

A study of *N*-methylacetamide in water clusters: Based on atom-bond electronegativity equalization method fused into molecular mechanics

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N-methylacetamide (NMA) is a very interesting compound and often serves as a model of the peptide bond. The interaction between NMA and water provides a convenient prototype for the solvation of the peptides in aqueous solutions. Here we present NMA-water potential model based on atom-bond electronegativity equalization method fused into molecular mechanics (ABEEM/MM) that is to take ABEEM charges of all atoms, bonds, and lone-pair electrons of NMA and water molecules into the electrostatic interaction term in molecular mechanics. The model has the following characters: (1) it allows the charges in system to fluctuate responding to the ambient environment; (2) for two major types of intermolecular hydrogen bonds, which are the hydrogen bond forming between the lone-pair electron on amide oxygen and the water hydrogen, and the one forming between the lone-pair electron on water oxygen and the amide hydrogen, we take special treatments in describing the electrostatic interaction by the use of the parameters $k_{\text{lpO}=\text{H}}$ and $k_{\text{lpO}-\text{HN}-}$, respectively. The newly constructed potential model based on ABEEM/MM is first applied to amide-water clusters and reproduces gas-phase state properties of $\text{NMA}(\text{H}_2\text{O})_n$ ($n=1-3$) including optimal structures, dipole moments, ABEEM charge distributions, energy difference of the isolated *trans*- and *cis*-NMA, interaction energies, hydrogen bonding cooperative effects, and so on, whose results show the good agreement with those measured by available experiments and calculated by *ab initio* methods. In order to further test the reasonableness of this model and the correctness and transferability of the parameters, many static properties of the larger NMA-water complexes $\text{NMA}(\text{H}_2\text{O})_n$ ($n=4-6$) are also studied including optimal structures and interaction energies. The results also show fair consistency with those of our quantum chemistry calculations. © 2006 American Institute of Physics. [DOI: 10.1063/1.2210940]

I. INTRODUCTION

The nature of the amide functional group has long been of fundamental interest because of its presence as a repeat unit in proteins and peptides. For understanding the structural properties and biological functions of proteins, it is important to know how they interact with an aqueous environment through the hydrogen bonds. *N*-methylacetamide (NMA), one of the simplest representative models for the main chain of proteins, has been extensively studied in this aspect. So far, the important structural information of NMA has been determined by some available experimental techniques,¹⁻⁸ such as gas-phase electron diffraction,¹ x-ray diffraction² in a crystal, etc.

To the best of our knowledge, the two major types of intermolecular hydrogen bonds⁹⁻¹¹ that occur in amide-water complexes are $\text{C}=\text{O}\cdots\text{H}-\text{O}-\text{H}$ and $\text{N}-\text{H}\cdots\text{OH}_2$, respectively. The former forms between the amide oxygen in NMA molecule and the water hydrogen; the latter forms between amide hydrogen and the water oxygen. Both are the key to the stabilities of the secondary and tertiary structures of protein in aqueous phase. These special types of nonbonded interactions have been studied by *ab initio*¹²⁻²⁰ and molecular mechanics methods.²⁰⁻³⁵ *Ab initio* calculations at different

levels of methods have been carried out for NMA-water systems, and can investigate intermolecular interaction, and yield theoretical structures and other static properties. Dixon *et al.*¹⁴ investigated the strengths of the hydrogen bonds between a water molecule and model amide (NMA) by using *ab initio* molecule orbital theory, and performed the extensive calculations at the MP2 level with correlation consistent basis sets. Han and Suhai¹⁵ studied the conformations, hydrogen bonding effects, and the stabilities of different methyl group orientations of isolated *trans*- and *cis*-NMA and of $\text{NMA}(\text{H}_2\text{O})_n$ ($n=1-3$) complexes, using all kinds of the density functional theory (DFT) functionals, such as B3LYP, BLYP, and basis set 6-311++G(*d,p*). Recently, in order to fit the hydrogen bonding parameters for the molecular mechanics force field MM4, Langley and Allinger²⁰ performed the calculations for the amide-water and formamide dimer systems at the MP2/6-311++G(2*d*,2*p*) level. Therefore, with computational power increasing, all the above *ab initio* results provide reliable references for us to construct a new NMA-water potential model. Because modeling of an aqueous environment requires knowledge of the intermolecular potentials for various interacting molecules, the construction of such potentials turns to be more and more necessary and important. Up to date, a majority part of potential functions for studying amide-water complex systems employ rigid po-

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tential models.^{20–30} Studies of combining quantum mechanical and molecular mechanical (QM/MM) simulations of *N*-methylacetamide in aqueous solution have been carried out to investigate the charge polarization of the solute and to explore the feasibility of hybrid QM/MM calculations using *ab initio* methods by Gao and Freindorf.³¹ In addition, the fluctuating charge models in combination with molecular mechanics have been widely developed in the past few years. For example, Rick and Berne³² and Rick *et al.*³³ have developed dynamical fluctuating charge (FQ) force field to study the aqueous solution of amides, Patel *et al.*³⁴ and Patel and Brooks³⁵ have developed CHARMM FQ force field, which is applied to the protein simulations, and based on the atom-bond electronegativity equalization method^{36–42} (ABEEM) fused into MM, and Yang *et al.*⁴³ and Wu and Yang⁴⁴ have reported the ABEEM-7P water model, which has been applied successfully to the water clusters,⁴³ ion-water clusters,⁴⁵ and their molecular dynamics simulations,^{44,46,47} and also have been engaged in the research on conformations of organic molecules and peptides^{48,49} in terms of ABEEM/MM, etc.

The primary aim of this work is to construct a new amide-water interaction potential model by means of the combination of ABEEM and MM, and to make an extensive investigation on the potential model. The essence of this potential model is to take ABEEM charges of all atoms, bonds, and lone-pair electrons of the system into the electrostatic interaction term in molecular mechanics. It has the following features: on the one hand, the combination of ABEEM and MM can well deal with the charge response when the geometry and ambient environment change; on the other hand, we give the special treatments of the two types of intermolecular hydrogen bonds in NMA-water clusters, the first one forming between the lone-pair electrons on amide oxygen and the water hydrogen, and the second one forming between the lone-pair electrons on the water oxygen and the amide hydrogen. This provides further understanding of the formation and properties of the hydrogen bonds. Through careful and extensive investigation of the static properties of NMA(H₂O)_{*n*} (*n*=1–6), we first test the newly constructed potential model.

The remainder of this article is organized as follows. In Sec. II, we describe the new potential model on the basis of the combination of the atom-bond electronegativity equalization method and molecular mechanics. In Sec. III, we elucidate the process of parameterization in detail. In Sec. IV, we give the results and discussion for NMA-water clusters. Finally, conclusion is given in Sec. V.

II. METHODOLOGY

Based on the combination of ABEEM and MM, the potential energy $E_{\text{ABEEM/MM}}$ of amide-water system is expressed as

$$E_{\text{ABEEM/MM}} = \sum_{\text{bonds}} E_b + \sum_{\text{angles}} E_\theta + \sum_{\text{torsions}} E_{\text{tors}} + \sum_{\text{imptors}} E_{\text{imptors}} + \sum_{\text{nonbonded}} (E_{\text{vdW}} + E_{\text{elec}}), \quad (1)$$

where E_b , E_θ , E_{tors} , E_{improper} , E_{vdW} , and E_{elec} stand for the energies of individual bond stretching, angle bending, dihedral angle torsion, improper torsion, van der Waals, and electrostatic interaction, respectively. This moment, the cross terms, such as stretch-bend coupling, stretch-torsion coupling, etc., are omitted in Eq. (1).

For an amide molecule, the harmonic potentials describing E_b and E_θ [(2a) and (2b)] are chosen in present treatment, and E_{tors} [(2c)] is almost always expressed as a cosine series expansion, and at the same time the energy term E_{imptors} [(2d)] of improper torsion is applied.

$$E_b(r) = k_r(r - r_{\text{eq}})^2, \quad (2a)$$

$$E_\theta(\theta) = f_\theta(\theta - \theta_{\text{eq}})^2, \quad (2b)$$

$$E_{\text{tors}} = \frac{1}{2}[\nu_1(1 + \cos \phi) + \nu_2(1 - \cos 2\phi) + \nu_3(1 + \cos 3\phi)], \quad (2c)$$

$$E_{\text{imptors}} = \nu(1 - \cos 2\phi). \quad (2d)$$

Here, k_r , f_θ , ν_1 , ν_2 , ν_3 , and ν represent the force constants of bond stretching, angle bending, dihedral angle torsion, and improper torsion, respectively. r_{eq} and θ_{eq} are used to denote the equilibrium values of the bond length and bond angle. r , θ , and ϕ stand for the actual values of bond lengths, bond angles, and dihedral angles. The nonbonded interactions existing in amide molecule are represented by a sum of the Lennard-Jones and Coulomb terms.

$$E_{\text{nb}} = \sum_{i \in \text{NMA}} \left\{ \sum_a \sum_b \varepsilon_{ia,ib} \left[\left(\frac{r_{\text{min}_{ia,ib}}}{r_{ia,ib}} \right)^{12} - 2 \left(\frac{r_{\text{min}_{ia,ib}}}{r_{ia,ib}} \right)^6 \right] f_{ia,ib} + \sum_c \sum_{d \geq c+6} k \frac{q_{ic}q_{id}}{R_{ic,id}} \right\}, \quad (3)$$

where standard combining rules are used,

$$\varepsilon_{a,b} = (\varepsilon_{aa}\varepsilon_{bb})^{1/2}, \quad r_{\text{min}_{a,b}} = \frac{1}{2}(r_{\text{min}_{a-a}} + r_{\text{min}_{b-b}}).$$

Furthermore, among all pairs of atoms ($a < b$) separated by three or more bonds, $f_{ia,ib} = 1.0$ except for intramolecular 1,4 interactions for which $f_{ia,ib} = 0.5$ in NMA molecule. For intramolecular electrostatic interactions, as far as all the site points of system are concerned, we consider interactions of the site points that have greater than or equal to 1,6 bonding relationships. Then in Eq. (3), q_{ic} and q_{id} are point charges, which have above the mentioned bonding relationship in NMA molecule. $R_{ic,id}$ is the distance between the site points c and d in molecule i , $k = 0.57$, which is an overall optimized correction coefficient.

For amide-water and water-water intermolecular interactions, viz.,

$$E_{\text{nb}} = \sum_i \sum_j \left\{ \sum_a \sum_b \varepsilon_{ia,jb} \left[\left(\frac{r_{\text{min}_{ia,jb}}}{r_{ia,jb}} \right)^{12} - 2 \left(\frac{r_{\text{min}_{ia,jb}}}{r_{ia,jb}} \right)^6 \right] + E_{\text{elec}} \right\}, \quad (4)$$

where the electrostatic interaction E_{elec} is taken from the last term of Eq. (A1) in the Appendix, in which the outline of ABEEM for describing NMA in water is detailed. This is the essence of ABEEM fused into MM, which is to take the ABEEM charges of all atoms, bonds, and lone-pair electrons

in system to the intermolecular electrostatic interactions term of MM.

In the present work, we still adopted the ABEEM-7P model to describe water properties. The ABEEM-7P model^{43,44} assumes that water molecule is composed of seven charge centers and allowed the vibration of bond length and bond angle. The Morse potential is used to represent the O–H bond stretching, the harmonic potential is employed to represent the H–O–H angle bending, and the Lennard-Jones interaction between water molecules involves oxygen-oxygen, hydrogen-hydrogen, and oxygen-hydrogen interactions. The detailed information concerning ABEEM-7P water can be found in Refs. 43 and 44.

