

# Microsolvation of aminoethanol: a study using DFT combined with QTAIM

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**Abstract** The microsolvation of aminoethanol (AE) with one, two, three or four water molecules was investigated using a density functional theory (DFT) approach. Quantum theory of atoms in molecules (QTAIM) analyses were employed to elucidate the hydrogen-bonding characteristics of  $\text{AE}-(\text{H}_2\text{O})_n$  ( $n = 1-4$ ) complexes. The results showed that AE tends to break its intramolecular  $\text{OH}^{\text{AE}} \cdots \text{N}^{\text{AE}}$  hydrogen bond (H-bond) upon microsolvation and form intermolecular H-bonds with water molecules, while complexes that retain the intramolecular  $\text{OH}^{\text{AE}} \cdots \text{N}^{\text{AE}}$  H-bond show reduced stabilities. The intermolecular H-bond that forms between the nitrogen atom of AE and the hydroxyl of a water molecule is the strongest one for the most stable  $\text{AE}-(\text{H}_2\text{O})_n$  ( $n = 1-4$ ) complexes, and as  $n$  increases from 1 to 4 they grow stronger. The partial covalent character of this H-bond was confirmed by QTAIM analyses. Many-body interaction analysis showed that the relaxation energies and two- and three-body energies make significant contributions to the binding energies of the complexes.

**Keywords** Microsolvation · Hydrogen bond · Aminoethanol · QTAIM · Many-body interaction analysis · DFT

## Introduction

2-Aminoethanol (AE) has been the subject of numerous experimental, theoretical and combined studies over the

past decade (e.g., see [1] and references therein). Because the AE backbone is common to ephedrine, pseudoephedrine, and 2-amino-1-phenylethanol, AE may be the simplest model system to exhibit conformational changes upon complexation [2, 3]. X-ray spectroscopy has shown that AE exists predominantly in crystalline form as the *trans* conformer (with respect to the rotation around the C–C bond) and is linked through intermolecular  $\text{OH} \cdots \text{N}$  and  $\text{NH} \cdots \text{O}$  bonds into angular chains [4]. Microwave [2], infrared spectroscopic [5] and ab initio [1] studies have shown that AE exists predominantly in the gas phase as the *gauche* conformer stabilized by an intramolecular  $\text{OH}^{\text{AE}} \cdots \text{N}^{\text{AE}}$  H-bond. However, the preferences of AE in solution have been the subject of some disagreement. Infrared [6] and dipole moment [7] studies have reported a *gauche* preference for AE in nonpolar solutions, while another infrared study [7] that took into account NMR chemical shift data reported a *trans* preference. A Raman spectroscopic study showed that both *trans* and *gauche* conformers exist in aqueous solution, and the *gauche* form was likely to be more prevalent [8]. Molecular dynamics studies of AE in aqueous solution have variously reported *gauche* preferences [9, 10], or, depending on the way the conformational equilibria were calculated, quite high variability with changes in concentration but still essentially an overwhelming preference for the *gauche* conformer in concentrated solutions (mole fraction 0.8–1.0) and a significant *trans* preference at lower concentrations (mole fractions of 0.03–0.1) [11]. In conclusion, because aqueous solutions play an important role in the conformation of AE, it is important to investigate the weakly bonded molecular cluster that forms between an AE molecule and a few water molecules (i.e., the process of microsolvation) in order to study the conformation of AE in aqueous solution.

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Therefore, the aim of this work was to study the microsolvation of AE, which constitutes a bridge between the gas phase and the solution phase. Theoretical and computational studies of the effect of microsolvation on AE can enhance our fundamental understanding of solvent–solute interactions at the molecular level, including structural, spectral, energetic and thermodynamic properties, which can then be used to make accurate predictions and to aid in future experimental and theoretical studies.

Hydrogen bonding has a considerable effect on the microscopic and macroscopic properties of biomolecules, and plays a fundamental role in the comprehension and design of processes of biological and environmental importance [12, 13]. For example, large biomolecules have many sites that can participate in hydrogen-bonding interactions, and the lowest-energy conformations are often stabilized by intramolecular hydrogen bonds between these sites. In some cases, however, the lowest-energy conformation of the isolated molecule does not form the strongest intermolecular hydrogen bonds, meaning that the energy dependence of the preferred conformation is related to the environment. Similarly, hydrogen bonding is the major interaction of AE in solution, and it plays an important role in the microsolvation of AE. However, hydrogen bonding is weaker than chemical bonding, and not all theoretical methods reliably describe H-bonds. In general, the MP2 method is a reliable method for describing hydrogen-bonding interactions, but it is too time-consuming to apply to large biomolecular systems, even with a medium-sized basis set. Compared with MP2, density functional theory (DFT) is a cost-effective approach, but conventional DFT methods such as B3LYP only treat electron correlations in an approximate manner, and do not describe hydrogen-bonding interactions very well (e.g., see [14, 15] and references therein). Recently, some new DFT methods (such as B2PLYP [16], M06L [17, 18] and  $\omega$ B97XD [19]) have been developed that can more accurately treat hydrogen bonding and van der Waals interactions. A comprehensive review of such methods is provided by Johnson et al. [20]. Many studies have shown that these new DFT methods can give reliable results for a wide variety of weakly bonded systems [16, 21–26].

This work focuses on the effect of the microsolvation of AE through its interaction with 1–4 water molecules via hydrogen-bonding interactions. Quantum theory of atoms in molecules (QTAIM) analyses were employed to elucidate the hydrogen-bonding interaction characteristics of these complexes. The stable structures, binding energies and contributions of many-body energies to the binding energies are discussed.

## Computational details

### DFT calculation

All DFT calculations were performed with Gaussian 09 [27]. In this paper, the  $\omega$ B97XD functional [19] with the 6-311++G(2d,2p) basis set [28, 29] was used. The  $\omega$ B97XD functional includes empirical dispersion and can better treat hydrogen bonding and van der Waals interactions than conventional DFT. First, the geometries of the isolated AE and the water monomers were fully optimized. The  $\text{AE}-(\text{H}_2\text{O})_n$  ( $n = 1-4$ ) complexes were constructed starting from the most stable AE and water monomers. All complexes were also fully optimized at the same level. The counterpoise (CP) correction [30] was implemented in order to ensure that complexes and monomers were being computed with a consistent basis set. The harmonic vibrational frequencies were calculated with analytic second derivatives at the same level, which confirmed that the structures were minima.

### QTAIM analyses

QTAIM analysis was also implemented using the AIM2000 software [31] with  $\omega$ B97XD wavefunctions and employing the 6-311++G(2d,2p) basis set to provide complementary information on the H-bond. QTAIM has been shown to be a very useful tool for describing electron densities in H-bond systems [32–37]. According to QTAIM, the bond critical point (BCP) is a point in chemical bond space at which the first derivative of the electron density is equal to zero, and the topological properties of the BCP between the H-donor (X–H) and the H-acceptor (Y), such as the electron density ( $\rho_b$ ) and its Laplacian ( $\nabla^2\rho_b$ ), can be used to study the nature of the H-bond.  $\rho_b$  is directly derived from the wavefunction of the molecule, and  $\nabla^2\rho_b$  can be obtained from the second derivatives of  $\rho_b$ . Two quantitative criteria proposed by Koch and Popelier are usually used to characterize the strength of an H-bond [38]:  $\rho_b$  and  $\nabla^2\rho_b$  should fall within the ranges 0.002–0.04 and 0.02–0.15 a.u., respectively. These criteria provide a basis for distinguishing these interactions from van der Waals interactions, and they have been shown to be valid for normal and unconventional H-bonds. In addition, the ring and cage structures that can form when there are many H-bonds are characterized by the ring critical point (RCP) and cage critical point (CCP), respectively.

### Many-body interaction analysis

The two-, three-, four- and five-body contributions to the total binding energy are calculated using many-body

analysis [39–44]. The decomposition of the total energy of the complex can be written as

$$\begin{aligned} \Delta E &= E(12345) - \{E_{AE} + 4E_W\} \\ &= \sum_i E(i) - \{E_{AE} + 4E_W\} \quad \text{relaxation energy} \\ &\quad + \sum_{i=1}^4 \sum_{j>i}^5 \Delta^2 E(ij) \quad \text{two-body energy} \\ &\quad + \sum_{i=1}^3 \sum_{j>i}^4 \sum_{k>j}^5 \Delta^3 E(ijk) \quad \text{three-body energy} \\ &\quad + \sum_{i=1}^2 \sum_{j>i}^3 \sum_{k>j}^4 \sum_{m>k}^5 \Delta^4 E(ijkm) \quad \text{four-body energy} \\ &\quad + \Delta^5 E(12345) \quad \text{five-body energy} \end{aligned} \quad (1)$$

where  $E(i)$ ,  $E(ij)$ ,  $E(ijk)$ ,  $E(1234)$  are the BSSE-corrected energies of the various monomers, dimers, trimers, tetramers and pentamer in the complex, and  $E_{AE}$  and  $E_W$  are the energies of the isolated AE and water molecules, respectively. The pairwise additive two-body interaction energies and higher three-body, four-body and five-body nonadditive interaction energies with BSSE correction are defined as in the following equations:

$$\Delta^2 E(ij) = E(ij) - \{E(i) + E(j)\} \quad (2)$$

$$\begin{aligned} \Delta^3 E(ijk) &= E(ijk) - \{E(i) + E(j) + E(k)\} \\ &\quad - \{\Delta^2 E(ij) + \Delta^2 E(ik) + \Delta^2 E(jk)\} \end{aligned} \quad (3)$$

$$\begin{aligned} \Delta^4 E(ijkm) &= E(ijkm) - \{E(i) + E(j) + E(k) + E(m)\} - \{\Delta^2 E(ij) + \Delta^2 E(ik) + \Delta^2 E(im) + \Delta^2 E(jk) + \Delta^2 E(jm) + \Delta^2 E(km)\} \\ &\quad - \{\Delta^3 E(ijk) + \Delta^3 E(ijm) + \Delta^3 E(ikm) + \Delta^3 E(jkm)\} \end{aligned} \quad (4)$$

$$\begin{aligned} \Delta^5 E(12345) &= E(12345) - \sum_{i=1}^5 E(i) \\ &\quad - \left\{ \Delta^2 E(12) + \Delta^2 E(13) + \Delta^2 E(14) + \Delta^2 E(15) + \Delta^2 E(23) + \Delta^2 E(24) \right. \\ &\quad \left. + \Delta^2 E(25) + \Delta^2 E(34) + \Delta^2 E(35) + \Delta^2 E(45) \right\} \\ &\quad - \left\{ \Delta^3 E(123) + \Delta^3 E(124) + \Delta^3 E(125) + \Delta^3 E(134) + \Delta^3 E(135) \right. \\ &\quad \left. + \Delta^3 E(145) + \Delta^3 E(234) + \Delta^3 E(235) + \Delta^3 E(245) + \Delta^3 E(345) \right\} \\ &\quad - \{E(1234) + E(1345) + E(1245) + E(1235) + E(2345)\} \end{aligned} \quad (5)$$

The total binding energy of the complex is the sum of the relaxation energy and the  $n$ -body interaction energies.

