W	−811.13287	−811.21716	−811.21978
W–C5A–W	−811.13176	−811.22499	−811.22282

Those in gas are also included

Table 3 The relative single point energies (kJ/mol) of the 12 dihydrated conformers of Na^+–AD complex ion in water solvent, computed at the level of B3LYP/6-311++G** using IEFPCM solvent model

Species	Relative energy at the level of B3LYP/6-311++G** in gas	Relative energy at the level of B3LYP/6-311 ++G** using the IEFPCM sovent model in water
2W–C7AB	0.0	0.0
2W–C7′AB	8.8	14.8
W–C7AB_N(2)–W	14.8	26.1
W–C7AB_N(1)–W	15.7	27.3
W–C7′AB_N(1)–W	19.3	36.9
W–C7′AB_N(2)–W	20.8	22.9
2W–$C7_{eq}B$	32.1	25.2
2W–C5A	32.7	15.7
2W–$C7_{ax}B$	37.2	29.3
W–$C7_{eq}B$–W	54.2	45.2
W–C5A–W	57.1	37.2
W–$C7_{ax}B$–W	74.6	60.7

Those in gas are also included

Table 4 The solvation energies ΔE (kJ/mol) of the six conformers of Na^+–AD complex ion in water obtained at the B3LYP/6-311++G** level using the IEFPCM solvent model

Species	C7AB	C7′AB	C5A	$C7_{eq}B$	$C7_{ax}B$	α′B
Solvation energy ΔE (kJ/mol)	−243.1	−243.0	−271.7	−268.7	−265.7	−294.2

Table 5 The Zero-point energies and Gibbs free energies of AD, $[Na(H_2O)_6]^+$, $AD[Na(H_2O)_4]^+$ and H_2O in the solvent of water, obtained at the B3LYP/6-311++G** level using the IEFPCM solvent model

Species	AD[a]	$[Na(H_2O)_6]^+$	$AD[Na(H_2O)_4]^+$ [b]	H_2O
Zero-point energy (Hartree)	0.18553	0.14916	0.28604	0.02129
Total free energies in water (kJ/mol)	−496.0	−621.1	−964.2	−76.5

[a] The most stable conformer C7AB of AD was used here

[b] The bidentate tetrahydrated conformer $AD[Na(H_2O)_4]^+$ obtained from the optimization of $2H_2O$–2W–C7AB cluster was used here

Na^+–AD complex ion shows that H_2O molecules are prone to bind with Na^+ and form ion-lone pair interaction with the Na–O bond length about 2.1–2.3 Å. The H_2O molecule can also bind with the backbone of the Na^+–AD complex ion, forming O_W–H_W···O(1), O_W–H_W···O(2), N(1)–H(1)···O_W or N(1)–H(1)···O_W hydrogen bonds. W–C7AB and 2W–C7AB are the most stable monohydrated and dihydrated conformers of the Na^+–AD complex ion. The introduction of a single H_2O molecule into the backbone of α'B and the incorporation of two H_2O molecules into α'B from the near side of Na^+ both induce the collapse of the backbone and result in the structures of C7AB–W and 2W–$C7_{eq}B$, respectively.

The IEFPCM solvation model can present relatively reasonable results of the solvation effects of water on the Na^+–AD complex ion. In the solvent of water, the relative stabilities of the six conformers of the Na^+–AD complex ion are $C7AB > C7'AB > C5A > C7_{eq}B > C7_{ax}B$, as compared to $C7AB > C7'AB > C7_{eq}B > C5A > C7_{ax}B > \alpha'B$ in gas. The α'B conformer can exist stably only in the gaseous state, and C5A is more stable than $C7_{eq}B$ in the solution.

References

Beachy MD, Chasman D, Murphy RB, Halgren TA, Friesner RA (1997) Accurate ab initio quantum chemical determination of the relative energetics of peptide conformations and assessment of empirical force fields. J Am Chem Soc 119:5908–5920

Becke AD (1993) Density-functional thermochemistry. III. The role of exact exchange. J Chem Phys 98:5648–5652

Boehm HJ, Brode S (1991) Ab initio SCF calculations on low-energy conformers of *N*-acetyl-*N*′-methylalaninamide and *N*-acetyl-*N*′-methylglycinamide. J Am Chem Soc 113:7129–7135

Branden C, Tooz J (1998) Introduction to protein structure. Garland Publishing, New York

Foresman JB, Keith TA, Wiberg KB, Snoonian J, Frisch MJ (1996) Solvent effects. 5. Influence of cavity shape, truncation of electrostatics, and electron correlation on ab initio reaction field calculations. J Phys Chem 100:16098–16104