Finally, when taking the last term of Eq. (A1), where i is not equal to j , into the force field Eq. (1), we obtain the energy expression based on ABEEM/MM,

$$\begin{aligned} E = & \sum_{\text{bonds} \in \text{NMA}} k_r (r - r_{\text{eq}})^2 + \sum_{\text{bonds} \in \text{H}_2\text{O}} D [e^{-2\alpha(r-r_{\text{eq}})} - 2e^{-\alpha(r-r_{\text{eq}})}] + \sum_{\text{angles}} f_{\theta} (\theta - \theta_{\text{eq}})^2 + \frac{1}{2} \sum_{\text{torsions}} [\nu_1 (1 + \cos \phi) + \nu_2 (1 \\ & - \cos 2\phi) + \nu_3 (1 + \cos 3\phi)] + \sum_{\text{imptors}} \nu (1 - \cos 2\phi) + \sum_{i \in \text{NMA}} \left[\sum_a \sum_b \varepsilon_{ia,ib} \left[\left(\frac{r_{\text{min}_{ia,ib}}}{r_{ia,ib}} \right)^{12} - 2 \left(\frac{r_{\text{min}_{ia,ib}}}{r_{ia,ib}} \right)^6 \right] f_{ia,ib} \right. \\ & \left. + \sum_c \sum_{d \geq c+6} k \frac{q_{ic} q_{id}}{R_{ic, id}} \right] + \sum_{i=1}^{N_{\text{mol}}} \sum_{j=1(\neq i)}^{N_{\text{mol}}} \left\{ \sum_a \sum_b \varepsilon_{ia,jb} \left[\left(\frac{r_{\text{min}_{ia,jb}}}{r_{ia,jb}} \right)^{12} - 2 \left(\frac{r_{\text{min}_{ia,jb}}}{r_{ia,jb}} \right)^6 \right] + \sum_{\substack{H \in i \text{ lp} \in j \\ H, \text{lp} \text{ in HBIR}}} k_{H, \text{lp}} (R_{iH, j(\text{lp})}) \frac{q_{iH} q_{j(\text{lp})}}{R_{iH, j(\text{lp})}} \right. \\ & \left. + k \left(\frac{1}{2} \sum_a \sum_b \frac{q_{ia} q_{jb}}{R_{ia, jb}} + \frac{1}{2} \sum_m \sum_k \frac{q_{im} q_{jk}}{R_{im, jk}} + \frac{1}{2} \sum_{a-b} \sum_{g-h} \frac{q_{i(a-b)} q_{j(g-h)}}{R_{i(a-b), j(g-h)}} + \frac{1}{2} \sum_{\sigma m=n} \sum_{\sigma k=l} \frac{q_{i(\sigma m=a)} q_{j(\sigma k=l)}}{R_{i(\sigma m=n), j(\sigma k=l)}} \right. \right. \\ & \left. \left. + \frac{1}{2} \sum_{\pi m=n} \sum_{\pi k=l} \frac{q_{i(\pi m=n)} q_{j(\pi k=l)}}{R_{i(\pi m=n), j(\pi k=l)}} + \frac{1}{2} \sum_{\text{lp}} \sum_{\text{lp}'} \frac{q_{i(\text{lp})} q_{j(\text{lp}')}}{R_{i(\text{lp}), j(\text{lp}')}} + \sum_a \sum_{g-h} \frac{q_{ia} q_{j(g-h)}}{R_{ia, j(g-h)}} + \sum_a \sum_m \frac{q_{ia} q_{jm}}{R_{ia, jm}} + \sum_a \sum_{\sigma m=n} \frac{q_{ia} q_{j(\sigma m=n)}}{R_{ia, j(\sigma m=n)}} \right. \right. \\ & \left. \left. + \sum_a \sum_{\pi m=n} \frac{q_{ia} q_{j(\pi m=n)}}{R_{ia, j(\pi m=n)}} + \sum_a \sum_{\substack{\text{lp} \\ (a \neq H, H \text{ in HBIR} \\ \text{and lp not in HBIR)}}} \frac{q_{ia} q_{j(\text{lp})}}{R_{ia, j(\text{lp})}} + \sum_m \sum_{a-b} \frac{q_{im} q_{j(a-b)}}{R_{im, j(a-b)}} + \sum_m \sum_{\sigma k=l} \frac{q_{im} q_{j(\sigma k=l)}}{R_{im, j(\sigma k=l)}} + \sum_m \sum_{\pi k=l} \frac{q_{im} q_{j(\pi k=l)}}{R_{im, j(\pi k=l)}} \right. \right. \\ & \left. \left. + \sum_m \sum_{\text{lp}} \frac{q_{im} q_{j(\text{lp})}}{R_{im, j(\text{lp})}} + \sum_{a-b} \sum_{\sigma m=n} \frac{q_{i(a-b)} q_{j(\sigma m=n)}}{R_{i(a-b), j(\sigma m=n)}} + \sum_{a-b} \sum_{\pi m=n} \frac{q_{i(a-b)} q_{j(\pi m=n)}}{R_{i(a-b), j(\pi m=n)}} + \sum_{a-b} \sum_{\text{lp}} \frac{q_{i(a-b)} q_{j(\text{lp})}}{R_{i(a-b), j(\text{lp})}} + \sum_{\sigma m=n} \sum_{\pi k=l} \frac{q_{i(\sigma m=n)} q_{j(\pi k=l)}}{R_{i(\sigma m=n), j(\pi k=l)}} \right. \right. \\ & \left. \left. + \sum_{\sigma m=n} \sum_{\text{lp}} \frac{q_{i(\sigma m=n)} q_{j(\text{lp})}}{R_{i(\sigma m=n), j(\text{lp})}} + \sum_{\pi m=n} \sum_{\text{lp}} \frac{q_{i(\pi m=n)} q_{j(\text{lp})}}{R_{i(\pi m=n), j(\text{lp})}} \right\}, \quad (5) \end{aligned}$$

in which q is the charge on every site point of system and R is the distance between sites. $R_{iH, j(\text{lp})}$ is the distance between the hydrogen atom belonging to molecule i and the lone-pair electron belonging to molecule j in the hydrogen bond

interaction region (HBIR). The parameter $k_{H, \text{lp}} (R_{iH, j(\text{lp})})$ is used to describe the electrostatic interaction between the hydrogen atom and the lone-pair electron. First of all, we use the ABEEM to compute the charges of all atoms, bonds, and

TABLE I. ABEEM parameters (χ^* , η^* , C , and D are the parameters in Eqs. (A2); the explanation concerning water molecule parameters is shown in Refs. 43 and 44; in NMA molecule, for the methyl H, the parameter C stands for $c_{\text{H,C-H}}$, for amide H, the parameter C stands for the $C_{\text{H,N-H}}$, for methyl C, the parameter C stands for the relationship between this atom and its directly connected bond, for the double bond atom C, the meanings of parameter C is the same as the methyl C, the parameter D stands for the relationship between this atom and its π bond, for the amide N and carbonyl oxygen atoms, the meanings of the parameters C and D are the same as the double bond atoms C, for an arbitrary the single bond or σ bond region of double bond, the parameter C stands for the relationship between this region and its directly connected atom which has the smaller atomic number than the other, the parameter D stands for the relationship between this bond and its directly connected atom which has the larger atomic number than the other, for the single bond C C, the value of the parameter C is equal to that of the parameter D , for an arbitrary π bond region of double bond or lone-pair electron, the parameter C stands for the relationship between this region and its connected atom: χ^0 is the Pauling electronegativity scale) of the NMA-H₂O system.

		χ^*	$2\eta^*$	C	D	χ^0
Water	H-	2.023	3.774	2.161		2.200
	O-	3.773	26.098	11.493	5.312	3.440
	H-O	5.136	24.767	2.161	11.493	
	lpO-	3.308	6.692	5.312		
NMA	H-	2.162	4.023	2.995		2.200
	H(NH-)	2.204	6.189	5.245		2.200
	C-	2.544	6.091	4.055		2.550
	C=	2.711	5.183	6.260	2.153	2.550
	N-	3.325	16.095	8.730	1.155	3.040
	O=	3.883	7.760	7.741	2.652	3.440
	C-H	3.468	6.625	2.995	2.935	
	N-H	3.722	6.955	5.245	3.997	
	C-C	3.795	7.465	2.285	2.285	
	C-N	3.401	10.495	3.055	3.325	
	$\sigma\text{C}=\text{O}$	3.827	12.248	3.524	7.741	
	$\sigma\text{C}-\text{N}$	3.769	5.608	2.027	1.730	
	$\pi\text{C}=\text{O}$	3.012	25.000	2.153		
	$\pi\text{O}=\text{O}$	3.855	80.960	2.652		
	$\pi\text{N}-\text{N}$	4.211	30.555	1.155		
lpO=	3.885	7.660	2.652			

lone-pair electrons, then we use Eq. (5) to compute the total energy of the system. When there is a change of bond length, bond angle, or dihedral angle, or a change of the relative position between the NMA and water molecules, we recalculate the charges by using the ABEEM from time to time, then recalculate the total potential energy by Eq. (5). Therefore, the combination of ABEEM and molecular mechanics (MM) cannot only truly reflect the electrostatic polarization by way of the fluctuating charges but also well describe the NMA-water interaction explicitly.

III. CALIBRATION OF PARAMETERS

A. The fitting of ABEEM parameters

Because the fitting of ABEEM parameters is a very key link to compute all the properties, it is desirable to determine the parameters in a suitable way so that they can be

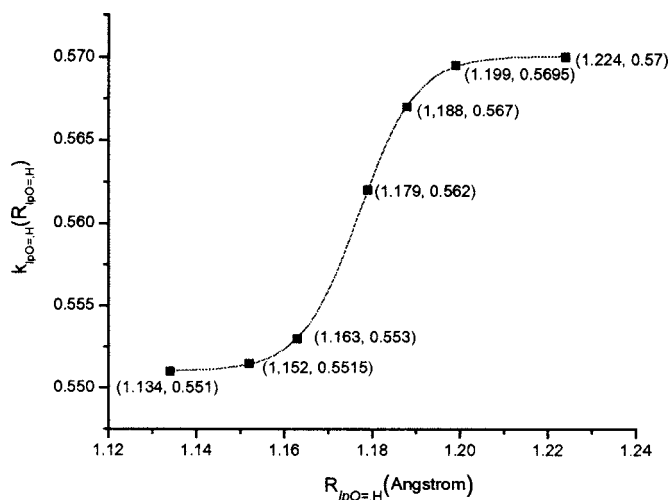


FIG. 1. The function $k_{\text{lpO}=\text{H}}(R_{\text{lpO}=\text{H}})$ relates to the distance between the lone-pair electron on the amide oxygen and the water hydrogen which will form the first type of hydrogen bond. The fitted data are in parentheses.

transferred from small NMA-water clusters to the larger NMA-water clusters and aqueous solution, and even to other biochemical systems. At first, the parameters χ^* , η^* , C , and D are fitted through a regression and least squares optimization procedure and listed in Table I including the Pauling electronegativity, where the scaling Pauling electronegativity unit is used. Compared with those of the previous MEEM and ABEEM,³⁶⁻⁴² the parameters for NMA molecule have been slightly changed. Previous parameters are fitted to calculate mainly single organic large molecules, such as $\text{C}_{24}\text{O}_2\text{N}_2\text{H}_{52}$, $\text{C}_{15}\text{O}_2\text{NH}_{33}$, and so on, whereas now the parameters are refitted to calculate the properties for an organic molecule in water system. Furthermore, now the parameters are fitted not only to reproduce the charges of *ab initio* calculation but also to fit the dipole moments, structures, and interaction energies given by experimental measurements and *ab initio* calculation results. As we have known, there are two types of hydrogen bonds between NMA and water molecules. The first is the hydrogen bond forming between the lone-pair electron on amide oxygen and the water hydrogen (i.e., $\text{lpO}=\cdots\text{H}-\text{O}$); the second is the hydrogen bond forming between the lone-pair electron on water oxygen and amide hydrogen (i.e., $\text{lpO}-\cdots\text{H}-\text{N}$). In order to well depict the nature of the two types of hydrogen bonds, we take the special treatments by introducing the parameters $k_{\text{lpO}=\text{H}}(R_{\text{lpO}=\text{H}})$, and $k_{\text{lpO}-,\text{HN}-}(R_{\text{lpO}-,\text{HN}-})$ to describe the electrostatic interactions of the two types of hydrogen bonds. It is very important to include the effects of hydrogen bonding in molecular simulations based on classical force fields if one hopes to reproduce and explain a wide range of chemical phenomena. The two parameters $k_{\text{lpO}=\text{H}}(R_{\text{lpO}=\text{H}})$ and $k_{\text{lpO}-,\text{HN}-}(R_{\text{lpO}-,\text{HN}-})$, and previous hydrogen bond parameter $k_{\text{lpO}-,\text{H}}(R_{\text{lpO}-,\text{H}})$ (Refs. 43 and 44) in pure water system are all included in the parameter $k_{\text{H,lp}}(R_{\text{H,j(lp)}})$ which is extracted from k in Eq. (5), and the correction factor k is the same value of 0.57 as in the MEEM and previous ABEEM.³⁶⁻⁴² The fitted expressions of $k_{\text{lpO}=\text{H}}(R_{\text{lpO}=\text{H}})$ and $k_{\text{lpO}-,\text{HN}-}(R_{\text{lpO}-,\text{HN}-})$ are expressed as follows:

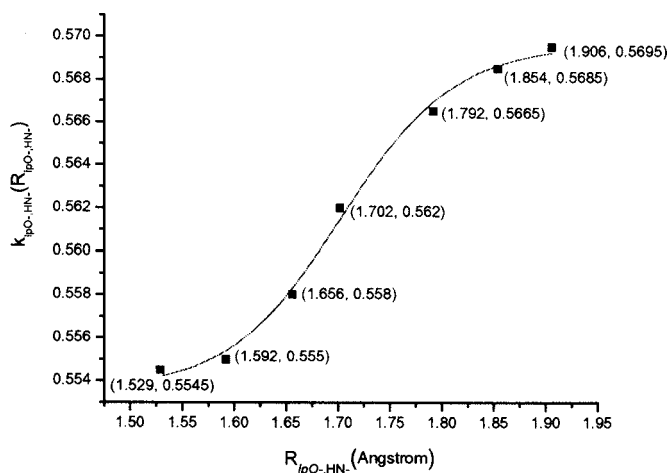


FIG. 2. The function $k_{lpO-HN-}(R_{lpO-HN-})$ relates to the distance between the lone-pair electron on the water oxygen and the amide hydrogen which will form the second type of hydrogen bond. The fitted data are in parentheses.

$$k(P_{lpO=H}) = 0.570 - \frac{0.019}{1 + \exp[(R_{lpO=H} - 1.177)/0.007]}, \quad (6a)$$

$$k(R_{lpO-,NH-}) = 0.570 - \frac{0.016}{1 + \exp[(R_{lpO-,NH-} - 1.704)/0.055]}. \quad (6b)$$

The corresponding plots of $k_{lpO=H}(R_{lpO=H})$ and $k_{lpO-,NH-}(R_{lpO-,NH-})$ are given in Figs. 1 and 2, respectively.

B. The force field parameters for ABEEM/MM

For the force field parameters of the bond stretching and angle bending in NMA molecule, we adopt the parameters of OPLS/AA force field based on the following considerations. Firstly, the experimental data from the literatures¹⁻⁸ are not complete, and we also recognize that different experimental techniques might provide different “equilibrium” values, especially when the experiments are performed at different temperatures. Secondly, the bond-stretching and angle-bending terms are often regarded as “hard” degrees of freedom, in which quite substantial energies are required to cause significant deformations from their reference values. Thus, the force field parameters of some bond and angle can be transferred from one force field to another force field. For example, for some bond and angle in the amide system, the same force constants, equilibrium bond lengths, and bond angles are used in both AMBER (Refs. 50 and 51) and OPLS/AA (Refs. 52 and 53) force fields.

In contrast to the bond-stretching and angle-bending terms, the torsion terms are often regarded as “soft” degrees of freedom, in which most of the variation in structure and relative energies is due to the complex interplay between the torsional and nonbonded contributions. In our model for NMA-water system, we take the torsion and improper

torsion parameters of OPLS/AA as a reference and refit those through the least square optimization procedure in order to make the interaction energies of the structures of NMA-water clusters be in good agreement with those from our *ab initio* calculations and also make the energy difference of isolated conformers be in agreement with the experimental data.⁸

In addition, the Lennard-Jones parameters are very necessary to be adjusted to reproduce clusters interaction energies for small NMA-water clusters. The parameters of torsion, improper torsion, and Lennard-Jones are all summarized in Ref. 54.

For water in the NMA-water system, the ABEEM force field parameters originate from the ABEEM-7P model,^{43,44} in which we consider a transferable intermolecular potential of seven points fluctuating charge model for a water molecule. In Eq. (5), at the equilibrium geometry of a water molecule, the bond length of O–H and the bond angle of H–O–H are set to their experimental values, 0.9572 Å and 104.52°, respectively, and the lone pair center is 0.74 Å far from the oxygen nucleus and with an intervening angle of 109.47°, and the O–H bond dissociation energy D is 529.6 kcal/mol and the angle force constant f_θ is 34.05 kcal/mol deg² for water molecule. All these parameters are directly transferred to the present work without any modification to compute various static properties of NMA-water clusters. Then, in this way, the ABEEM-7P model and its parameters are further tested.

IV. RESULTS AND DISCUSSION

In this section, we first present the properties including the equilibrium geometries, ABEEM charge distributions, dipole moments, etc., for isolated NMA. Then we compute several properties of NMA-water clusters $NMA(H_2O)_n$ ($n = 1-3$), such as optimized geometries, ABEEM charge distributions, dipole moments, interaction energies, and the hydrogen bonding cooperative effects. We make a clear comparison with the available experimental data, *ab initio* calculations, and other force field results. It is noteworthy that we focus here only on the hydrogen-bonded complexes of NMA and water because our primary aim of this work is to construct and test the NMA-water potential model and fit the parameters from the static properties available from experimental and *ab initio* data, and then to apply them to the larger NMA-water complexes and aqueous solution in the future rather than to search the lowest energy conformations of small NMA-water complexes. Finally, in order to test and verify the fitted parameters, we transfer them to the research of the larger NMA-water complexes. In the previous literatures, unfortunately, calculations on $NMA(H_2O)_n$ for $n = 4-6$ at any basis set sizes have not been reported. Therefore, we have carried out quantum chemistry calculations at the MP2/6-311++G(2d,2p)//MP2/6-31++G(d,p) level with counterpoise correction for NMA-water complexes.

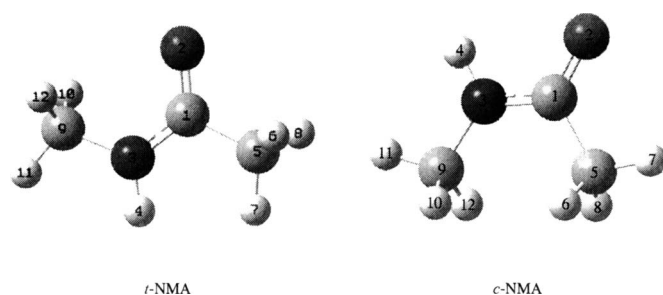


FIG. 3. The conformers of isolated NMA.

A. Properties of isolated *trans*- and *cis*-NMA

Previous *ab initio* studies¹² showed that the lowest energy conformation for NMA is nonplanar structure, but the energy difference between the lowest energy conformations of the planar and nonplanar structures is generally very small. Furthermore, hydrogen bonding of NMA to other molecules (e.g., water or formamide) moves the nonplanar minimum toward the planar conformation. This shows that the structure of C_s symmetry for NMA is satisfactory for studying the hydrogen bonding of NMA. Isolated *t*-NMA and *c*-NMA structures with C_s symmetry are presented in Fig. 3,

where *t*-NMA structure has the methyl group orientations of $\Phi=180^\circ$ and $\Psi=0^\circ$. $\Phi=180^\circ$ means that one of the hydrogen atoms (H11, which is on the C9–N3–C1–C5 plane) in the (N)CH₃ group is *trans* to the N3–C1 bond, and $\Psi=0^\circ$ means that one hydrogen (H7, also on the C9–N3–C1–C5 plane) of the (C)CH₃ group is *cis* to the N3–C1 bond. Isolated *c*-NMA structure has the methyl group orientation of $\Phi=\Psi=180^\circ$.

Table II presents the internal geometries of isolated NMA from ABEEM/MM model calculations, experimental,^{1,2,6} and *ab initio* calculations. Comparison of the structures for *t*-NMA shows satisfactory agreement for bond lengths, bond angles, and torsional angles. The most obvious discrepancy occurs for the C1–N3 bond length, i.e., the bond length for ABEEM/MM model is 1.3284 Å versus the value of 1.290 Å for x-ray diffraction experimental data. As discussed by Guo and Karplus,¹² the bond length of C1–N3 (1.290 Å) obtained in a crystal by x-ray diffraction seems too short. Upon going from the *trans* to the *cis* conformer, ABEEM/MM force field reproduces predicted changes as in the *ab initio* B3LYP(BLYP)/6-311++G(*d,p*) structures for a majority of bond lengths and bond angles except for the C1–N3 bond, i.e., our calculated bond length is 1.3332 Å, a bit shorter than the values of *ab initio*

TABLE II. Comparison of the geometries of isolated NMA.

	<i>t</i> -NMA					<i>c</i> -NMA		
	ABEEM/MM	<i>ab initio</i> ^a	Expt. ^b	Expt. ^c	Servey ^d	ABEEM/MM	B3LYP ^a	BLYP ^e
Bond lengths (Å)								
N3–C9	1.4436	1.4558	1.465(13)	1.469(6)	1.45(2)	1.4610	1.4543	1.4677
C1–N3	1.3284	1.3642	1.290(13)	1.386(4)	1.33(1)	1.3332	1.3695	1.3828
O2–C1	1.2301	1.2216	1.236(12)	1.225(3)	1.23(1)	1.2366	1.2215	1.2348
C1–C5	1.5199	1.5191	1.536(16)	1.520(5)	1.52(1)	1.5196	1.5180	1.5307
H4–N3	1.0038	1.0060				1.0022	1.0095	1.0176
H–C	1.0889	1.0919		1.107(5)		1.0896	1.0925	1.0091
Bond angles (degree)								
C1–N3–C9	121.49	121.45	120.0	119.7(8)	122(1)	126.63	127.18	127.54
O2–C1–N3	122.90	121.89	123.0	1218(4)	123(1)	122.23	121.25	121.09
C5–C1–N3	116.90	116.06	116.5	114.1(5)	116(2)	116.92	116.32	116.34
C5–C1–O2	120.20	122.05	120.5	124.1(15)	121(4)	120.85	122.44	122.57
H4–N3–C1	120.12	119.35	119.5	110.0(50)		115.44	114.04	113.87
H–C–H ^f	108.60	108.66		110.4(20)		108.49	108.33	108.30
Torsional angles (degree)								
H7–C5–C1–N3	0.0	0.0	0.0	180.0 ^f				
H6–C5–C1–N3	120.9	121.66						
C5–C1–N3–C9	180.0		180.0	180.0				
C1–N3–C9–H11	180.0	180.0	180.0	18.0 ^f				
C1–N3–C9–H10	59.77	59.86						
O2–C1–N3–H5	180.0		180.0	180.0				

^aGeometry optimization in calculating the bond lengths and bond angles was performed at the B3LYP/6-311++G(*d,p*) level taken from Ref. 5, but geometry optimization during comparing the torsional angles was performed at the MP2/6-31G^a level taken from Ref. 2.

^bReference 2: *t*-NMA geometries determined in a crystal by x-ray diffraction. Standard deviations are also in parentheses (unit is 0.001 Å).

^cReference 1: isolated *t*-NMA geometries obtained from gas-phase electron diffraction. Standard deviations are also in parentheses.

^dReference 6.

^eReference 15: geometry optimization at the BLYP/6-311G(*d,p*) level.

^fAssumed values.