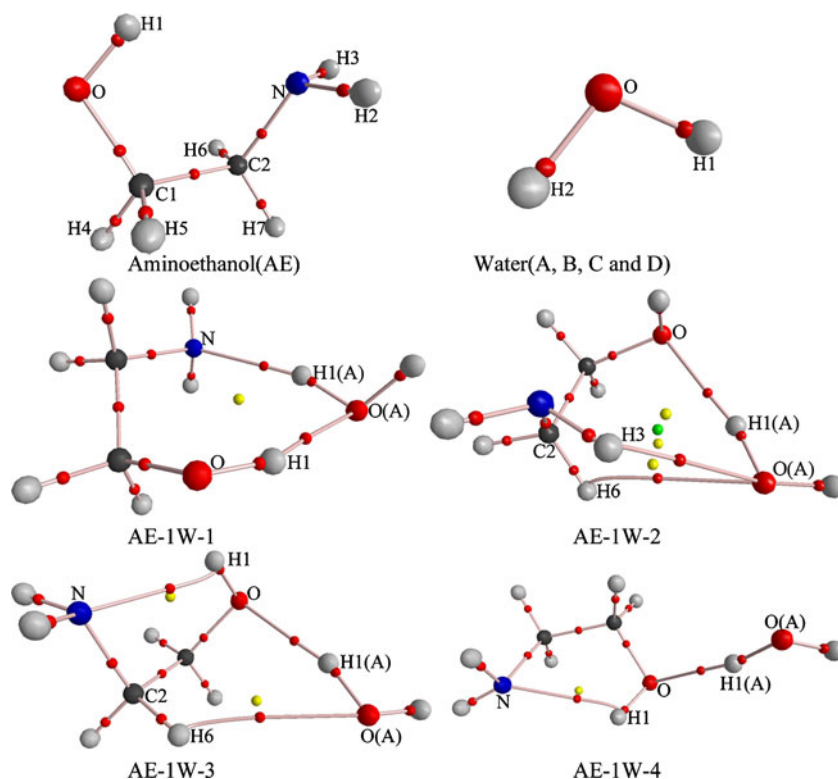
### Results and discussion

The structures of AE and water (A, B, C and D) obtained at the  $\omega$ B97XD/6-311++G(2d,2p) level are presented in Fig. 1 AE can offer several possible donor/acceptor sites to form H-bonds. The hydroxyl and amino groups of AE can act as either H-donors or H-acceptors to form H-bonds. The methylenes of AE can act as H-donors and form H-bonds with water in some complexes as well. For a water molecule, the hydroxyls are strong H-donors, while the oxygen atom acts as an H-acceptor and can form an H-bond

too. Previous studies [1, 2, 5] have shown that AE exists predominantly in the gas phase as the gauche conformer (g' Gg') stabilized by an  $\text{OH}1^{\text{AE}} \cdots \text{N}^{\text{AE}}$  intramolecular H-bond, but the presence of this H-bond cannot be confirmed by QTAIM since no BCP was found for the  $\text{H}1 \cdots \text{N}$  bond. Therefore, other methods might be more amenable for determining this H-bond.

The molecular graphs of  $\text{AE}-(\text{H}_2\text{O})_n$  ( $n = 1-4$ ) complexes formed by hydrogen bonding interactions are shown in Figs. 1, 2, 3, and 4, and the structural parameters ( $R_{\text{X-H}}$ ,  $\Delta R_{\text{X-H}}$ ,  $R_{\text{H}\cdots\text{Y}}$  and  $\angle \text{X-H}\cdots\text{Y}$ ) as well as the electron-topological properties ( $\rho_b$  and  $\nabla^2 \rho_b$ ) of the QTAIM analyses are listed in Tables 1, 2, 3, and 4. Vibrational frequency calculations show that none of the complexes have imaginary frequencies and all are stable structures.

**Fig. 1** Molecular graphs of AE–(H<sub>2</sub>O) complexes and monomers of free aminoethanol (AE) as well as water (A, B, C and D). Large circles correspond to attractors that are attributed to the atomic positions of H (gray), N (blue), C (black), O (red). Small circles are attributed to the following critical points: red bond critical point, yellow ring critical point, green cage critical point (the color figure can be viewed in the online version of this issue)



### AE–(H<sub>2</sub>O)

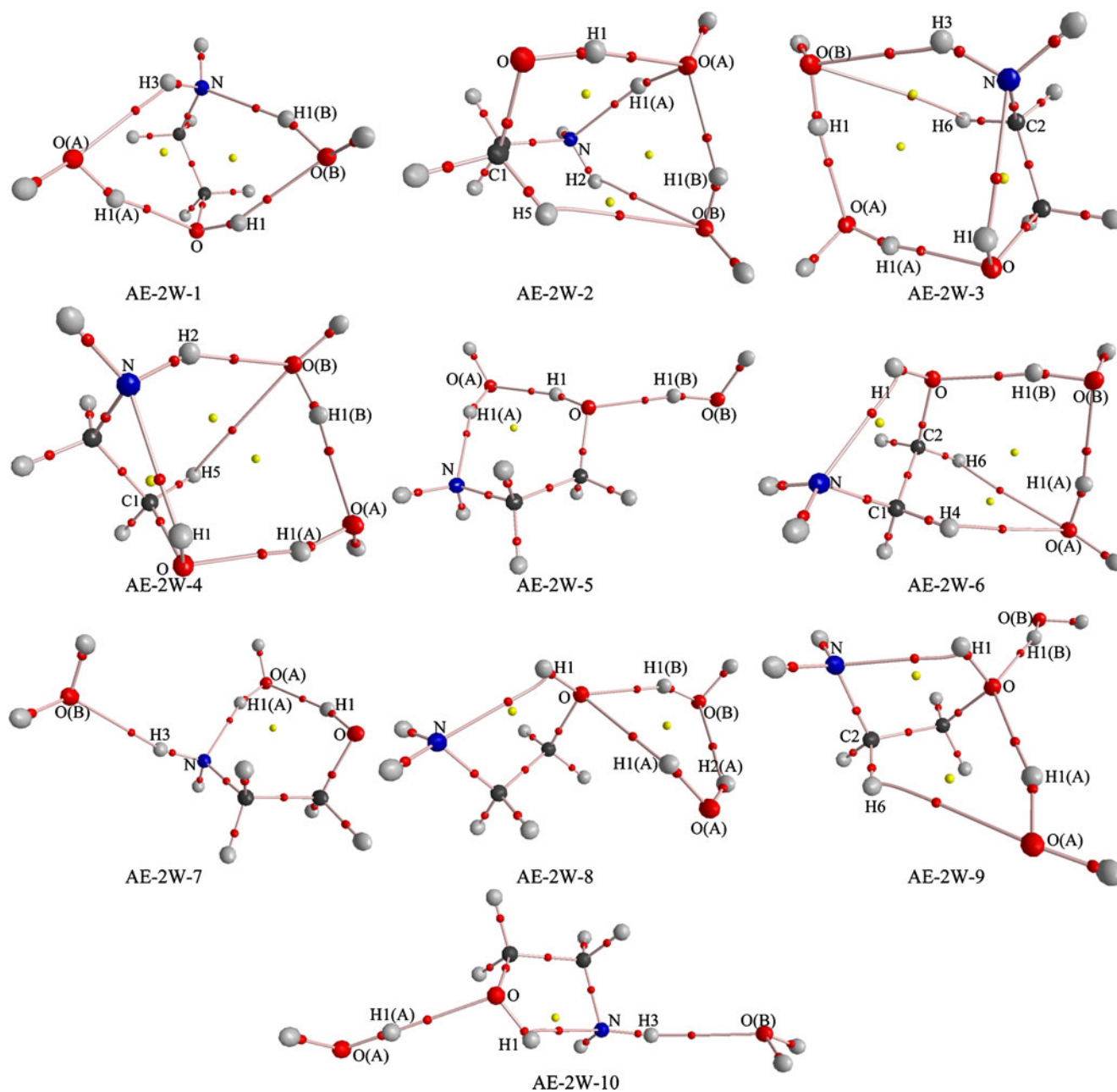
Four 1:1 complexes of AE with water formed by hydrogen bonding interactions were found at the  $\omega$ B97XD/6-311++G(2d,2p) level. The gauche conformer (g'Gg') of AE was retained in AE–(H<sub>2</sub>O) complexes. As shown in Fig. 1, all H-bonds in AE–(H<sub>2</sub>O) complexes are characterized by BCPs for XH<sup>A</sup>⋯Y. Two intermolecular H-bonds formed in AE-1-W-1, in which the hydroxyls of water and AE act as the H-donors, respectively. Two intermolecular H-bonds, OH1<sup>A</sup>⋯O<sup>AE</sup> and C2H6<sup>AE</sup>⋯O<sup>A</sup>, were involved in AE-1W-3 as well. Only one intermolecular H-bond (OH1<sup>A</sup>⋯O<sup>AE</sup>) between a hydroxyl of water and the oxygen atom of the AE moiety was involved in AE-1W-4. For AE-1W-2, except for the intermolecular OH1<sup>A</sup>⋯O<sup>AE</sup> H-bond, one bifurcated H-bond involving the amino and methylene of AE as H-donors simultaneously formed; these H-bonds resulted in a cage structure that was characterized by one CCP. Aside from the intermolecular H-bonds in AE-1W-3 and AE-1W-4, one intramolecular OH1<sup>AE</sup>⋯N<sup>AE</sup> H-bond formed. However, the short distance between the BCP and corresponding RCP indicates that this intramolecular H-bond is very weak.