Frey RF, Coffin J, Newton SQ, Ramek M, Cheng VKW, Momany FA, Schaefer L (1992) Importance of correlation-gradient geometry optimization for molecular conformational analyses. J Am Chem Soc 114:5369–5377

Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA Jr, Stratmann RE, Burant C, Dapprich S, Millam JM, Daniels JD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Rega N, Salvador P, Dannenberg JJ, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Baboul AG, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA (1998) Gaussian 98 (Revision A.11.2), Gauss

Glendening ED, Feller D (1995) Cation–water interactions: the $M^+(H_2O)_n$ clusters ($n = 1, 6$) for Alkali metals, M = Li, Na, K, Rb, and Cs. J Phys Chem 99:3060–3067

Godfrey PD, Brown RD (1995) Shape of glycine. J Am Chem Soc 117:2019–2023

Godfrey PD, Firth S, Hatherly LD, Brown RD, Pierlot AP (1993) Millimeter-wave spectroscopy of biomolecules: alanine. J Am Chem Soc 115:9687–9691

Gould IR, Kollman PA (1992) Ab initio SCF and MP2 calculations on four low-energy conformers of *N*-acetyl-*N*′-methylalaninamide. J Phys Chem 96:9255–9258

Gould IR, Cornell WD, Hillier IH (1994) A quantum mechanical investigation of the conformational energetics of the alanine and glycine dipeptides in the gas phase and in aqueous solution. J Am Chem Soc 116:9250–9256

Heaton AL, Moision RM, Armentrout PB (2008) Experimental and theoretical studies of sodium cation interactions with the acidic amino acids and their amide derivatives. J Phys Chem A 112:3319–3327

Hu CH, Shen MZ, Schaefer HF III (1993) Glycine conformational analysis. J Am Chem Soc 115:2923–2929

Jensen JH, Gordon MS (1991) Conformational potential energy surface of glycine: a theoretical study. J Am Chem Soc 113:7917–7924

Kaschner R, Hohl D (1998) Density functional theory and biomolecules: a study of glycine, alanine, and their oligopeptides. J Phys Chem A 102:5111–5116

Lee C, Yang W, Parr RG (1988) Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Phys Rev B 37:785–789

Li P, Bu YX, Ai HQ (2004) Density functional studies on conformational behaviors of glycinamide in solution. J Phys Chem B 108:1405–1413

Mennucci B, Cancès E, Tomasi J (1997) Evaluation of solvent effects in isotropic and anisotropic dielectrics and in ionic solutions with a unified integral equation method: theoretical bases, computational implementation, and numerical applications. J Phys Chem B 101:10506–10517

Miertug S, Scrocco E, Tomasi J (1981) Electrostatic interaction of a solute with a continuum. A direct utilization of ab initio molecular potentials for the prevision of solvent effects. Chem Phys 55:117–122

Mirsky AE, Pauling L (1936) On the structure of native, denatured, and coagulated proteins. Proc Natl Acad Sci USA 22:439–447

Perczel A, Farkas Ö, Csizmadia IG (1995) Peptide models. 17. The role of the water molecule in peptide folding. an ab initio study on the right-handed helical conformations of *N*-formylglycinamide and *N*-formyl-L-alaninamide monohydrates [H(CONH–CHR–CONH)–H·H_2O; R=H or CH_3]. J Am Chem Soc 117:1653–1654

Qiao LG, Fan JF, Yang CH (2007) Density functional theory study on the structures of Na^+-alanine dipetide ion-complexes. Acta Chimica Sinica 65:1751–1756

Scarsdale JN, Van Alsenoy C, Klimkowski VJ, Schaefer L, Momany FA (1983) Ab initio studies of molecular geometries. 27. Optimized molecular structures and conformational analysis of *N*.alpha-acetyl-*N*-methylalaninamide and comparison with peptide crystal data and empirical calculations. J Am Chem Soc 105:3438–3445

Selvarengan P, Kolandaivel P (2005) Study of metal ions (Na^+, K^+) interaction with different conformations of glycine molecule. J Quant Chem 102:427–434

Thirumoorthy K, Nandi N (2007) Water catalyzed peptide bond formation in L-alanine dipeptide: the role of weak hydrogen bonding. J Mol Struct THEOCHEM 818:107–118

Tomasi J, Mennucci B, Cammi R (2005) Quantum mechanical continuum solvation models. Chem Rev 105:2999–3093

Vargas R, Garza J, Hay BP, Dixon DA (2002) Conformational study of the alanine dipeptide at the MP2 and DFT levels. J Phys Chem A 106:3213–3218

Wang ZX, Duan Y (2004) Solvation effects on alanine dipeptide: a MP2/cc-pVTZ//MP2/6–31G** study of (Φ,Ψ) energy maps and conformers in the gas phase, ether, and water. J Comput Chem 25:1699–1716