TABLE III. The charge distributions (The geometries are in Fig. 3. q_{C1} , q_{O2} , q_{N3} , and q_{H4} are the charges on the site of the carbonyl C, carbonyl O, amide N, and amide H of peptide bond: q_{C5} , q_{H6} , q_{H7} , and q_{H8} are the charges of atoms on (C)CH₃: q_{C9} , q_{H10} , q_{H11} , and q_{H12} are charges of the atoms on (N)CH₃: $q_{\sigma C=O}$, $q_{\sigma C-N}$, q_{C-C} , q_{C-N} , and q_{H-C} are the bond charges on the sites of the ratio of covalent atomic radii of the directly bonded atoms: q_{lpO} is the charge on the site 0.74 Å from the amide O, $q_{\pi C=}$, $q_{\pi O=}$; and $q_{\pi N-}$ are the charges of π bond region of double bond atoms C, O, and amide N.) for isolated NMA by the ABEEM/MM model.

	<i>t</i> -NMA	<i>c</i> -NMA		<i>t</i> -NMA	<i>c</i> -NMA		<i>t</i> -NMA	<i>c</i> -NMA
q_{C1}	0.6653	0.6680	q_{H12}	0.2306	0.2014	q_{H12-C9}	-0.2863	-0.2924
q_{O2}	-0.0597	-0.0529	$q_{\sigma C1=O2}$	-0.1439	-0.1461	q_{lpO2}	-0.1704	-0.1632
q_{N3}	0.4111	0.4096	$q_{\sigma C1-N3}$	-0.1682	-0.1619	q_{lpO2}	-0.1647	-0.1644
q_{H4}	0.5937	0.6174	q_{C1-C5}	-0.2316	-0.2351	$q_{\pi C1=}$	-0.0105	-0.0099
q_{C5}	0.4076	0.4063	q_{C1-N3}	-0.1464	-0.1522	$q_{\pi C1=}$	-0.0105	-0.0099
q_{H6}	0.2143	0.1945	q_{H4-N3}	-0.8020	-0.7992	$q_{\pi O2=}$	-0.0104	-0.0101
q_{H7}	0.1818	0.2338	q_{H6-C5}	-0.2891	-0.2956	$q_{\pi O2=}$	-0.0104	-0.0101
q_{H8}	0.2143	0.1945	q_{H7-C5}	-0.2981	-0.2860	$q_{\pi N3-}$	-0.0313	-0.0310
q_{C9}	0.3750	0.3852	q_{H8-C5}	-0.2891	-0.2956	$q_{\pi N3-}$	-0.0313	-0.0310
q_{H10}	0.2306	0.2014	q_{H10-C9}	-0.2863	-0.2924			
q_{H11}	0.2058	0.2134	q_{H11-C9}	-0.2899	-0.2862			

calculations,¹⁵ 1.3695 and 1.3828 Å, respectively. Though difference of this bond length is larger than those of others, this distinction might arise partly from the different theory levels and the basis sets used in *ab initio* calculations. It is interesting that the bond length of 1.338 Å for C1–N3 of CHARMM structure²³ is in good agreement with ours.

The ABEEM/MM model makes a full consideration on the conformational changes and gives the explicitly quantitative charges of all molecular regions, such as atoms, single bonds, σ and π bond regions of double bonds, and lone-pair electrons. The charges of the isolated *t*-NMA and *c*-NMA calculated by the ABEEM/MM model are listed in Table III, from which we can see the following features: (1) the positive charges located on all the atoms (including all the single bond atoms and double bond atoms) are balanced by the negative charges located on the amide oxygen atom, all the bonds (including all the single bonds and σ and π bond regions of double bonds), and all the lone-pair electrons. (2) The charge distributions of isolated *t*- and *c*-NMA are very different from each other, which is mainly due to the intramolecular environment changes. This is the merit of our ABEEM/MM fluctuating charge model, i.e., charges fluctuating upon the ambient environment. In addition, the dipole moments of the two conformers are 3.62 and 3.81 D for the ABEEM/MM model, respectively, and are presented in Table IV as well as the comparison with experimental data and

other force field results. Seen from Table IV, satisfactory result is obtained, i.e., the *cis* conformer has a slightly higher dipole moment than the *trans* conformer, which is also found in other electronic structure calculations,^{17–19,21} for example, Radzicka *et al.*,¹⁷ and Jorgensen and Gao²¹ both gave 4.03 D for *trans* and 4.21 D for *cis*, whereas Tannor *et al.*¹⁹ gave 3.78 D for *trans* and 3.96 D for *cis*. These studies showed that the dipole moment changes with conformation for two reasons: the location of the point charges changes, and the point charges change in magnitude because of charge redistribution. Many studies have shown that the *cis* isomer of NMA is less stable than the *trans* isomer of NMA.⁵⁵ An experimental NMR measurement estimates the energy difference to be 2.8 kcal/mol,⁸ and our result is 2.77 kcal/mol in accord with the experimental data. These results show that our ABEEM/MM potential model can correctly predict and reflect many static properties for the isolated NMA.

B. Properties of NMA(H₂O)_n (*n*=1–3) clusters

1. Optimal structures

Seven *t*-NMA-water complexes and five *c*-NMA-water complexes with *C_s* symmetries have been studied here. The water positions in *t*- and *c*-NMA-water complexes are illus-

TABLE IV. ABEEM/MM results for *cis*- and *trans*-NMA for the dipole moments in debye of the gas phase.

	ABEEM/MM	FQ ^a	Radzicka ^b	Tannor ^c	GDAC ^d	Expt. ^e	Expt. ^f
<i>trans</i> -NMA	3.62	3.58	4.03	3.78	3.67	3.71	3.73
<i>cis</i> -NMA	3.81	3.77	4.21	3.96			

^aReference 32.

^bReference 17.

^cReference 19.

^dReference 25: the geometry-dependent net atomic charges (GDAC) method is extended from the modified partial equalization of orbital electronegativity (MPEOE) method.

^eReference 58.

^fReference 7: the Boltzmann weighted average of the dipole moments of the *cis* and *trans* conformers (which consist mainly of the *trans* form) of NMA in the gas phase is 3.73 D.

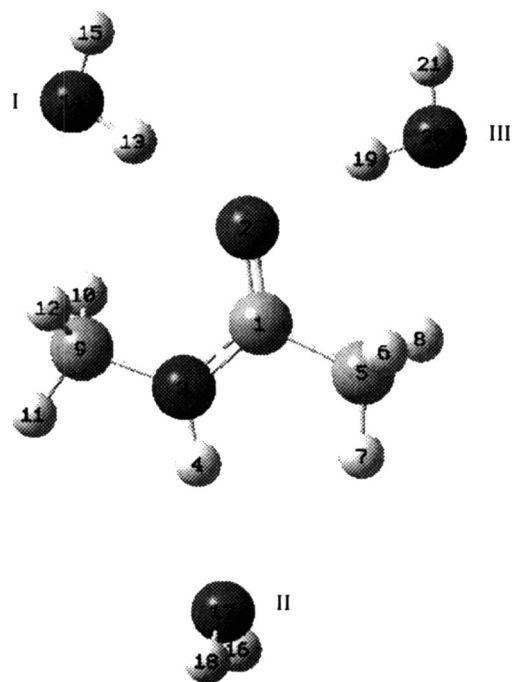


FIG. 4. Atom labels for *t*-NMA with $\Phi=180^\circ$ (H11–C9 *trans* to C1–N3) and $\Psi=0^\circ$ (H7–C5 *cis* to C1–N3). Three water positions for forming *t*-NMA-water complexes are shown.

trated in Figs. 4 and 5, respectively. *trans*-NMA with $\Phi=180^\circ$ and $\Psi=0^\circ$ is shown in Fig. 4 with three possible positions (I–III) for forming a hydrogen bond (or simply H bond). (1) One water interacting with the C=O of the NMA at position I, i.e., the C=O \cdots H hydrogen bond eclipsing the C–N bond. We call this complex T_I . (2) One water interacting with the NH group of the NMA at position II. We call it T_{II} . (3) One water interacting with the C=O of the NMA at position III, i.e., the C=O \cdots H hydrogen bond *trans* to the C–N bond. We call it T_{III} . (4) One water interacting with the C=O at position I and another water interacting with the N–H group at position II. We call this complex $T_{I,II}$. (5) Two waters interacting with the C=O at positions I and III. We

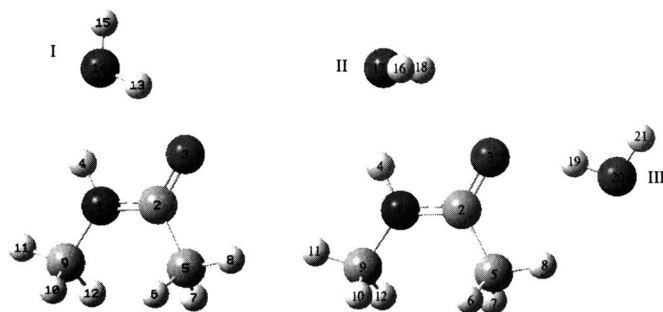


FIG. 5. *c*-NMA with $\Phi=180^\circ$ (H11–C9 *trans* to C1–N3) and $\Psi=180^\circ$ (H7–C5 *trans* to C1–N3). H bonds forming positions with water are shown.

call this complex $T_{I,III}$. (6) One water interacting with the N–H group at position II and another water interacting with the C=O at position III. We call this complex $T_{II,III}$. (7) Two waters interacting with the C=O at positions I and III, and one water interacting with the N–H group at position II. We call this complex $T_{I,II,III}$.

For the *c*-NMA complexes, the optimal structures from ABEEM/MM potential model are similar to those of Dixon *et al.*,¹⁴ Han and Suhai,¹⁵ and MirKin and Krimm.¹⁶ Here we studied three one-water *c*-NMA complexes: C_I , C_{II} , and C_{III} , whose water positions are shown in Fig. 5. Two *c*-NMA + 2H₂O complexes are studied here. They are conformers $C_{I,III}$ and $C_{II,III}$. The unique feature in C_I and $C_{I,III}$ is that one water molecule can act as an acceptor and a donor simultaneously and form two hydrogen bonds with the N–H and C=O groups of *c*-NMA. All the studied *c*-NMA structures in our complexes have the methyl group orientations of $\Phi=\Psi=180^\circ$.

Six different configurations for the NMA-water dimer are T_I , T_{II} , T_{III} , C_I , C_{II} , and C_{III} , which all have C_s symmetries. The calculated equilibrium geometries (such as H bond lengths and H bond angles) are listed in Table V. The ABEEM/MM hydrogen bonding equilibrium geometries values for C=O \cdots H–O–H bonds and N–H \cdots OH₂ bonds are a bit longer than those of our *ab initio* calculations at the

TABLE V. Calculated hydrogen bonding geometries (bond lengths are in angstroms and angles are in degrees) in NMA-water dimers.

Dimer ^a	Geometry	C=O \cdots H–O–H bond				N–H \cdots OH ₂ bond			
		<i>l</i> O \cdots H	θ C=O \cdots H	θ O \cdots H–O	<i>l</i> O \cdots O	<i>l</i> H \cdots O	θ N–H \cdots O	θ H \cdots O–H	<i>l</i> N \cdots O
T_I	ABEEM/MM	1.911	132.8	174.4	2.871				
	MP2 ^b	1.894	133.7	174.5	2.865				
T_{II}	ABEEM/MM					2.040	179.7	126.2	3.049
	MP2 ^b					2.015	179.2	126.4	3.025
T_{III}	ABEEM/MM	1.883	113.9	166.3	2.829				
	MP2 ^b	1.875	112.5	166.7	2.834				
C_I	ABEEM/MM	1.893	110.1	149.6	2.771	2.060	142.0	79.2	2.922
	MP2 ^b	1.876	110.7	149.7	2.766	2.052	142.7	79.3	2.924
C_{II}	ABEEM/MM					2.120	149.4	88.2	3.030
	MP2 ^b					2.109	150.4	88.3	3.034
C_{III}	ABEEM/MM	1.876	117.1	165.7	2.825				
	MP2 ^b	1.872	116.1	165.9	2.828				

^aThe geometries are in Figs. 4 and 5.