Structural parameters of H-bonds can give preliminary information on the nature of the H-bond. It is well known that H-bond formation is connected with the elongation of the proton-donating X–H bond (except in the special case of so-called blueshifting H-bonds) as well as the shortening

of the H⋯Y bond. The shorter the H⋯Y bond or the longer the X–H bond, the stronger the interaction, and vice versa [45]. As shown in Table 1, except for the C2H6<sup>AE</sup>⋯O<sup>A</sup> H-bond in AE-1W-3, which has a negative value of  $\Delta R_{X-H}$ , all H-bonds have positive  $\Delta R_{X-H}$  values and are redshifting H-bonds. Moreover, because of larger  $\Delta R_{X-H}$  and shorter H⋯Y bonds, the H-bonds that have the hydroxyl of water as H-donor are usually stronger than other H-bonds that have the O atom of water as H-acceptor. The OH1<sup>A</sup>⋯N<sup>AE</sup> H-bond (which has the maximum  $\rho_b$ ) of AE-1W-1 is the strongest H-bond, since it involves the largest  $\Delta R_{X-H}$  (0.023 Å) and the shortest  $R_{H-Y}$  (1.868 Å), while the X–H bond length of the C2H6<sup>AE</sup>⋯O<sup>A</sup> H-bond in both AE-1W-2 and AE-1W-3 remains almost unchanged, which indicates that these H-bonds are very weak. Therefore, the order of H-donors is: hydroxyl > amino > methylene.

### AE–(H<sub>2</sub>O)<sub>2</sub>

Ten 1:2 complexes of AE with water formed by hydrogen-bonding interactions were found at the  $\omega$ B97XD/6-311++G(2d,2p) level. The gauche conformer (g'Gg') of AE was retained in the AE–(H<sub>2</sub>O)<sub>2</sub> complexes, except for AE-2W-1, which presented the conformer (g'Gg). As shown in Fig. 2, neither intermolecular H-bonds between two water molecules nor intramolecular H-bonds are seen in AE-2W-1, AE-2W-5, or AE-2W-7. Each water molecule formed two H-bonds with AE simultaneously in



**Fig. 2** Molecular graphs of AE-(H<sub>2</sub>O)<sub>2</sub> complexes. Large circles correspond to attractors attributed to the atomic positions of H (gray), N (blue), C (black), O (red). Small circles are attributed to the

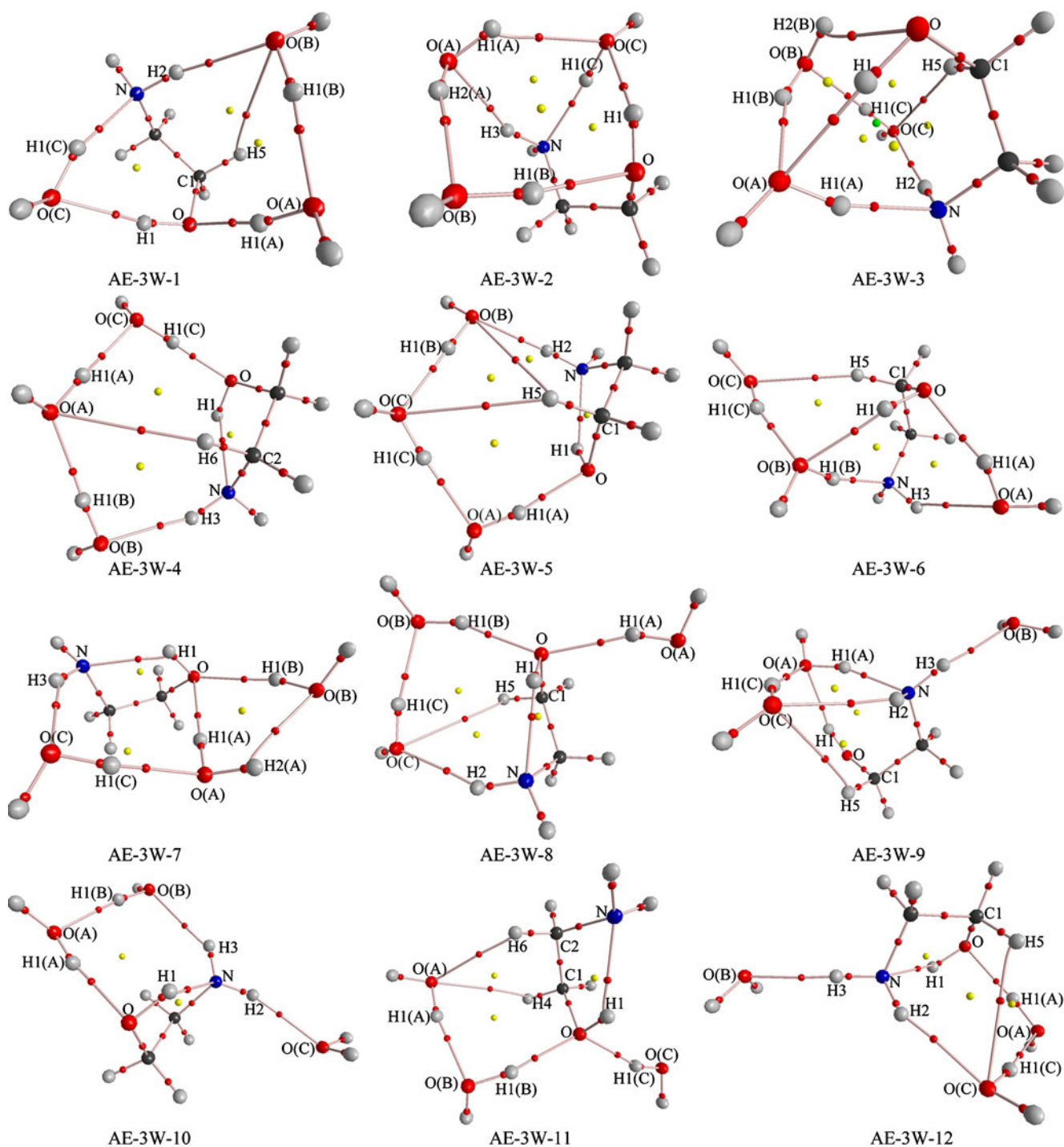
following critical points: red bond critical point, yellow ring critical point (the color figure can be viewed in the online version of this issue)

AE-2W-1, in which the hydroxyl/amino of AE acts as H-donor/H-acceptor. Aside from the above AE-(H<sub>2</sub>O)<sub>2</sub> complexes, no intramolecular H-bond formed in AE-2W-2 either, while one bifurcated H-bond formed between AE and one of the water molecules in AE-2W-2. In contrast, an intramolecular OH1<sup>AE</sup>...N<sup>AE</sup> H-bond formed in other AE-(H<sub>2</sub>O)<sub>2</sub> complexes. Moreover, intermolecular H-bonds between two water molecules were also seen in these complexes, except for AE-2W-9 and AE-2W-10. In addition, a bifurcated H-bond was seen in some AE-

(H<sub>2</sub>O)<sub>2</sub> complexes. For AE-2W-8 and AE-2W-9, one bifurcated H-bond formed between AE and two water molecules, where AE accepted protons from two water molecules simultaneously. For AE-2W-3, AE-2W-4, and AE-2W-6, a bifurcated H-bond formed between AE and one of the water molecules, where the amino and methylenes of AE both acted as H-donors simultaneously.

As shown in Table 2, the OH1<sup>A</sup>...N<sup>AE</sup> H-bond in AE-2W-2 is the strongest H-bond, since it involves the largest  $\Delta R_{X-H}$  (0.034 Å). Moreover, the  $\rho_b$  value of 0.04477 a.u. is



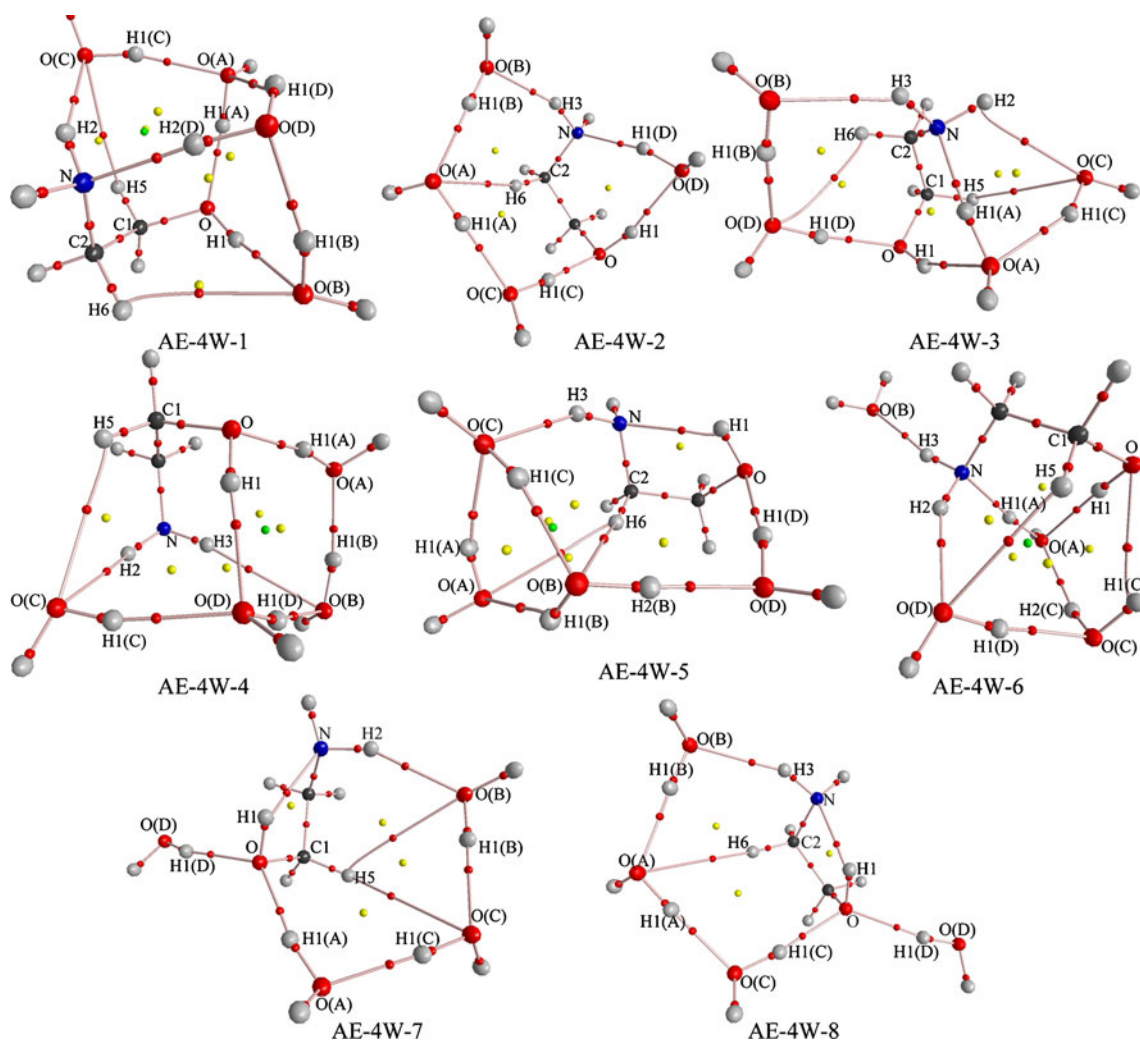


**Fig. 3** Molecular graphs of AE-(H<sub>2</sub>O)<sub>3</sub> complexes. Large circles correspond to attractors attributed to the atomic positions of H (gray), N (blue), C (black), O (red). Small circles are attributed to the

following critical points: red bond critical point, yellow ring critical point, green cage critical point (the color figure can be viewed in the online version of this issue)

beyond the upper limit for H-bonds proposed by Koch and Popelier, which indicates that it has partial covalent character. The OH1<sup>A</sup>...N<sup>AE</sup> H-bond in AE-2W-7 is the second strongest H-bond, as can be discerned from the structural and QTAIM results shown in Table 2. Moreover, because of the larger values of  $\Delta R_{X-H}$  (0.023~0.034 Å), the

H-bonds where the N atom of the amino in AE acts as the H-acceptor are stronger than the H-bonds between the hydroxyls and O of AE and water; this is further confirmed by the QTAIM analyses. The H-bonds where the methylene acts as the H-donor are the weakest, and the values of  $\rho_b$  that are close to the lower limit for H-bonds indicate



**Fig. 4** Molecular graphs of AE-(H<sub>2</sub>O)<sub>4</sub> complexes. Large circles correspond to attractors attributed to the atomic positions of H (gray), N (blue), C (black), O (red). Small circles are attributed to the

following critical points: red bond critical point, yellow ring critical point, green cage critical point (the color figure can be viewed in the online version of this issue)

that they possess partial van der Waals interaction character. Moreover, the negative values of  $\Delta R_{X-H}$  mean that they are blueshifted H-bonds, as confirmed by the vibrational frequency shifts. In addition, the intramolecu-

lar OH1<sup>AE</sup>...N<sup>AE</sup> H-bond is weaker than intermolecular H-bonds mentioned above, which indicates that AE would rather form intermolecular H-bonds with two water molecules than the intramolecular OH1<sup>AE</sup>...N<sup>AE</sup> H-bond.

**Table 1** Structural parameters and electronic density analysis of H-bonds in AE-(H<sub>2</sub>O) complexes calculated at the  $\omega$ B97XD/6-311++G(2d,2p) level<sup>a</sup>

Complex	H-bond	$R_{X-H}$	$\Delta R_{X-H}$	$R_{H...Y}$	$\theta_{X-H...Y}$	$\rho_b$	$\nabla^2 \rho_b$
AE-1W-1	OH1 <sup>A</sup> ...N <sup>AE</sup>	0.980	0.023	1.868	160.5	0.03672	0.08733
	OH1 <sup>AE</sup> ...O <sup>A</sup>	0.968	0.005	1.912	163.1	0.02788	0.08836
AE-1W-2	NH3 <sup>AE</sup> ...O <sup>A</sup>	1.011	0.002	2.430	126.8	0.00921	0.03440
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.969	0.012	1.918	156.3	0.02765	0.08789
AE-1W-3	C2H6 <sup>AE</sup> ...O <sup>A</sup>	1.092	0.001	2.655	109.1	0.00714	0.02792
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.969	0.012	1.880	162.3	0.02947	0.09419
AE-1W-4	C2H6 <sup>AE</sup> ...O <sup>A</sup>	1.090	-0.001	2.703	125.9	0.00561	0.02208
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.966	0.003	2.192	116.4	0.02093	0.08227
AE-1W-4	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.968	0.012	1.881	165.7	0.02904	0.09390
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.966	0.003	2.169	117.5	0.02152	0.08351

<sup>a</sup> Bond lengths are in angstroms and bond angles are in degrees; electron densities ( $\rho_b$ ) and their Laplacians ( $\nabla^2 \rho_b$ ) are in a.u.

**Table 2** Structural parameters and electronic density analysis of H-bonds in AE-(H<sub>2</sub>O)<sub>2</sub> complexes calculated at the  $\omega$ B97XD/6-311++G(2d,2p) level<sup>a</sup>

Complex	H-bond	$R_{X-H}$	$\Delta R_{X-H}$	$R_{H...Y}$	$\theta_{X-H...Y}$	$\rho_b$	$\nabla^2 \rho_b$
AE-2W-1	OH1 <sup>AE</sup> ...O <sup>B</sup>	0.969	0.007	1.911	150.8	0.02795	0.09152
	NH3 <sup>AE</sup> ...O <sup>A</sup>	1.015	0.006	2.175	139.5	0.01517	0.05752
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.973	0.016	1.847	160.0	0.03201	0.09899
	OH1 <sup>B</sup> ...N <sup>AE</sup>	0.982	0.026	1.874	158.2	0.03636	0.08533
AE-2W-2	NH2 <sup>AE</sup> ...O <sup>B</sup>	1.016	0.005	2.264	135.3	0.01299	0.04757
	OH1 <sup>B</sup> ...O <sup>A</sup>	0.968	0.011	1.920	152.3	0.02551	0.08990
	C1H5 <sup>AE</sup> ...O <sup>B</sup>	1.097	-0.002	2.987	129.2	0.00429	0.01360
	OH1 <sup>AE</sup> ...O <sup>A</sup>	0.964	0.001	1.960	160.0	0.02429	0.08247
AE-2W-3	OH1 <sup>A</sup> ...N <sup>AE</sup>	0.991	0.034	1.784	156.3	0.04477	0.09226
	NH3 <sup>AE</sup> ...O <sup>B</sup>	1.012	0.003	2.147	142.0	0.01680	0.05988
	C2H6 <sup>AE</sup> ...O <sup>B</sup>	1.090	-0.001	2.755	117.3	0.00697	0.02467
	OH1 <sup>B</sup> ...O <sup>A</sup>	0.973	0.016	1.837	170.5	0.03142	0.09912
AE-2W-4	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.977	0.020	1.792	167.5	0.03646	0.10626
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.971	0.009	2.072	119.1	0.02648	0.09238
	NH2 <sup>AE</sup> ...O <sup>B</sup>	1.017	0.005	2.120	152.3	0.01793	0.06127
	C1H5 <sup>AE</sup> ...O <sup>B</sup>	1.095	-0.004	2.700	125.0	0.00573	0.02154
AE-2W-5	OH1 <sup>B</sup> ...O <sup>A</sup>	0.973	0.017	1.832	169.5	0.03177	0.10009
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.976	0.020	1.803	162.1	0.03560	0.10641
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.972	0.009	2.022	122.1	0.02829	0.09801
	OH1 <sup>A</sup> ...N <sup>AE</sup>	0.980	0.023	1.869	158.8	0.03672	0.08734
AE-2W-6	OH1 <sup>AE</sup> ...O <sup>A</sup>	0.971	0.008	1.849	162.6	0.03192	0.09863
	OH1 <sup>B</sup> ...O <sup>AE</sup>	0.969	0.012	1.866	166.6	0.02923	0.09656
	OH1 <sup>B</sup> ...O <sup>AE</sup>	0.976	0.020	1.775	168.8	0.03688	0.11129
	C2H6 <sup>AE</sup> ...O <sup>A</sup>	1.089	-0.002	2.618	122.7	0.00784	0.02507
AE-2W-7	C1H4 <sup>AE</sup> ...O <sup>A</sup>	1.088	-0.002	2.649	122.5	0.00629	0.02333
	OH1 <sup>A</sup> ...O <sup>B</sup>	0.972	0.015	1.838	168.0	0.03167	0.10010
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.967	0.004	2.144	118.2	0.02265	0.08459
	OH1 <sup>AE</sup> ...O <sup>A</sup>	0.968	0.005	1.909	162.0	0.02802	0.08935
AE-2W-8	OH <sup>A</sup> ...N <sup>AE</sup>	0.984	0.027	1.837	162.8	0.03968	0.08822
	NH3 <sup>AE</sup> ...O <sup>B</sup>	1.014	0.005	2.142	154.5	0.01657	0.05819
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.961	0.004	2.142	145.4	0.01780	0.05965
	OH2 <sup>A</sup> ...O <sup>B</sup>	0.963	0.006	2.180	138.2	0.01627	0.05576
AE-2W-9	OH1 <sup>B</sup> ...O <sup>AE</sup>	0.966	0.010	1.924	154.7	0.02426	0.08866
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.966	0.003	2.168	116.2	0.02180	0.08333
	OH1 <sup>B</sup> ...O <sup>AE</sup>	0.967	0.010	1.904	164.4	0.02741	0.09074
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.967	0.010	1.915	158.8	0.02722	0.08966
AE-2W-10	C2H6 <sup>AE</sup> ...O <sup>A</sup>	1.090	-0.001	2.640	126.2	0.00624	0.02398
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.971	0.008	2.083	119.9	0.02539	0.09060
	NH3 <sup>AE</sup> ...O <sup>B</sup>	1.012	0.003	2.122	158.0	0.01696	0.06008
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.969	0.013	1.864	170.0	0.03005	0.09600
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.968	0.005	2.128	119.0	0.02338	0.08594

<sup>a</sup> Bond lengths are in angstroms and bond angles are in degrees; electron densities ( $\rho_b$ ) and their Laplacians ( $\nabla^2 \rho_b$ ) are in a.u.