^bAt the MP2/6-31++G(*d,p*) level in this work.

TABLE VI. The charge distributions (The geometries are in Figs. 4 and 5, respectively, The descriptions concerning the charges of NMA is the same as those of Table VI. For water molecules, q_{H13} , q_{O14} , q_{H15} , $q_{H13-O14}$, $q_{H15-O14}$, q_{lpO14} , and q_{lpO14} are charges of all atoms, bonds, and lone-pair electrons in water molecule at position I; q_{H16} , q_{O17} , q_{H18} , $q_{H16-O17}$, $q_{H18-O17}$, q_{lpO17} , and $q_{lp'O17}$ are the charges of all atoms, bonds, and lone-pair electrons in water molecule at position II; and q_{H19} , q_{O20} , q_{H21} , $q_{H19-O20}$, $q_{H21-O20}$, q_{lpO20} , and $q_{lp'O20}$ are the charges of all atoms, bonds, and lone-pair electrons in water molecule at position III.) of NMA-H₂O by the ABEEM/MM model.

Sym.	T_I C_s	T_{II} C_s	C_{II} C_s	Sym.	T_I C_s	T_{II} C_s	C_{II} C_s
q_{C1}	0.6497	0.6609	0.6615	q_{H6-C5}	-0.2883	-0.2904	-0.2954
q_{O2}	-0.0779	-0.0622	-0.0633	q_{H7-C5}	-0.2975	-0.2976	-0.2859
q_{N3}	0.4126	0.4175	0.4153	q_{H8-C5}	-0.2883	-0.2904	-0.2954
q_{H4}	0.5971	0.6325	0.6419	q_{H10-C9}	-0.2851	-0.2872	-0.2924
q_{C5}	0.4055	0.4084	0.4062	q_{H11-C9}	-0.2889	-0.2898	-0.2848
q_{H6}	0.2190	0.2061	0.1952	q_{H12-C9}	-0.2851	-0.2872	-0.2924
q_{H7}	0.1864	0.1950	0.2344	$q_{H13-O14}$	-0.1444
q_{H8}	0.2190	0.2061	0.1952	$q_{H15-O14}$	-0.1504
q_{C9}	0.3686	0.3782	0.3830	$q_{H16-O17}$...	-0.1459	-0.1464
q_{H10}	0.2491	0.2232	0.2036	$q_{H18-O17}$...	-0.1459	-0.1464
q_{H11}	0.2160	0.2024	0.2227	$q_{H19-O20}$
q_{H12}	0.2491	0.2232	0.2036	$q_{H21-O20}$
q_{H13}	0.3831	q_{lpO14}	-0.2176
q_{O14}	0.0987	$q_{lp'O14}$	-0.2176
q_{H15}	0.2482	q_{lpO17}	...	-0.2046	-0.2196
q_{H16}	...	0.3022	0.3073	$q_{lp'O17}$...	-0.2039	-0.1994
q_{O17}	...	0.0960	0.0972	q_{lpO20}
q_{H18}	...	0.3022	0.3073	$q_{lp'O20}$
q_{H19}	q_{lpO2}	-0.2124	-0.1676	-0.1837
q_{O20}	$q_{lp'O2}$	-0.1672	-0.1729	-0.1655
q_{H21}	$q_{\pi C1=}$	-0.0103	-0.0108	-0.0104
$q_{\sigma C1=O2}$	-0.1301	-0.1425	-0.1401	$q_{\pi C1=}$	-0.0103	-0.0108	-0.0104
$q_{\sigma C1-N3}$	-0.1679	-0.1680	-0.1642	$q_{\sigma O2=}$	-0.0105	-0.0105	-0.0104
q_{C1-C5}	-0.2296	-0.2308	-0.2351	$q_{\pi O2=}$	-0.0105	-0.0105	-0.0104
q_{H4-N3}	-0.8026	-0.8153	-0.8092	$q_{\pi N3-}$	-0.0309	-0.0309	-0.0306
q_{C9-N3}	-0.1475	-0.1472	-0.1523	$q_{\pi N3-}$	-0.0309	-0.0309	-0.0306

MP2 level, by 0.004–0.025 Å. Through the analysis on hydrogen bonding geometries, it is obviously knowable that our ABEEM/MM can correctly obtain structural results for these NMA-water complexes.

2. ABEEM charge distributions

The charges of neutral molecules NMA-water systems with one water molecule are listed in Table VI, respectively. For the model water, ABEEM-7P model⁴³ gives the explicitly quantitative charges of all atoms, bonds, and lone-pair electrons: the positive charges located on the O atom (0.1125) and H atoms (0.2897) are balanced by the negative charges located on the O–H bonds (–0.1552) and the lone-pair electrons (–0.1908). For the isolated NMA, the charges are also listed in Table III. As seen from the data of Tables VI and III, when one water interacts with NMA at position I, II, or III, the charges of all sites for each complex are different from an isolated water and NMA molecules, which is consequential upon environment change, i.e., for an isolated water or NMA molecule, no other molecule affects its electron cloud, but for a NMA-water dimer, the different position of

water molecule relative to NMA molecule affects the redistribution of the electron cloud. Moreover, the intermolecular hydrogen bonds between NMA and water (i.e., the first type of hydrogen bond and the second type of hydrogen bond) also directly influence the charge distribution. In the same way, this is also true of the clusters NMA(H₂O)₂ and NMA(H₂O)₃, whose charges are all listed in Ref. 54, as well as those of other NMA-water complexes with one water molecule.

Through analyzing the data in Tables VI and III, we can draw the following two conclusions: (1) the remarkable change of charges takes place at the position where the hydrogen bond forms. For example, seen from the charge distribution for complex T_I , obvious polarization takes place for the charges of H13 of H₂O and lpO2= of NMA forming the hydrogen bond, i.e., q_{H13} is 0.3831 versus the isolated water hydrogen 0.2897, and q_{lpO2} is –0.2124 versus the lone-pair electron on amide oxygen in isolated *t*-NMA –0.1632. The change is reasonable, in that the water hydrogen and the lone-pair electron on amide oxygen are main contributors of the first type of hydrogen bond. Similarly, for complex C_{II} obvious polarization takes place for the charges of H4 and lpO17, i.e., and q_{H4} is 0.6419 versus the charge 0.6174 of

TABLE VII. Interaction energies ΔE (kcal/mol) of NMA-H₂O complexes, compared with those of *ab initio* calculations and other force fields.

	<i>Ab initio</i>					Force field	
	ABEEM/MM	MP2 ^a	B3LYP ^b	B3LYP ^c	MP2 ^d	CHARM/AA ^e	MM4 ^f
T_I	-6.80	-7.03	-7.68	-7.20	-6.98	-7.3	-6.89
T_{II}	-4.41	-4.68	-5.36	-4.49	-4.09	-4.23	-6.28
T_{III}	-7.02	-7.06	-7.72	-7.31	-7.01	-6.92	-6.84
C_I	-8.87	-8.89	-10.23	-9.74			
C_{II}	-5.94	-6.03	-6.90	-6.12			
C_{III}	-6.99	-7.04	-7.86	-7.45	-6.99		-6.22
$T_{I,II}$	-11.97	-12.20	-13.67	-12.30		-12.03	
$T_{II,III}$	-12.10	-12.26	-13.76	-12.42			
$T_{I,III}$	-13.32	-13.31	-14.59	-13.54		-13.60	
$C_{I,III}$	-15.40	-15.49	-17.80	-16.76			
$C_{II,III}$	-12.72	-12.84	-14.66	-13.35			
$T_{I,II,III}$	-18.45	-18.91	-21.16	-19.17		-19.01	

^aAt the MP2/6-311++G(2d,2p)//MP2/6-31++G(d,p) level with counterpoise correction in this work.

^bReference 15: at the B3LYP/6-311++G(d,p) level with basis set superposition error correction.

^cReference 15: at the B3LYP/6-311++G(d,p) level after counterpoise correction.

^dReference 20: at the MP2/6-311++G(2d,2p)//MP2/6-311++G(2d,2p) level, with counterpoise correction.

^eReference 22.

^fReference 20.

amide hydrogen in isolated *c*-NMA, and q_{lpO17} is -0.2196 versus the charge -0.1908 of lone-pair electron on water oxygen. It is also reasonable that the amide hydrogen in NMA and the lone-pair electron on water oxygen are main contributors of the second type of hydrogen bond. (2) Seen from the charges of NMA-water system, we can predict the orientation of the water molecules interacting with NMA molecule. Take cluster T_I as an example, it can be seen that the different charges [such as 0.3831 (H13) and 0.2482 (H15)] of hydrogen atoms of H₂O molecule manifest the different polarization extent, and further reflect that the hydrogen atom (H13) with more positive charge points to the

lone-pair electron (lpO2) with more negative charge -0.2124 on the amide oxygen. In the same way, the lone-pair electron with more negative charge on the water oxygen points to the amide hydrogen. For cluster T_{II} , the lone-pair electrons lpO17 and lp'O17 on water oxygen have almost identical charges (such as -0.2046 and -0.2039), so we can tell that the line connecting the amide hydrogen and the water oxygen can approximately halve the intervening angle of the water molecule.

To summarize, the fluctuating charges of the NMA and the water(s) molecules can correctly reflect the redistribution with the changed ambient environment and make a compen-

TABLE VIII. The interaction energies $\Delta\Delta E$ (kcal/mol) of NMA-water representing the cooperative effects in hydrogen bonding for the ABEEM/MM model, compared with those of *ab initio* calculations and other force fields.

Method complexes	ABEEM/MM		MP2 ^a		B3LYP ^b		CHARM/AA ^c	
	ΔE	$\Delta\Delta E$	ΔE	$\Delta\Delta E$	ΔE	$\Delta\Delta E$	ΔE	$\Delta\Delta E$
T_I	-6.80		-7.03		-7.20		-7.3	
T_{II}	-4.41		-4.68		-4.49		-4.23	
T_{III}	-7.02		-7.06		-7.31		-6.92	
C_I	-8.87		-8.89		-9.74			
C_{II}	-5.94		-6.03		-6.12			
C_{III}	-6.99		-7.04		-7.45			
$T_{I,II}$	-11.97	-0.76	-12.20	-0.49	-12.30	-0.61	-12.03	-0.50
$T_{II,III}$	-12.10	-0.67	-12.26	-0.52	-12.42	-0.63		
$T_{I,III}$	-13.32	+0.50	-13.31	+0.78	-13.54	+0.97	-13.60	+0.62
$C_{I,III}$	-15.40	+0.46	-15.49	+0.44	-16.76	+0.43		
$C_{II,III}$	-12.72	+0.21	-12.84	+0.23	-13.35	+0.22		
$T_{I,II,III}$	-18.45	-0.22	-18.91	-0.14	-19.17	-0.18	-19.01	-0.56

^aAt the MP2/6-311++G(2d,2p)//MP2/6-31++G(d,p) level with counterpoise correction in this work.

^bReference 15: at the B3LYP/6-311++G(d,p) level after counterpoise correction.

^cReference 22.

sation for the shortages of fixed-point charge models. Meanwhile, the fluctuating charges are very important in the calculations of the interaction energies.

3. Interaction energies and cooperative effects

In order to further examine whether our ABEEM/MM potential model can reproduce the *ab initio* interaction energies and cooperative effects,^{19,56,57} the interaction energies ΔE and cooperative effects $\Delta\Delta E$ of given complexes are calculated subject to the C_s symmetries for ABEEM/MM potential model, and are compared with those from other theoretical calculations,^{12–15,20,25} and then are listed in Tables VII and VIII, respectively. The hydrogen bonding interaction ΔE is defined as the difference between the total energy of a complex and the sum of the total energies for each of the separated molecules [i.e., isolated NMA with the same methyl orientations and water(s)]. The cooperative effect $\Delta\Delta E$ for the multiple-water complexes is defined as the difference between the ΔE of a multiple-water complex and the sum of the ΔE values for each of the corresponding complexes involving a single water molecule.