### AE-(H<sub>2</sub>O)<sub>3</sub>

Twelve 1:3 complexes of AE with water formed by hydrogen-bonding interactions were found at the  $\omega$ B97XD/6-311++G(2d,2p) level. The gauche conformer (g'Gg') of AE was retained in most of the AE-(H<sub>2</sub>O)<sub>3</sub> complexes, while a different conformer (g'Gg) was seen for

AE-3W-2 and AE-3W-6. As shown in Fig. 3, multiple H-bonds formed between AE and the water molecules in each complex. The intramolecular OH1<sup>AE</sup>...N<sup>AE</sup> H-bond can be found in some complexes (AE-3W-4, AE-3W-5, AE-3W-7, AE-3W-8, AE-3W-10, AE-3W-11, and AE-3W-12). Upon comparing Tables 1, 2 and 3, it is clear that the intramolecular OH1<sup>AE</sup>...N<sup>AE</sup> H-bonds in AE-(H<sub>2</sub>O)<sub>3</sub> are



**Table 3** Structural parameters and electronic density analysis of H-bonds in AE-(H<sub>2</sub>O)<sub>3</sub> complexes calculated at the  $\omega$ B97XD/6-311++G(2d,2p) level<sup>a</sup>

Complex	H-bond	$R_{X-H}$	$\Delta R_{X-H}$	$R_{H...Y}$	$\theta_{X-H...Y}$	$\rho_b$	$\nabla^2 \rho_b$
AE-3W-1	NH2 <sup>AE</sup> ...O <sup>B</sup>	1.019	0.008	2.014	164.8	0.02163	0.07413
	C1H5 <sup>AE</sup> ...O <sup>B</sup>	1.094	-0.005	2.921	123.0	0.00499	0.01624
	OH1 <sup>B</sup> ...O <sup>A</sup>	0.975	0.018	1.792	169.1	0.03483	0.10808
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.980	0.023	1.750	166.9	0.03941	0.11534
	OH1 <sup>AE</sup> ...O <sup>C</sup>	0.973	0.010	1.827	165.5	0.03326	0.10059
	OH1 <sup>C</sup> ...N <sup>AE</sup>	0.988	0.031	1.800	155.5	0.04341	0.09354
AE-3W-2	NH3 <sup>AE</sup> ...O <sup>A</sup>	1.020	0.010	2.032	153.8	0.02308	0.07472
	OH1 <sup>A</sup> ...O <sup>C</sup>	0.961	0.004	2.253	138.5	0.01278	0.04645
	OH2 <sup>A</sup> ...O <sup>B</sup>	0.970	0.013	1.886	161.9	0.02838	0.09249
	OH1 <sup>B</sup> ...O <sup>AE</sup>	0.975	0.019	1.788	166.9	0.03592	0.10863
	OH1 <sup>AE</sup> ...O <sup>C</sup>	0.970	0.007	1.860	158.4	0.03034	0.09912
	OH1 <sup>C</sup> ...N <sup>AE</sup>	0.986	0.030	1.833	153.0	0.03961	0.09035
AE-3W-3	NH2 <sup>AE</sup> ...O <sup>C</sup>	1.020	0.008	2.038	155.0	0.02047	0.07263
	C1H5 <sup>AE</sup> ...O <sup>C</sup>	1.096	-0.003	2.591	137.1	0.00729	0.02524
	OH1 <sup>C</sup> ...O <sup>B</sup>	0.976	0.019	1.807	168.7	0.03454	0.10404
	OH2 <sup>B</sup> ...O <sup>AE</sup>	0.961	0.005	2.409	128.7	0.01121	0.03753
	OH1 <sup>B</sup> ...O <sup>A</sup>	0.968	0.012	1.901	153.2	0.02636	0.09396
	OH1 <sup>AE</sup> ...O <sup>A</sup>	0.965	0.002	1.938	167.4	0.02541	0.08434
	OH1 <sup>A</sup> ...N <sup>AE</sup>	0.995	0.039	1.747	161.3	0.04920	0.09106
	NH3 <sup>AE</sup> ...O <sup>B</sup>	1.015	0.006	2.042	155.1	0.02111	0.07189
AE-3W-4	OH <sup>B</sup> ...O <sup>A</sup>	0.974	0.017	1.799	177.6	0.03379	0.10667
	C2H6 <sup>AE</sup> ...O <sup>A</sup>	1.091	0.000	2.881	155.2	0.00474	0.01468
	OH <sup>A</sup> ...O <sup>C</sup>	0.977	0.020	1.764	176.2	0.03710	0.11197
	OH <sup>C</sup> ...O <sup>AE</sup>	0.980	0.023	1.744	171.2	0.04033	0.11502
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.973	0.010	2.050	121.2	0.02750	0.09333
	OH <sup>A</sup> ...O <sup>AE</sup>	0.980	0.023	1.747	168.4	0.03983	0.11514
	OH <sup>C</sup> ...O <sup>A</sup>	0.978	0.021	1.761	173.9	0.03759	0.11256
	C1H5 <sup>AE</sup> ...O <sup>C</sup>	1.095	-0.004	2.928	148.7	0.00442	0.01406
AE-3W-5	OH <sup>B</sup> ...O <sup>C</sup>	0.975	0.018	1.793	178.9	0.03449	0.10691
	NH2 <sup>AE</sup> ...O <sup>B</sup>	1.017	0.006	2.051	156.9	0.02062	0.07050
	C1H5 <sup>AE</sup> ...O <sup>B</sup>	1.095	-0.004	2.862	124.8	0.00413	0.01635
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.972	0.010	2.026	122.3	0.02826	0.09629
	NH3 <sup>AE</sup> ...O <sup>A</sup>	1.015	0.006	2.144	139.0	0.01615	0.06184
	OH <sup>A</sup> ...O <sup>AE</sup>	0.972	0.016	1.851	159.7	0.03165	0.09824
	OH1 <sup>AE</sup> ...O <sup>B</sup>	0.966	0.003	1.993	146.7	0.02312	0.07972
	OH <sup>B</sup> ...N <sup>AE</sup>	0.994	0.037	1.776	163.7	0.04572	0.08896
AE-3W-6	OH <sup>C</sup> ...O <sup>B</sup>	0.968	0.011	1.885	163.9	0.02770	0.09334
	C1H5 <sup>AE</sup> ...O <sup>C</sup>	1.092	-0.007	2.527	162.4	0.00901	0.02699
	NH3 <sup>AE</sup> ...O <sup>C</sup>	1.013	0.004	2.081	146.6	0.01909	0.06787
	OH1 <sup>C</sup> ...O <sup>A</sup>	0.974	0.017	1.820	165.9	0.03252	0.10338
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.968	0.011	1.925	168.3	0.02738	0.08520
	OH2 <sup>A</sup> ...O <sup>B</sup>	0.961	0.004	2.323	122.4	0.01234	0.04471
	OH1 <sup>B</sup> ...O <sup>AE</sup>	0.966	0.009	1.958	155.1	0.02271	0.08248
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.974	0.011	2.023	120.6	0.02908	0.09741
AE-3W-7	NH2 <sup>AE</sup> ...O <sup>C</sup>	1.015	0.004	2.107	149.1	0.01759	0.06375
	C1H5 <sup>AE</sup> ...O <sup>C</sup>	1.093	-0.006	2.833	121.1	0.00581	0.01846
	OH1 <sup>C</sup> ...O <sup>B</sup>	0.972	0.015	1.843	169.3	0.03103	0.09811
	OH1 <sup>B</sup> ...O <sup>AE</sup>	0.974	0.017	1.834	160.5	0.03288	0.10222

**Table 3** (continued)

Complex	H-bond	$R_{X-H}$	$\Delta R_{X-H}$	$R_{H...Y}$	$\theta_{X-H...Y}$	$\rho_b$	$\nabla^2 \rho_b$
AE-3W-9	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.967	0.010	1.913	159.7	0.02725	0.09007
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.979	0.016	1.933	125.4	0.03404	0.10616
	NH3 <sup>AE</sup> ...O <sup>B</sup>	1.014	0.005	2.136	163.0	0.01660	0.05743
	NH2 <sup>AE</sup> ...O <sup>C</sup>	1.015	0.004	2.357	132.2	0.01091	0.03927
	C1H5 <sup>AE</sup> ...O <sup>C</sup>	1.097	-0.002	2.956	131.4	0.00448	0.01389
	OH1 <sup>C</sup> ...O <sup>A</sup>	0.968	0.012	1.906	155.2	0.02648	0.09134
AE-3W-10	OH1 <sup>AE</sup> ...O <sup>A</sup>	0.964	0.002	1.955	159.3	0.02443	0.08342
	OH1 <sup>A</sup> ...N <sup>AE</sup>	0.997	0.041	1.744	158.6	0.04947	0.09185
	NH2 <sup>AE</sup> ...O <sup>C</sup>	1.010	-0.001	2.158	158.9	0.01601	0.05557
	NH3 <sup>AE</sup> ...O <sup>B</sup>	1.011	0.002	2.189	141.3	0.01555	0.05486
	OH <sup>B</sup> ...O <sup>A</sup>	0.973	0.016	1.839	172.2	0.03139	0.09863
	OH <sup>A</sup> ...O <sup>AE</sup>	0.978	0.021	1.784	168.3	0.03719	0.10735
AE-3W-11	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.974	0.011	2.021	121.4	0.02935	0.09700
	OH1 <sup>C</sup> ...O <sup>AE</sup>	0.966	0.010	1.920	161.6	0.02659	0.08866
	C2H6 <sup>AE</sup> ...O <sup>A</sup>	1.089	-0.002	2.536	126.8	0.00886	0.02859
	C1H4 <sup>AE</sup> ...O <sup>A</sup>	1.088	-0.002	2.667	120.7	0.00615	0.02284
	OH1 <sup>A</sup> ...O <sup>B</sup>	0.971	0.014	1.846	166.6	0.03103	0.09896
	OH1 <sup>B</sup> ...O <sup>AE</sup>	0.974	0.017	1.803	168.4	0.03453	0.10680
AE-3W-12	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.973	0.010	2.035	121.9	0.02765	0.09511
	NH3 <sup>AE</sup> ...O <sup>B</sup>	1.011	0.002	2.144	168.9	0.01672	0.05623
	NH2 <sup>AE</sup> ...O <sup>C</sup>	1.015	0.004	2.141	151.9	0.01662	0.05854
	OH1 <sup>C</sup> ...O <sup>A</sup>	0.973	0.016	1.835	170.6	0.03165	0.09928
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.978	0.021	1.786	162.9	0.03697	0.10941
	C1H5 <sup>AE</sup> ...O <sup>C</sup>	1.095	-0.004	2.901	120.5	0.00518	0.01675
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.975	0.012	1.975	124.2	0.03130	0.10218

<sup>a</sup> Bond lengths are in angstroms and bond angles are in degrees; electron densities ( $\rho_b$ ) and their Laplacians ( $\nabla^2 \rho_b$ ) are in a.u.

stronger than those of both AE-(H<sub>2</sub>O) and AE-(H<sub>2</sub>O)<sub>2</sub> since they involve larger  $\Delta R_{X-H}$  values, as confirmed by the QTAIM analyses. The strongest OH1<sup>AE</sup>...N<sup>AE</sup> H-bond formed in AE-3W-8, since it involves the largest  $\Delta R_{X-H}$  (0.016 Å) and  $\rho_b$  (0.03404 a.u.) as well as  $\nabla^2 \rho_b$  (0.10616 a.u.) values. The weakest OH1<sup>AE</sup>...N<sup>AE</sup> H-bond of the AE-(H<sub>2</sub>O)<sub>3</sub> complexes formed in AE-3W-11 is still stronger than those of both AE-(H<sub>2</sub>O) and AE-(H<sub>2</sub>O)<sub>2</sub> complexes, except for the one in AE-2W-4, as noted in QTAIM analyses.

As shown in Fig. 3, more intermolecular H-bonds formed between water molecules. For example, in some complexes (AE-3W-2, AE-3W-3, AE-3W-4, AE-3W-5, and AE-3W-7), each water molecule formed at least one H-bond with the other water molecules, and bifurcated H-bonds that form when one water molecule accepts protons from AE and another water molecule simultaneously can also be found in these complexes except for AE-3W-7. For other complexes (AE-3W-1, AE-3W-6, AE-3W-8, AE-3W-9, AE-3W-10, AE-3W-11, and AE-3W-12), only two water molecules can form intermolecular H-bonds, and there are

no hydrogen-bonding interactions between them and the third one; moreover, bifurcated H-bonds formed in these complexes when one water molecule accepted protons from AE, except in the cases of AE-3W-6 and AE-3W-10. No bifurcated H-bond formed in AE-3W-10, while the bifurcated H-bond in AE-3W-6 was similar to those in AE-3W-2 and AE-3W-3, which involved one water molecule accepting protons from AE and another water molecule simultaneously. In addition, bifurcated H-bonds that form when two water molecules donate protons to AE simultaneously can be found in AE-3W-7, AE-3W-8, and AE-3W-10.

As shown in Table 3, the intermolecular OH<sup>water</sup>...N<sup>AE</sup> H-bonds are the strongest H-bonds in some complexes (AE-3W-1, AE-3W-2, AE-3W-3, AE-3W-6, and AE-3W-9), which indicates that it is easier for the N atom than the O atom in AE to accept a proton to form an intermolecular H-bond. Moreover, according to QTAIM, the  $\rho_b$  values of the intermolecular OH<sup>water</sup>...N<sup>AE</sup> H-bonds in these complexes (except for AE-3W-2) are beyond the upper limit proposed by Koch and Popelier, which indicates that they have partial covalent character. Even the weakest OH<sup>water</sup>...N<sup>AE</sup>

**Table 4** Structural parameters and electronic density analysis of H-bonds in AE-(H<sub>2</sub>O)<sub>4</sub> complexes calculated at the  $\omega$ B97XD/6-311++G(2d,2p) level<sup>a</sup>

Complex	H-bond	$R_{X-H}$	$\Delta R_{X-H}$	$R_{H...Y}$	$\theta_{X-H...Y}$	$\rho_b$	$\nabla^2 \rho_b$
AE-4W-1	NH2 <sup>AE</sup> ...O <sup>C</sup>	1.018	0.007	2.079	155.5	0.01963	0.06684
	OH1 <sup>C</sup> ...O <sup>A</sup>	0.973	0.016	1.842	164.8	0.03127	0.09941
	C1H5 <sup>AE</sup> ...O <sup>C</sup>	1.091	-0.008	2.783	127.4	0.00488	0.01756
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.986	0.030	1.684	174.1	0.04580	0.12695
	OH1 <sup>D</sup> ...O <sup>A</sup>	0.963	0.006	2.138	140.2	0.01679	0.06007
	OH2 <sup>D</sup> ...N <sup>AE</sup>	0.987	0.030	1.824	173.7	0.04077	0.08702
	OH1 <sup>AE</sup> ...O <sup>B</sup>	0.976	0.013	1.780	164.0	0.03647	0.11061
	C2H6 <sup>AE</sup> ...O <sup>B</sup>	1.092	0.001	2.775	117.8	0.00558	0.02035
AE-4W-2	OH1 <sup>D</sup> ...N <sup>AE</sup>	0.989	0.032	1.799	163.1	0.04371	0.08959
	OH1 <sup>AE</sup> ...O <sup>D</sup>	0.975	0.013	1.799	164.9	0.03572	0.10680
	NH3 <sup>AE</sup> ...O <sup>B</sup>	1.018	0.009	2.020	154.8	0.02203	0.07555
	OH1 <sup>B</sup> ...O <sup>A</sup>	0.975	0.018	1.790	177.9	0.03468	0.10804
	C2H6 <sup>AE</sup> ...O <sup>A</sup>	1.091	0.000	2.827	161.3	0.00521	0.01625
	OH1 <sup>A</sup> ...O <sup>C</sup>	0.978	0.021	1.755	174.9	0.03761	0.11411
AE-4W-3	OH1 <sup>C</sup> ...O <sup>AE</sup>	0.981	0.025	1.726	174.1	0.04174	0.11750
	NH3 <sup>AE</sup> ...O <sup>B</sup>	1.014	0.005	2.113	140.4	0.01829	0.06546
	NH2 <sup>AE</sup> ...O <sup>C</sup>	1.012	0.001	2.538	116.3	0.00793	0.02985
	OH1 <sup>A</sup> ...N <sup>AE</sup>	1.004	0.047	1.710	162.9	0.05398	0.08937
	OH1 <sup>C</sup> ...O <sup>A</sup>	0.968	0.011	1.925	153.7	0.02535	0.08845
	C1H5 <sup>AE</sup> ...O <sup>C</sup>	1.093	-0.006	2.665	136.3	0.00677	0.02116
	OH1 <sup>B</sup> ...O <sup>D</sup>	0.973	0.017	1.823	171.9	0.03204	0.10192
	OH1 <sup>D</sup> ...O <sup>AE</sup>	0.978	0.022	1.779	172.7	0.03708	0.10703
AE-4W-4	C2H6 <sup>AE</sup> ...O <sup>D</sup>	1.090	0.000	2.660	123.8	0.00649	0.02590
	OH1 <sup>AE</sup> ...O <sup>A</sup>	0.968	0.006	1.894	154.2	0.02844	0.09507
	NH3 <sup>AE</sup> ...O <sup>B</sup>	1.011	0.002	2.532	170.9	0.00850	0.02652
	NH2 <sup>AE</sup> ...O <sup>C</sup>	1.015	0.003	2.225	152.7	0.01476	0.04924
	C1H5 <sup>AE</sup> ...O <sup>C</sup>	1.093	-0.006	2.757	128.4	0.00517	0.01798
	OH1 <sup>C</sup> ...O <sup>D</sup>	0.968	0.011	1.880	164.7	0.02746	0.09434
	OH1 <sup>D</sup> ...O <sup>B</sup>	0.981	0.025	1.729	168.0	0.04034	0.11908
	OH1 <sup>AE</sup> ...O <sup>D</sup>	0.968	0.005	1.885	167.8	0.02863	0.09155
AE-4W-5	OH1 <sup>B</sup> ...O <sup>A</sup>	0.980	0.023	1.746	165.8	0.03916	0.11610
	OH1 <sup>A</sup> ...O <sup>AE</sup>	0.981	0.024	1.745	166.6	0.04017	0.11455
	OH1 <sup>D</sup> ...O <sup>AE</sup>	0.978	0.021	1.760	169.1	0.03875	0.11305
	OH2 <sup>B</sup> ...O <sup>D</sup>	0.974	0.018	1.790	174.5	0.03463	0.10737
	C2H6 <sup>AE</sup> ...O <sup>B</sup>	1.090	-0.001	2.797	156.1	0.00566	0.01747
	C2H6 <sup>AE</sup> ...O <sup>A</sup>	1.090	-0.001	2.793	133.5	0.00450	0.01662
	OH1 <sup>B</sup> ...O <sup>A</sup>	0.965	0.008	2.080	139.8	0.01924	0.06798
	OH1 <sup>A</sup> ...O <sup>C</sup>	0.969	0.012	1.940	151.2	0.02522	0.08578
AE-4W-6	OH1 <sup>C</sup> ...O <sup>B</sup>	0.983	0.027	1.736	160.1	0.04105	0.11886
	NH3 <sup>AE</sup> ...O <sup>C</sup>	1.013	0.004	2.114	151.0	0.01784	0.06278
	OH1 <sup>AE</sup> ...N <sup>AE</sup>	0.971	0.008	2.072	120.6	0.02624	0.09117
	NH3 <sup>AE</sup> ...O <sup>B</sup>	1.014	0.005	2.142	169.2	0.01635	0.05611
	NH2 <sup>AE</sup> ...O <sup>D</sup>	1.019	0.007	2.079	153.6	0.01881	0.06675
	OH1 <sup>A</sup> ...N <sup>AE</sup>	1.001	0.044	1.716	162.8	0.05325	0.08989
	OH1 <sup>AE</sup> ...O <sup>A</sup>	0.965	0.003	1.940	165.5	0.02510	0.08428
	OH2 <sup>C</sup> ...O <sup>A</sup>	0.969	0.012	1.898	152.7	0.02672	0.09461
OH1 <sup>C</sup> ...O <sup>AE</sup>	0.962	0.006	2.325	131.6	0.01302	0.04356	
OH1 <sup>D</sup> ...O <sup>C</sup>	0.976	0.020	1.805	170.2	0.03480	0.10410	