As it can be seen from Table VII, the interaction energy ΔE values of $\text{NMA}(\text{H}_2\text{O})_n$ calculated by the ABEEM/MM potential model are found to be in excellent agreement with our quantum chemistry calculations and other reported *ab initio* calculations in the case of $n\text{H}_2\text{O}$ complexes for $n = 1–3$. Not surprisingly, the most stable dimer is the cyclic doubly bonded form, i.e., having one hydrogen bond of the first type and one hydrogen bond of the second type. The comparison in Table VIII manifests that the $\Delta\Delta E$ values for our ABEEM/MM model are in qualitative agreement with those of the reported *ab initio* methods and other force fields. For all of the *t*- and *c*-NMA+2H₂O cases, we may observe a cooperative effect in hydrogen bonding for the $T_{\text{I,II}}$ and $T_{\text{II,III}}$ complexes, i.e., the interaction energies (ΔE) of these two complexes are larger than the sum of the ΔE values of the corresponding single-water complexes ($\Delta\Delta E$ values are negative for $T_{\text{I,II}}$ and $T_{\text{II,III}}$). This indicates that as a result of the cooperative effect, the hydrogen bonds in the $T_{\text{I,II}}$ and $T_{\text{II,III}}$ complexes are more stable than those in T_{I} , T_{II} , and T_{III} . On the contrary, the $\Delta\Delta E$ values of the $T_{\text{I,III}}$, $C_{\text{I,III}}$, and $C_{\text{II,III}}$ complexes are all positive. This also indicates that the H bonds in $T_{\text{I,III}}$, $C_{\text{I,III}}$, and $C_{\text{II,III}}$ are less stable than those in their corresponding single-water complexes. For NMA, the “cooperative effect” apparently passes through the peptide linkage. As discussed by Guo and Karplus,¹² this cooperative effect may enhance the hydrogen bonding between peptide bonds and make the formation of secondary structures more favorable. Thus, a *t*-NMA complex with one H bond (T_{I} , T_{II} , and T_{III}) on either N–H or C=O group favors a second H bond formed at the other group because of the cooperative effect. Although the structure of the $T_{\text{I,III}}$ is unstable, the structure with an extra hydrogen bond on the N–H group is

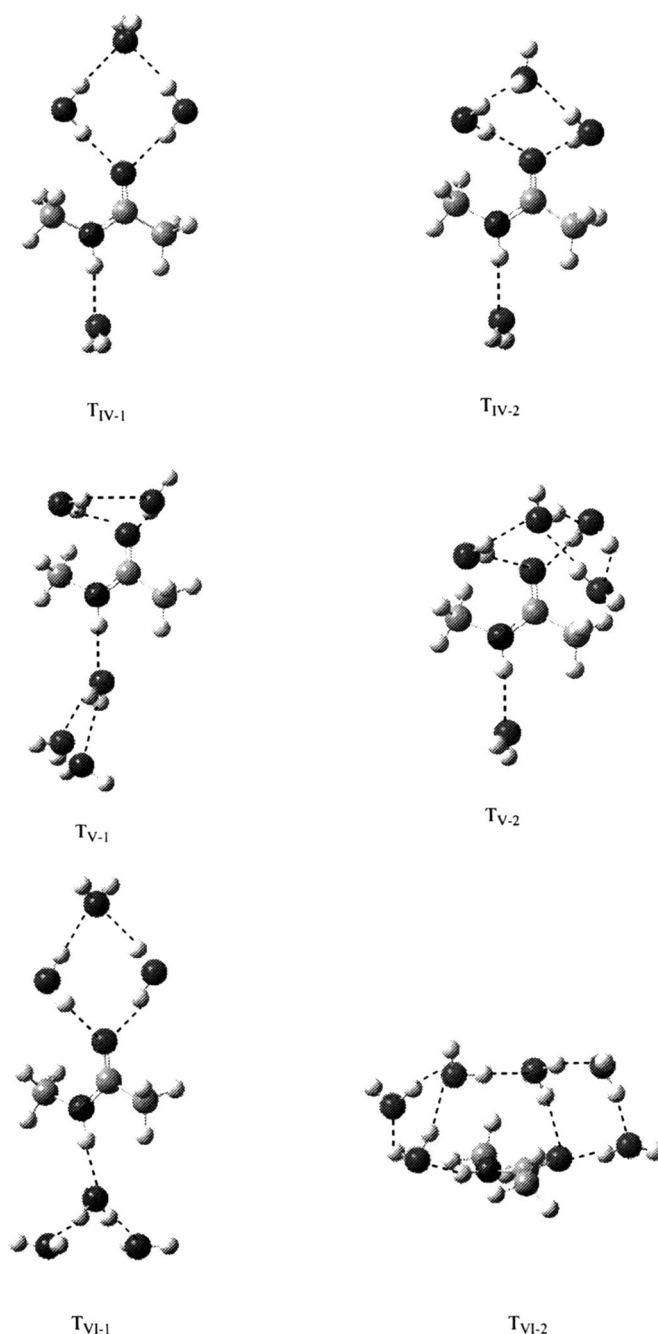


FIG. 6. The structures for the complexes of $\text{NMA}(\text{H}_2\text{O})_n$ ($n=4–6$) by the ABEEM/MM model.

stable, i.e., the $\Delta\Delta E$ value of $T_{\text{I,II,III}}$ is negative, meaning the hydrogen bond in $T_{\text{I,II,III}}$ is again cooperative. On the other hand, no cooperative effect is observed in $C_{\text{I,III}}$ and $C_{\text{II,III}}$ because of their having the positive $\Delta\Delta E$. Comparing the interaction energies of trimers ($T_{\text{I,III}}$, $T_{\text{I,II}}$, $T_{\text{II,III}}$, $C_{\text{I,III}}$, and $C_{\text{II,III}}$) shows that $C_{\text{I,III}}$ is the lowest one. This does not mean *c*-NMA is more stable than *t*-NMA in water, but it can explain the experimental observation that *c*-NMA can exist in aqueous solution. In a word, we draw a conclusion from the above analysis that our ABEEM/MM potential model can well give rise to and correctly calculate the static properties, and compare quite well with *ab initio* calculations and other force fields.

TABLE IX. Interaction energies ΔE (kcal/mol) of larger NMA-water complexes $\text{NMA}(\text{H}_2\text{O})_n$ ($n=4-6$) calculated by the ABEEM/MM model, compared with *ab initio* calculations.

n	Complexes	Sym.	ABEEM/MM	<i>Ab initio</i> ^a
4	T_{IV1}	C_s	-22.27	-24.64
	T_{IV2}	c_1	-21.61	-24.89
5	T_{V1}	C_1	-32.52	-33.03
	T_{V2}	C_1	-35.90	-38.44
6	T_{VI1}	C_s	-34.71	-37.88
	T_{VI2}	C_1	-55.74	-56.13

^aAt the MP2/6-311++G(2d,2p)//MP2/6-31++G(d,p) level with counterpoise correction in this work.

C. Testing the correctness and transferability of parameters

In order to further test and verify the reasonableness of the ABEEM/MM potential model and the correctness and transferability of the parameters, for the first time we transfer them to the larger NMA-water complexes $\text{NMA}(\text{H}_2\text{O})_n$ ($n=4-6$), and calculate various static properties, which have not been reported previously. Their structure optimized using the ABEEM/MM model are presented in Fig. 6.

For $\text{NMA}+4\text{H}_2\text{O}$ complexes, there are two structures to be studied. One is the structure T_{IV-1} with C_s symmetry, i.e., adding one water molecule to the complex $T_{I,II,III}$ to make two extra hydrogen bonds be formed between water and water molecules; the other is the structure T_{IV-2} , which has no symmetry constraint. For $\text{NMA}+5\text{H}_2\text{O}$ complexes, there are also two structures (T_{V-1} and T_{V-2}) to be investigated, and they have no symmetries. For $\text{NMA}+6\text{H}_2\text{O}$ complexes, there is a representative structure T_{VI-1} with C_s symmetry, i.e., adding two water molecules to T_{IV-1} ; there is another structure T_{VI-2} having no symmetry, and six water molecules are distributed at one side of the NMA molecule. Their interaction energies are also listed in Table IX as well as the comparison with those from our quantum chemistry calculations. The good accordance with *ab initio* results in Table IX reflects that the ABEEM/MM model can correctly predict the static properties of larger clusters $\text{NMA}(\text{H}_2\text{O})_n$, $n > 6$. It also can be seen that the model will provide reliable evidence for more accurate and clear simulations of aqueous solution.

V. CONCLUSION

Based on the atom-bond electronegativity equalization method (ABEEM) fused into molecular mechanics (MM), we have constructed the NMA-water potential for the first time, and then applied the potential to NMA-water complexes $\text{NMA}(\text{H}_2\text{O})_n$, $n=1-6$. This potential model has the following characteristic elements: (1) ABEEM/MM model can quantitatively give the charges of all atoms (including all single bond atoms and double bond atoms), bonds (including all single bonds and σ and π bonds of double bonds), and lone-pair electrons, and the charges can fluctuate upon the different ambient environment. (2) The ABEEM/MM model also carry out special treatments for the two types of intermolecular hydrogen bonds between NMA and H_2O mol-

ecules, which are the hydrogen bond forming between the lone-pair electron on amide oxygen and the water hydrogen, and the hydrogen bond forming between the lone-pair electron on water oxygen and the amide hydrogen. In particular, in order to correctly reflect the polarization effect, two parameters $k_{\text{lpO}=\text{H}}$ and $k_{\text{lpO}-,\text{HN}-}$ are introduced to describe the electrostatic interactions of the donors and the acceptors forming the above mentioned hydrogen bonds.

Based on the ABEEM/MM model, we have computed several static properties of NMA-water complexes $\text{NMA}(\text{H}_2\text{O})_n$ ($n=1-3$), including the optimized structures, dipole moments, energy difference of the isolated *t*- and *c*-NMA, ABEEM charge distributions, interaction energies, hydrogen bonding cooperative effects, and so on. It shows that the results are in good and reasonable agreement with those from the available experimental data and *ab initio* calculations. Moreover, we have also presented several static properties for the larger NMA-water complexes $\text{NMA}(\text{H}_2\text{O})_n$ ($n=4-6$), such as optimized geometries and interaction energies, which were calculated for the first time. The above results can provide the reliable evidence for testing the reasonableness of this model and the correctness and transferability of the parameters.

Overall, the key feature of the ABEEM/MM potential model is a well geometry-adopted and charge-distributed description for NMA-water clusters. The new constructed NMA-water potential, together with the ABEEM-7P water model, provides an important proof for the dynamics simulation of NMA.

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APPENDIX: ABEEM FORMALISM

Here we present the details concerning the outline of ABEEM for describing NMA in water. The atom-bond electronegativity equalization method³⁶⁻⁴² (ABEEM) has been developed in the framework of density functional theory^{59,60} and electronegativity equalization principle.^{61,62} In this work, when extending this model to the NMA-water system, the energy expression should be modified to some degree to describe NMA-water interaction energy and rewritten as follows:

$$\begin{aligned}
E = & \sum_{l=1}^{N_{\text{mol}}} \left\{ \sum_a (E_{ia}^* - \mu_{ia}^* q_{ia} + \eta_{ia}^* q_{ia}^2) + \sum_m (E_{im}^* - \mu_{im}^* q_{lm} + \eta_{im}^* q_{lm}^2) + \sum_{a-b} (E_{i(a-b)}^* - \mu_{i(a-b)}^* q_{i(a-b)} + \eta_{i(a-b)}^* q_{i(a-b)}^2) \right. \\
& + \sum_{\sigma m=n} (E_{i(\sigma m=n)}^* - \mu_{i(\sigma m=n)}^* q_{i(\sigma m=n)} + \eta_{i(\sigma m=n)}^* q_{i(\sigma m=n)}^2) + \sum_{\pi m=n} (E_{i(\pi m=n)}^* - \mu_{i(\pi m=n)}^* q_{i(\pi m=n)} + \eta_{i(\pi m=n)}^* q_{i(\pi m=n)}^2) \\
& + \sum_{lp} (E_{i(lp)}^* - \mu_{i(lp)}^* q_{i(lp)} + \eta_{i(lp)}^* q_{i(lp)}^2) + \sum_{g-h} \sum_{a=(g,h)} \frac{k_{ia,i(g-h)} q_{ia} q_{i(g-h)}}{R_{ia,i(g-h)}} + \sum_a \sum_{lp \in a} \frac{k_{ia,i(lp)} q_{ia} q_{i(lp)}}{R_{ia,i(lp)}} + \sum_m \sum_{lp \in m} \frac{k_{im,i(lp)} q_{im} q_{i(lp)}}{R_{im,i(lp)}} \\
& + \sum_{\sigma k=l} \sum_{m=(k,l)} \frac{k_{im,i(\sigma k=l)} q_{im} q_{i(\sigma k=l)}}{R_{im,i(\sigma k=l)}} + \sum_m \sum_{\pi k=l \in m} \frac{k_{im,i(\pi k=l)} q_{im} q_{i(\pi k=l)}}{R_{im,i(\pi k=l)}} \left. \right\} + \sum_{i=1}^{N_{\text{mol}}} \left\{ \sum_{j=1}^{N_{\text{mol}}} \left[\sum_{\substack{H \in i \quad lp \in j (\equiv i) \\ H, lp \text{ in HBIR}}} k_{H,lp}(R_{iH,j(lp)}) \frac{q_{iH} q_{j(lp)}}{R_{H,j(lp)}} \right. \right. \\
& + k \left(\frac{1}{2} \sum_a \sum_b \frac{q_{ia} q_{jb}}{R_{ia,jb}} + \frac{1}{2} \sum_m \sum_k \frac{q_{im} q_{jk}}{R_{im,jk}} + \frac{1}{2} \sum_{a-b} \sum_{g-h} \frac{q_{i(a-b)} q_{j(g-h)}}{R_{i(a-b),j(g-h)}} + \frac{1}{2} \sum_{\sigma m=n} \sum_{\sigma k=l} \frac{q_{i(\sigma m=n)} q_{j(\sigma k=l)}}{R_{i(\sigma m=n),j(\sigma k=l)}} \right. \\
& + \frac{1}{2} \sum_{\pi m=n} \sum_{\pi k=l} \frac{q_{i(\pi m=n)} q_{j(\pi k=l)}}{R_{i(\pi m=n),j(\pi k=l)}} + \frac{1}{2} \sum_{lp} \sum_{lp'} \frac{q_{i(lp)} q_{j(lp')}}{R_{i(lp),j(lp')}} + \sum_a \sum_{g-h} \frac{q_{ia} q_{j(g-h)}}{R_{ia,j(g-h)}} + \sum_a \sum_m \frac{q_{ia} q_{jm}}{R_{ia,jm}} + \sum_a \sum_{\sigma m=n} \frac{q_{ia} q_{j(\sigma m=n)}}{R_{ia,j(\sigma m=n)}} \\
& + \sum_a \sum_{\sigma m=n} \frac{q_{ia} q_{j(\sigma m=n)}}{R_{ia,j(\sigma m=n)}} + \sum_a \sum_{\pi m=n} \frac{q_{ia} q_{j(\pi m=n)}}{R_{ia,j(\pi m=n)}} + \sum_a \sum_{lp} \frac{q_{ia} q_{j(lp)}}{R_{ia,j(lp)}} + \sum_m \sum_{a-b} \frac{q_{im} q_{j(a-b)}}{R_{im,j(a-b)}} + \sum_m \sum_{\sigma k=l} \frac{q_{im} q_{j(\sigma k=l)}}{R_{im,j(\sigma k=l)}} \\
& + \sum_m \sum_{\pi k=l} \frac{q_{im} q_{j(\pi k=l)}}{R_{im,j(\pi k=l)}} + \sum_m \sum_{lp} \frac{q_{im} q_{j(lp)}}{R_{im,j(lp)}} + \sum_{a-b} \sum_{\sigma m=n} \frac{q_{i(a-b)} q_{j(\sigma m=n)}}{R_{i(a-b),j(\sigma m=n)}} + \sum_{a-b} \sum_{\pi m=n} \frac{q_{i(a-b)} q_{j(\pi m=n)}}{R_{i(a-b),j(\pi m=n)}} + \sum_{a-b} \sum_{lp} \frac{q_{i(a-b)} q_{j(lp)}}{R_{i(a-b),j(lp)}} \\
& \left. \left. + \sum_{\sigma m=n} \sum_{\pi k=l} \frac{q_{i(\sigma m=n)} q_{j(\pi k=l)}}{R_{i(\sigma m=n),j(\pi k=l)}} + \sum_{\sigma m=n} \sum_{lp} \frac{q_{i(\sigma m=n)} q_{j(lp)}}{R_{i(\sigma m=n),j(lp)}} + \sum_{\pi m=n} \sum_{lp} \frac{q_{i(\pi m=n)} q_{j(lp)}}{R_{i(\pi m=n),j(lp)}} \right] \right\}. \quad (\text{A1})
\end{aligned}$$

where N_{mol} represents the number of interacting molecules in the system, and the summation covers a NMA molecule and all water molecules. If y stands for an arbitrary region, then E_{iy}^* , μ_{iy}^* , η_{iy}^* , and q_{iy} are the valence-state energy, the valence-state chemical potential, the valence-state hardness, and the partial charge of the region y in molecule i , respectively. The y may be a single bond atom a , or double bond atom m , or single bond $a-b$, or σ bond region of double bond $m=n$, or π bond region of double bond $m=n$, or lone-pair electron lp in molecule i , respectively. R is the distance between the charge sites, for example, $R_{ia,ib}$, $R_{im,ik}$, $R_{i(a-b),i(g-h)}$, $R_{i(\sigma m=n),i(\sigma k=l)}$, and $R_{i(\pi m=n),i(\pi k=l)}$, and $R_{i(lp),i(lp')}$ are the distance between single bond atoms a and b , the distance between double bond atoms m and k , the distance between single bonds $a-b$ and $g-h$, the distance between σ bond regions of double bonds $m=n$ and $k=l$, the distance between π bond regions of double bonds $m=n$ and $k=l$, and the distance between lone-pair electrons lp and lp' in molecule i , respectively, in which the single bond charge and σ bond region charge of double bond are located on the points that partition the bond lengths according to the ratio of covalent atomic radii of two bonded atoms, and then charge centers of π bond region of double bond and the lone-pair electron are placed on the points that are covalent atomic radii far from the bonded atom nucleus. $k_{ia,i(g-h)}$, $k_{ia,i(lp)}$,

$k_{im,i(lp)}$, $k_{im,i(\sigma k=l)}$, and $k_{im,i(\pi k=l)}$ are regarded as adjustable parameters. In order to effectively describe the hydrogen bond interaction between amide and water, we introduce a new parameter $k_{H,lp}(R_{iH,i(lp)})$ extracted from k of Eq. (A1), the difference between k and $k_{H,lp}(R_{iH,i(lp)})$ is that the former is an overall optimized correction coefficient and the latter is dependent on the distance between hydrogen atom and its acceptor. In Eq. (A1), when i is equal to j , the summation of the first $\{\}$ term and the $()$ part of the second $\{\}$ term represents the intermolecular energies for water molecules and one NMA molecule, and when i is not equal to j , the second $\{\}$ term represents the intermolecular interaction energies between the water-water and NMA-water pairs.

The effective electronegativity of an atom or a chemical bond or a lone-pair electron is identified as the negative of the corresponding effective chemical potential, i.e., the partial derivative of total energy E with respect to the corresponding electron number or partial charge: $\mu_i = (\partial E / \partial N_i)_{R,N_j} = -(\partial E / \partial q_i)_{R,q_j} = -\chi_i$. Thus, based on Eq. (A1), we obtain Eqs. (A2) for the effective electronegativities of single bond atom a , double bond atom m , single bond $a-b$, σ bond region of double bond $m=n$, π bond region of double bond $m=n$, and lone-pair electron lp in molecule i , respectively.

$$\begin{aligned}
\chi_{ia} = & \chi_{ia}^* + 2\eta_{ia}^* q_{ia} + C_{ia} \sum_{a-b} q_{i(a-b)} + D_{ia} \sum_{lp \in a} q_{i(lp)} + k \left(\sum_{b \neq a} \frac{q_{ib}}{R_{ia,ib}} + \sum_m \frac{q_{im}}{R_{ia,im}} + \sum_{g-h \neq a-b} \frac{q_{i(g-h)}}{R_{ia,i(g-h)}} + \sum_{\sigma m=n} \frac{q_{i(\sigma m=n)}}{R_{ia,i(\sigma m=n)}} \right. \\
& + \left. \sum_{\pi m=n} \frac{q_{i(\pi m=n)}}{R_{ia,i(\pi m=n)}} + \sum_{lp \in a} \frac{q_{i(lp)}}{R_{ia,i(lp)}} \right) + \sum_{j \neq i} \left[\sum_{lp} k_{lp,H} (R_{iH,j(lp)}) \frac{q_{j(lp)}}{R_{ia,j(lp)}} + k \left(\sum_b \frac{q_{jb}}{R_{ia,jb}} + \sum_m \frac{q_{jm}}{R_{ia,jm}} + \sum_{g-h} \frac{q_{j(g-h)}}{R_{ia,j(g-h)}} \right. \right. \\
& \left. \left. + \sum_{\sigma m=n} \frac{q_{j(\sigma m=n)}}{R_{ia,j(\sigma m=n)}} + \sum_{\pi m=n} \frac{q_{j(\pi m=n)}}{R_{ia,j(\pi m=n)}} + \sum_{\substack{lp \\ lp \text{ not in HBIR}}} \frac{q_{j(lp)}}{R_{ia,j(lp)}} \right) \right], \tag{A2a}
\end{aligned}$$

$$\begin{aligned}
\chi_{im} = & \chi_{im}^* + 2\eta_{im}^* q_{im} + C_{im} \sum_{\sigma m=n} q_{i(\sigma m=n)} + D_{im} \left(\sum_{lp \in m} q_{i(lp)} + \sum_{\pi m=n} q_{i(\pi m=n)} \right) + k \left(\sum_a \frac{q_{ia}}{R_{im,ia}} + \sum_{k \neq m} \frac{q_{ik}}{R_{im,ik}} + \sum_{a-b} \frac{q_{i(a-b)}}{R_{im,i(a-b)}} \right. \\
& + \left. \sum_{\sigma k=l \neq \sigma m=n} \frac{q_{i(\sigma k=l)}}{R_{im,i(\sigma k=l)}} + \sum_{\pi k=l \neq \pi m=n} \frac{q_{i(\pi k=l)}}{R_{im,i(\pi k=l)}} + \sum_{lp \in m} \frac{q_{i(lp)}}{R_{im,i(lp)}} \right) + k \sum_{j \neq i} \left(\sum_a \frac{q_{ja}}{R_{im,ja}} + \sum_k \frac{q_{jk}}{R_{im,jk}} + \sum_{a-b} \frac{q_{j(a-b)}}{R_{im,j(a-b)}} \right. \\
& \left. + \sum_{\sigma k=l} \frac{q_{j(\sigma k=l)}}{R_{im,j(\sigma k=l)}} + \sum_{\pi k=l} \frac{q_{j(\pi k=l)}}{R_{im,j(\pi k=l)}} + \sum_{lp} \frac{q_{j(lp)}}{R_{im,j(lp)}} \right), \tag{A2b}
\end{aligned}$$