**Table 4** (continued)

Complex	H-bond	$R_{X-H}$	$\Delta R_{X-H}$	$R_{H...Y}$	$\theta_{X-H...Y}$	$\rho_b$	$\nabla^2 \rho_b$
AE-4W-7	C1H5 <sup>AE...O</sup> <sup>D</sup>	1.096	-0.003	2.587	137.7	0.00728	0.02531
	OH1 <sup>D...O</sup> <sup>AE</sup>	0.967	0.010	1.909	162.1	0.02741	0.09016
	OH1 <sup>A...O</sup> <sup>AE</sup>	0.977	0.020	1.776	167.5	0.03709	0.11082
	OH1 <sup>C...O</sup> <sup>A</sup>	0.977	0.020	1.771	174.1	0.03665	0.11061
	C1H5 <sup>AE...O</sup> <sup>C</sup>	1.093	-0.006	2.884	151.1	0.00477	0.01496
	OH1 <sup>B...O</sup> <sup>C</sup>	0.974	0.018	1.798	178.3	0.03399	0.10631
	C1H5 <sup>AE...O</sup> <sup>B</sup>	1.093	-0.006	2.887	123.0	0.00393	0.01588
	NH2 <sup>AE...O</sup> <sup>B</sup>	1.017	0.005	2.052	154.3	0.02057	0.07081
AE-4W-8	OH1 <sup>AE...N</sup> <sup>AE</sup>	0.978	0.016	1.954	124.5	0.03283	0.10292
	OH1 <sup>D...O</sup> <sup>AE</sup>	0.967	0.010	1.908	166.2	0.02706	0.08971
	NH3 <sup>AE...O</sup> <sup>B</sup>	1.015	0.006	2.034	154.5	0.02150	0.07326
	OH1 <sup>B...O</sup> <sup>A</sup>	0.973	0.017	1.802	176.3	0.03337	0.10635
	C2H6 <sup>AE...O</sup> <sup>A</sup>	1.091	0.000	2.814	156.5	0.00541	0.01638
	OH1 <sup>A...O</sup> <sup>C</sup>	0.976	0.019	1.773	176.8	0.03627	0.11020
	OH1 <sup>C...O</sup> <sup>AE</sup>	0.977	0.020	1.776	170.0	0.03721	0.11000
	OH1 <sup>AE...N</sup> <sup>AE</sup>	0.979	0.016	1.961	124.2	0.03270	0.10190

<sup>a</sup> Bond lengths are in angstroms and bond angles are in degrees; electron densities ( $\rho_b$ ) and their Laplacians ( $\nabla^2 \rho_b$ ) are in a.u.

H-bond in AE-3W-2, which has a  $\rho_b$  value of 0.03961 a.u., is very close to the upper limit, so it is still stronger than those formed between the hydroxyl of water and the O atom of AE/water. Aside from above AE-(H<sub>2</sub>O)<sub>3</sub> complexes, the H-bond that forms between the hydroxyl of water and the O atom of AE/water is the strongest one in the other AE-(H<sub>2</sub>O)<sub>3</sub> complexes. Moreover, aside from a few complexes (AE-3W-3, AE-3W-7, and AE-3W-9), the intermolecular OH<sup>water...O</sup><sup>AE</sup> H-bonds in AE-(H<sub>2</sub>O)<sub>3</sub> complexes are stronger than the intermolecular OH<sup>water...O</sup><sup>water</sup> H-bonds formed between two water molecules, which indicates that the proton-accepting ability of the O atom of AE is stronger than that of the O atom of a water molecule in these complexes. The H-bonds that have the methylene as the H-donor are still the weakest ones in AE-(H<sub>2</sub>O)<sub>3</sub> complexes, and they have blueshifts characterized by the negative values of  $\Delta R_{X-H}$ , which is consistent with the idea that those H-bonds use the methylene as H-donors in both AE-(H<sub>2</sub>O) and AE-(H<sub>2</sub>O)<sub>2</sub> complexes.

#### AE-(H<sub>2</sub>O)<sub>4</sub>

Eight 1:4 complexes of AE with water formed by hydrogen-bonding interactions were found at the  $\omega$ B97XD/6-311++G(2d,2p) level. The gauche conformer (g'Gg') of AE was retained in most of the AE-(H<sub>2</sub>O)<sub>4</sub> complexes, while gGg' and g'Gt conformers were noted for AE-4W-1 and AE-4W-4, respectively. As shown in Fig. 4, the CCPs in some complexes (AE-4W-1, AE-4W-4, AE-4W-5, and AE-4W-6) indicate that more complex

structures formed when the AE bonded with more water molecules. An intramolecular OH1<sup>AE...N</sup><sup>AE</sup> H-bond can be found in a few complexes (AE-4W-5, AE-4W-7, and AE-4W-8). Moreover, the results of the QTAIM analyses shown in Tables 3 and 4 show that the intramolecular OH1<sup>AE...N</sup><sup>AE</sup> H-bonds in both AE-4W-7 and AE-4W-8 are stronger than those of AE-(H<sub>2</sub>O)<sub>3</sub> complexes (except for AE-3W-8), which indicates that the intramolecular OH1<sup>AE...N</sup><sup>AE</sup> H-bond is strengthened when more water molecules are involved in the AE-(H<sub>2</sub>O)<sub>4</sub> complex. In addition, an intramolecular OH1<sup>AE...N</sup><sup>AE</sup> H-bond is not found in other AE-(H<sub>2</sub>O)<sub>4</sub> complexes (AE-4W-1, AE-4W-2, AE-4W-3, AE-4W-4, and AE-4W-6), due to substantial deformations in these complexes.

For some complexes (AE-4W-1, AE-4W-4, and AE-4W-5), each water molecule formed at least one intermolecular H-bond with other water molecules. For other complexes (AE-4W-2, AE-4W-6, AE-4W-7, and AE-4W-8), only three water molecules formed intermolecular H-bonds, and no H-bond formed between them and the fourth one. Two nearby water molecules formed H-bonds but did not hydrogen bond with other water molecules in AE-4W-3, in contrast to the above AE-(H<sub>2</sub>O)<sub>4</sub> complexes. The intermolecular OH<sup>water...N</sup><sup>AE</sup> H-bonds are the strongest H-bonds in some complexes (AE-4W-2, AE-4W-3, and AE-4W-6), which indicates that it is easier for the N atom than the O atom to accept a proton to form an intermolecular H-bond in these complexes. For other complexes (AE-4W-5, AE-4W-7, and AE-4W-8), the strongest intermolecular H-bond is the OH<sup>water...O</sup><sup>water</sup> H-bond formed between two water molecules, which is



still weaker than the above  $\text{OH}^{\text{water}}\cdots\text{N}^{\text{AE}}$  H-bonds. In addition, the intermolecular  $\text{OH}^{\text{water}}\cdots\text{O}^{\text{water}}$  H-bond has a similar strength to the  $\text{OH}^{\text{water}}\cdots\text{N}^{\text{AE}}$  H-bond in AE-4W-1, as are the strengths of the multiple H-bonds that are formed between the hydroxyl of AE/water and the O atom of AE/water in AE-4W-4. The  $\rho_b$  value of the strongest H-bond in each of the complexes except for AE-4W-7 and AE-4W-8 are above the upper limit proposed by Koch and Popelier, which indicates that this bond has partial covalent character. In particular, the  $\text{OH}^{\text{A}}\cdots\text{N}^{\text{AE}}$  H-bonds in both AE-4W-3 and AE-4W-6 are the two strongest H-bonds among all of the complexes, and have  $\rho_b$  values of 0.05398 and 0.05325 a.u., respectively, which indicates significant covalent character. In addition, the H-bonds that use methylene as the H-donor are still the weakest ones; they do not strengthen with the strengthening of other H-bonds, and partial van der Waals interaction character is attributed to them.

### Many-body interaction analysis

The role of hydrogen-bonding interactions in  $\text{AE}-(\text{H}_2\text{O})_n$  ( $n = 1-4$ ) complexes was analyzed quantitatively through the energy decomposition scheme mentioned in the “Many-body interaction analysis” section. The relaxation energy,  $n$ -body interaction energies and binding energies are listed in Table 5. As shown in Table 5, among the  $\text{AE}-\text{H}_2\text{O}$  complexes, AE-1W-1 is the most stable complex since it involves the lowest binding energy ( $E_{\text{bind}}$ ) of  $-9.91 \text{ kcal}\cdot\text{mol}^{-1}$ , while the stability of AE-1W-4 ( $E_{\text{bind}}$  of  $-6.87 \text{ kcal}\cdot\text{mol}^{-1}$ ) is the worst among the four  $\text{AE}-\text{H}_2\text{O}$  complexes. Aside from hydrogen-bonding interactions, structural deformation can affect the stability of  $\text{AE}-(\text{H}_2\text{O})_n$  complexes, as shown by the relaxation energy ( $E_{\text{relaxation}}$ ). The scission of the intramolecular  $\text{OH}^{\text{AE}}\cdots\text{N}^{\text{AE}}$  H-bond in AE-1W-1 leads to significant deformation, with  $E_{\text{relaxation}}$  values as large as  $1.68 \text{ kcal}\cdot\text{mol}^{-1}$ , which counteract the strong hydrogen bonding to a large extent. A similar degree of deformation also occurs in AE-1W-2, which is responsible for the large  $E_{\text{relaxation}}$  value of  $1.55 \text{ kcal}\cdot\text{mol}^{-1}$ . However, the deformations of both AE-1W-3 and AE-1W-4 are slight because the intramolecular  $\text{OH}^{\text{AE}}\cdots\text{N}^{\text{AE}}$  H-bond is retained. Therefore, because of the strong proton-donating/accepting ability of water, AE tends to break its intramolecular H-bond and form two new intermolecular H-bonds with water molecules via the hydroxyl group (H-donor) and the nitrogen of the amino group (H-acceptor).

For  $\text{AE}-(\text{H}_2\text{O})_2$  complexes, the major contributions to  $E_{\text{bind}}$  are the two-body energies  $E(2B)$ , while the three-body energies  $E(3B)$  are in favor of binding, except in the case of AE-2W-9. Moreover, for some complexes (AE-2W-3, AE-2W-4 and AE-2W-6), the absolute values of  $E(3B)$  are

larger than those of other  $\text{AE}-(\text{H}_2\text{O})_2$  complexes, which can be partially attributed to increased hydrogen bonding among the water molecules. AE-2W-1 is the most stable complex since it involves the lowest  $E_{\text{bind}}$  of  $-19.85 \text{ kcal}\cdot\text{mol}^{-1}$ , and it is also the complex that suffers the greatest deformation, with a  $\Delta E_{\text{relaxation}}$  value of  $2.26 \text{ kcal}\cdot\text{mol}^{-1}$ . Except in the case of AE-2W-1, large deformations of other complexes (AE-2W-2, AE-2W-5 and AE-2W-7) cause the scission of the intramolecular  $\text{OH}^{\text{AE}}\cdots\text{N}^{\text{AE}}$  H-bond, and their  $\Delta E_{\text{relaxation}}$  values are larger than about  $1.50 \text{ kcal}\cdot\text{mol}^{-1}$ . For the other  $\text{AE}-(\text{H}_2\text{O})_2$  complexes, the small  $\Delta E_{\text{relaxation}}$  values (less than  $0.70 \text{ kcal}\cdot\text{mol}^{-1}$ ) result in only slight deformations, since the intramolecular  $\text{OH}^{\text{AE}}\cdots\text{N}^{\text{AE}}$  H-bond is retained. The smallest  $\Delta E_{\text{relaxation}}$  value of  $-0.48 \text{ kcal}\cdot\text{mol}^{-1}$  was found for AE-2W-8, which is also the complex with the lowest stability.

For both  $\text{AE}-(\text{H}_2\text{O})_3$  and  $\text{AE}-(\text{H}_2\text{O})_4$  complexes, the scission of the intramolecular  $\text{OH}^{\text{AE}}\cdots\text{N}^{\text{AE}}$  H-bond in some complexes results in large deformations and  $\Delta E_{\text{relaxation}}$  values of more than  $1.3 \text{ kcal}\cdot\text{mol}^{-1}$ . The smaller  $\Delta E_{\text{relaxation}}$  values of other complexes indicate that they are slightly deformed and that the intramolecular  $\text{OH}^{\text{AE}}\cdots\text{N}^{\text{AE}}$  H-bond is retained. The most stable  $\text{AE}-(\text{H}_2\text{O})_3$  and  $\text{AE}-(\text{H}_2\text{O})_4$  complexes are AE-3W-2 and AE-4W-1, respectively, in which the intramolecular  $\text{OH}^{\text{AE}}\cdots\text{N}^{\text{AE}}$  H-bond is destroyed. Therefore, AE tends to break the intramolecular H-bond and form more intermolecular H-bonds when it meets water molecules. For both  $\text{AE}-(\text{H}_2\text{O})_3$  and  $\text{AE}-(\text{H}_2\text{O})_4$  complexes, the major contributions to  $E_{\text{bind}}$  come from  $E(2B)$  and  $E(3B)$ , which are all in favor of binding, while the four- and five-body energies are very small and their contributions to the binding energies can be ignored. The order of the  $n$ -body interaction energies in all complexes is:  $E(2B) > E(3B) > E(4B) > E(5B)$ .

In general, the changing conformation results in significant deformation, as demonstrated by the relaxation energy ( $E_{\text{relaxation}}$ ); see for example AE-2W-1, AE-3W-2, AE-3W-6, AE-4W-1, and AE-4W-4. However, as shown in Table 5, some complexes (AE-1W-1, AE-1W-2, AE-2W-7, AE-3W-1, AE-3W-9, and AE-4W-3) with larger values of  $E_{\text{relaxation}}$  retain the g'Gg' conformer of the AE moiety because the intramolecular  $\text{OH}^{\text{AE}}\cdots\text{N}^{\text{AE}}$  H-bond is replaced with two intermolecular H-bonds that form between one water molecule and the hydroxyl and amino groups of AE simultaneously.

### Conclusions

The microsolvation of AE with water molecules was investigated at the  $\omega\text{B97XD}/6-311++\text{G}(2\text{d},2\text{p})$  level. The geometries and energies of the hydrogen bonds were systematically investigated. QTAIM analyses were per-

**Table 5** Many-body (two-, three-, four- and five-body) interaction energies for AE-(H<sub>2</sub>O)<sub>n</sub> (*n* = 1–4) complexes using the ωB97XD/6-311++G(2d,2p) level. All energies are in kcal·mol<sup>-1</sup> and are BSSE corrected

Complex	<i>E</i> <sub>relaxation</sub>	<i>E</i> (2B)	<i>E</i> (3B)	<i>E</i> (4B)	<i>E</i> (5B)	<i>E</i> <sub>bind</sub>
AE-1W-1	1.68	-11.60				-9.91
AE-1W-2	1.55	-8.54				-6.99
AE-1W-3	-0.21	-7.49				-7.70
AE-1W-4	-0.21	-6.66				-6.87
AE-2W-1	2.26	-20.92	-1.19			-19.85
AE-2W-2	1.86	-19.00	-1.66			-18.80
AE-2W-3	0.70	-16.73	-2.54			-18.56
AE-2W-4	0.44	-16.04	-2.83			-18.42
AE-2W-5	1.49	-17.91	-0.52			-16.94
AE-2W-6	-0.32	-14.40	-2.24			-16.96
AE-2W-7	1.54	-15.08	-0.31			-13.85
AE-2W-8	-0.48	-13.78	-0.23			-14.49
AE-2W-9	-0.18	-13.89	0.35			-13.72
AE-2W-10	-0.40	-10.12	-0.22			-10.74
AE-3W-1	3.30	-27.73	-4.53	-0.15		-29.11
AE-3W-2	1.67	-28.96	-3.37	0.01		-30.66
AE-3W-3	1.44	-27.20	-4.60	-0.27		-30.63
AE-3W-4	-0.01	-23.11	-5.13	-0.40		-28.64
AE-3W-5	-0.09	-22.63	-5.50	-0.44		-28.66
AE-3W-6	2.55	-27.20	-2.44	0.00		-27.08
AE-3W-7	0.45	-22.71	-3.13	-0.08		-25.48
AE-3W-8	0.46	-23.46	-2.08	0.03		-25.05
AE-3W-9	1.70	-22.22	-2.02	0.02		-22.52
AE-3W-10	0.66	-20.32	-2.25	-0.04		-21.95
AE-3W-11	-0.16	-20.80	-1.73	0.00		-22.69
AE-3W-12	0.31	-19.49	-2.62	0.01		-21.79
AE-4W-1	3.82	-37.83	-9.11	-0.16	-0.01	-43.30
AE-4W-2	1.26	-33.97	-6.95	-0.64	-0.01	-40.30
AE-4W-3	2.49	-35.26	-5.62	-0.09	0.00	-38.48
AE-4W-4	1.51	-31.34	-7.61	-0.59	-0.01	-38.03
AE-4W-5	-0.53	-30.63	-6.40	-0.14	0.01	-37.70
AE-4W-6	1.38	-30.55	-4.99	-0.24	0.01	-34.39
AE-4W-7	0.06	-30.08	-4.81	-0.33	-0.01	-35.17
AE-4W-8	0.10	-29.69	-4.48	-0.36	0.00	-34.42

formed in order to elucidate the nature of the hydrogen bonding in these complexes. Unlike the AE monomer in the gas phase, the intramolecular OH1<sup>AE</sup>...N<sup>AE</sup> H-bond is not seen in the most stable AE-(H<sub>2</sub>O)<sub>n</sub> (*n* = 1–4) complexes, which indicates that AE tends to break its intramolecular OH1<sup>AE</sup>...N<sup>AE</sup> H-bond and form intermolecular H-bonds with water molecules, whereas the complexes that retain the intramolecular OH1<sup>AE</sup>...N<sup>AE</sup> H-bond have less stability. According to the structural and QTAIM analyses, the intermolecular H-bonds that formed between the nitrogen atom of AE and the hydroxyl of water are the strongest ones for the most stable AE-(H<sub>2</sub>O)<sub>n</sub> (*n* = 1–4) complexes; moreover, they grow stronger

as *n* increases from 1 to 4, and they have partial covalent character. Many-body interaction analysis showed that the relaxation energy and the two-body and three-body energies make significant contributions to the binding energies of complexes, whereas the four-body and five-body energies are negligible. Thus, the hydrogen-bonding interactions between AE and water molecules play a key role in the conformations of AE and cause the scission of the intramolecular OH1<sup>AE</sup>...N<sup>AE</sup> H-bond, and the gauche conformer (g'Gg') of the AE moiety was retained by most of the AE-(H<sub>2</sub>O)<sub>n</sub> (*n* = 1–4) complexes. This research may help to enhance our understanding of the interactions of AE and other neurotransmitters with different solvent molecules.

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