$$\begin{aligned}
\chi_{i(a-b)} = & \chi_{i(a-b)}^* + 2\eta_{i(a-b)}^* q_{i(a-b)} + C_{ia,i(a-b)} q_{ia} + D_{ib,j(a-b)} q_{ib} + k \left(\sum_{g \neq a,b} \frac{q_{ig}}{R_{i(a-b),ig}} + \sum_m \frac{q_{im}}{R_{i(a-b),im}} + \sum_{g-h \neq a-b} \frac{q_{i(g-h)}}{R_{i(a-b),i(g-h)}} \right. \\
& + \left. \sum_{\sigma m=n} \frac{q_{i(\sigma m=n)}}{R_{i(a-b),i(\sigma m=n)}} + \sum_{\pi m=n} \frac{q_{i(\pi m=n)}}{r_{i(a-b),i(\pi m=n)}} + \sum_{lp} \frac{q_{i(lp)}}{R_{i(a-b),i(lp)}} \right) + k \sum_{j \neq i} \left(\sum_g \frac{q_{jg}}{R_{i(a-b),jg}} + \sum_m \frac{q_{jm}}{R_{i(a-b),jm}} + \sum_{g-h} \frac{q_{j(g-h)}}{R_{i(a-b),j(g-h)}} \right. \\
& \left. + \sum_{\sigma m=n} \frac{q_{j(\sigma m=n)}}{R_{i(a-b),j(\sigma m=n)}} + \sum_{\pi m=n} \frac{q_{j(\pi m=n)}}{R_{i(a-b),j(\pi m=n)}} + \sum_{lp} \frac{q_{j(lp)}}{R_{i(a-b),j(lp)}} \right), \tag{A2c}
\end{aligned}$$

$$\begin{aligned}
\chi_{i(\sigma m=n)} = & \chi_{i(\sigma m=n)}^* + 2\eta_{i(\sigma m=n)}^* q_{i(\sigma m=n)} + C_{in,i(\sigma m=n)} q_{in} + D_{im,i(\sigma m=n)} q_{im} + k \left(\sum_a \frac{q_{ia}}{R_{i(\sigma m=n),ia}} + \sum_{k \neq m,n} \frac{q_{ik}}{R_{i(\sigma m=n),i(k)}} \right. \\
& + \left. \sum_{a-b} \frac{q_{i(a-b)}}{R_{i(\sigma m=n),i(a-b)}} + \sum_{\sigma k=l \neq \sigma m=n} \frac{q_{i(\sigma k=l)}}{r_{i(\sigma m=n),i(\sigma k=l)}} + \sum_{\pi k=l} \frac{q_{i(\pi k=l)}}{R_{i(\sigma m=n),i(\pi k=l)}} + \sum_{lp} \frac{q_{i(lp)}}{R_{i(\sigma m=n),i(lp)}} \right) + k \sum_{j \neq i} \left(\sum_a \frac{q_{ja}}{R_{i(\sigma m=n),ja}} \right. \\
& \left. + \sum_k \frac{q_{jk}}{R_{i(\sigma m=n),jk}} + \sum_{a-b} \frac{q_{j(a-b)}}{r_{i(\sigma m=n),j(a-b)}} + \sum_{\sigma k=l} \frac{q_{j(\sigma k=l)}}{R_{i(\sigma m=n),j(\sigma k=l)}} + \sum_{\pi k=l} \frac{q_{j(\pi k=l)}}{R_{i(\sigma m=n),j(\pi k=l)}} + \sum_{lp} \frac{q_{j(lp)}}{R_{i(\sigma m=n),j(lp)}} \right), \tag{A2d}
\end{aligned}$$

$$\begin{aligned}
\chi_{i(\pi m=n)} = & \chi_{i(\pi m=n)}^* + 2\eta_{i(\pi m=n)}^* q_{i(\pi m=n)} + C_{im,i(\pi m=n)} q_{im} + \left(\sum_a \frac{q_{ia}}{R_{i(\pi m=n),ia}} + \sum_{k \neq m,n} \frac{q_{ik}}{R_{i(\pi m=n),ik}} + \sum_{a-b} \frac{q_{i(a-b)}}{R_{i(\pi m=n),j(a-b)}} \right. \\
& + \left. \sum_{\sigma k=l} \frac{q_{i(\sigma k=l)}}{R_{i(\pi m=n),i(\sigma k=l)}} + \sum_{\pi k=l \neq \pi m=n} \frac{q_{i(\pi k=l)}}{R_{i(\pi m=n),i(\pi k=l)}} + \sum_{lp} \frac{q_{i(lp)}}{R_{i(\pi m=n),i(lp)}} \right) + k \sum_{j \neq i} \left(\sum_a \frac{q_{ja}}{R_{i(\pi m=n),ja}} + \sum_k \frac{q_{jk}}{R_{i(\pi m=n),jk}} \right. \\
& \left. + \sum_{a-b} \frac{q_{j(a-b)}}{R_{i(\pi m=n),j(a-b)}} + \sum_{\sigma k=l} \frac{q_{j(\sigma k=l)}}{R_{i(\pi m=n),j(\sigma k=l)}} + \sum_{\pi k=l} \frac{q_{j(\pi k=l)}}{R_{i(\pi m=n),j(\pi k=l)}} + \sum_{lp} \frac{q_{j(lp)}}{R_{i(\pi m=n),j(lp)}} \right), \tag{A2e}
\end{aligned}$$

$$\begin{aligned} \chi_{i(\text{lp})} = & \chi_{i(\text{lp})}^* + 2\eta_{i(\text{lp})}^* q_{i(\text{lp})} + C_{ia,i(\text{lp})} q_{ia} + D_{im,i(\text{lp})} q_{im} + k \left(\sum_{a \in \text{lp}} \frac{q_{ia}}{R_{i(\text{lp}),ia}} + \sum_{m \in \text{lp}} \frac{q_{im}}{R_{i(\text{lp}),im}} + \sum_{a-b} \frac{q_{i(a-b)}}{R_{i(\text{lp}),i(a-b)}} + \sum_{\sigma m=n} \frac{q_{i(\sigma m=n)}}{r_{i(\text{lp}),i(\sigma m=n)}} \right. \\ & \left. + \sum_{\pi m=n} \frac{q_{i(\pi m=n)}}{R_{i(\text{lp}),i(\pi m=n)}} + \sum_{\text{lp} \neq \text{lp}'} \frac{q_{i(\text{lp}')}}{R_{i(\text{lp}),i(\text{lp}')}} \right) + \sum_{j \neq i} \left[\sum_{\substack{a \\ a=H \\ \text{H Jp in HBI}}} k_{\text{lp,H}}(R_{i(\text{lp}),ja}) \frac{q_{ja}}{R_{i(\text{lp}),ja}} + k \left(\sum_{\substack{a \\ a=H \\ \text{H in HBIR}}} \frac{q_{ja}}{R_{i(\text{lp}),ja}} + \sum_m \frac{q_{jm}}{R_{i(\text{lp}),jm}} \right. \right. \\ & \left. \left. + \sum_{a-b} \frac{q_{j(a-b)}}{R_{i(\text{lp}),j(a-b)}} + \sum_{\sigma m=n} \frac{q_{j(\sigma m=n)}}{r_{i(\text{lp}),j(\sigma m=n)}} + \sum_{\pi m=n} \frac{q_{j(\pi m=n)}}{r_{i(\text{lp}),j(\pi m=n)}} + \sum_{\text{lp}'} \frac{q_{j(\text{lp}')}}{R_{i(\text{lp}),j(\text{lp}')}} \right) \right]. \end{aligned} \quad (\text{A2f})$$

Supposing

$$\begin{aligned} k_{ia,i(a-b)}/R_{ia,i(a-b)} = k_{ia,i(a-c)}/R_{ia,i(a-c)} = k_{ia,i(a-d)}/R_{ia,i(a-d)} \\ = k_{ia,i(a-e)}/R_{ia,i(a-e)} = C_{ia}, \end{aligned}$$

$$k_{ia,i(\text{lp})}/R_{ia,i(\text{lp})} = k_{ia,i(\text{lp}')}/R_{ia,i(\text{lp}')} = D_{ia},$$

$$k_{im,i(\sigma m=n)}/R_{im,i(\sigma m=n)} = k_{im,i(\pi m=n)}/R_{im,i(\pi m=n)} = C_{im},$$

$$k_{im,i(\pi m=n)}/R_{im,i(\pi m=n)} = k_{im,i(\text{lp})}/R_{im,i(\text{lp})} = D_{im},$$

$$k_{ia,i(a-b)}/R_{ia,i(a-b)} = C_{ia,i(a-b)},$$

$$k_{ib,i(a-b)}/R_{ib,i(a-b)} = D_{ib,i(a-b)},$$

$$k_{in,i(\sigma m=n)}/R_{in,i(\sigma m=n)} = C_{in,i(\sigma m=n)},$$

$$k_{im,i(\sigma m=n)}/R_{im,i(\sigma m=n)} = D_{im,i(\sigma m=n)},$$

$$k_{im,i(\pi m=n)}/R_{im,i(\pi m=n)} = C_{im,i(\pi m=n)},$$

$$k_{ia,i(\text{lp})}/R_{ia,i(\text{lp})} = C_{ia,i(\text{lp})},$$

and

$$k_{im,i(\text{lp})}/R_{im,i(\text{lp})} = D_{im,i(\text{lp})}.$$

All these C and D are regarded as adjustable parameters.

For a molecular system, the region charges are not all independent variables since there is a charge conservation constraint. For uncharged molecular system, the constraint can be of two types: (1) the entire system is constrained to be neutral; (2) each molecule is constrained to be neutral. In the case of this work, we employ the latter one from the experience of previous studies.⁴⁴

Each molecule is constrained to be neutral in the present treatment, so there is no intermolecular charge transfer. Therefore, there are N_{mol} charge constraint equations.

$$\begin{aligned} \sum_a^{N_a} q_{ia} + \sum_m^{N_m} q_{im} + \sum_{a-b}^{N_{a-b}} q_{i(a-b)} + \sum_{\sigma m=n}^{N_{\sigma m=n}} q_{i(\sigma m=n)} \\ + \sum_{\pi m=n}^{N_{\pi m=n}} q_{i(\pi m=n)} + \sum_{\text{lp}}^{N_{\text{lp}}} q_{i(\text{lp})} = 0 \quad (i = 1, 2, \dots, N_{\text{mol}}), \end{aligned} \quad (\text{A3})$$

where $i=1, 2, \dots, N_{\text{mol}}$ where N_{mol} is the number of molecules in the system.

Without intermolecular charge transfer, the effective electronegativity of a single bond atom, a double bond atom, a single bond, a σ bond region and π bond region of a double bond, and a lone-pair electron will only be equal within a molecule in the electronegativity equalization.

$$\chi_{ia} = \chi_{im} = \chi_{i(a-b)} = \chi_{i(\sigma m=n)} = \chi_{i(\pi m=n)} = \chi_{i(\text{lp})} = \dots \bar{\chi}_i$$

$$\chi_{ja} = \chi_{jm} = \chi_{j(a-b)} = \chi_{j(\sigma m=n)} = \chi_{j(\pi m=n)} = \chi_{j(\text{lp})} = \dots \bar{\chi}_j$$

\vdots ,

(A4)

where $i, j=1, 2, \dots, N_{\text{mol}}$. $\bar{\chi}_i$ and $\bar{\chi}_j$ stand for the effective electronegativities of molecules i and j in the system, respectively. However, all these effective electronegativities involve the interaction with other molecules.

For an arbitrary molecular system containing N_a single bond atoms, N_m double bond atoms, N_{a-b} single bonds, $N_{\sigma m=n}$ σ bond regions of double bonds, $N_{\pi m=n}$ π bond regions of double bonds, and N_{lp} lone-pair electrons, we yield $N_a + N_m + N_{a-b} + N_{\sigma m=n} + N_{\pi m=n} + N_{\text{lp}}$ simultaneous equations. These equations, along with N_{mol} charge constraint equations, can be solved to give the effective electronegativity of each molecule and the charges q on each single bond atom, each double bond atom, each single bond, each σ bond region of double bond, each π bond region of double bond, and each lone-pair electron on condition that the parameters of Eqs. (A2) are known.

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