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Correlation between electronic and molecular structure distortions and vibrational properties. II. Amide I modes of NMA– n D₂O complexes

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Hydration effects on the molecular structure and amide I mode frequency of a prototype peptide molecule, N-methylacetamide (NMA), when it is solvated by a few water molecules, were investigated by carrying out *ab initio* calculations for a number of NMA–water complexes. The harmonic frequency shift of the amide I mode in NMA– n D₂O ($n=1-5$) complex was found to originate from the combination of the molecular cubic anharmonicity and displacement of the amide I coordinate when the NMA is hydrated. Using a multivariate least-square fitting method, the effective transition charges of six NMA sites were determined. A brief discussion on how this empirical model can be used to quantitatively describe solvatochromic frequency shift of the NMA amide I mode in solution is presented. © 2003 American Institute of Physics.

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I. INTRODUCTION

The amide I band has attracted much attention since its location and shape can provide useful information on the secondary structures of polypeptides and proteins. Recently, two-dimensional IR pump–probe and photon echo methods have been used to study vibrational dynamics and spectral evolution of the amide I bands of short polypeptides, and it was found that a precise three-dimensional structure determination becomes possible.^{1–7} Therefore, understanding solvation effects on the vibrational properties of peptide bond, particularly amide I vibration, becomes even more critical than ever, not only to theoretically predict one-dimensional IR spectra but also to interpret the state-of-the-art multidimensional vibrational spectra of polypeptides.

There have been numerous theoretical attempts to quantitatively predict the vibrational frequency and intensity of the amide I band in solution. In particular, the N-methylacetamide (NMA) molecule has been served as a prototype molecule for peptide. Eaton *et al.* carried out extensive experiments systematically investigating the frequency shift of the amide I band when the NMA is dissolved in a variety of protic and aprotic solvents.⁸ They noted that the protic solvents such as water have a special ability to make the amide I band strongly redshifted, due to the hydrogen bonding interaction. In order to describe the hydrogen bonding effect on the frequency of the amide I vibrational mode, there exist some empirical expressions predicting the correlation between the amide I mode frequency and hydrogen-bond distance. One of the popular models that has been used extensively by other workers was to empirically estimate the amide I mode frequency shift, $\delta\bar{\nu}_I$, by using the following formula: $\delta\bar{\nu}_I = -\alpha_{\text{Hbd}}\{2.6 - r(\text{O}\cdots\text{H})\}$, where $r(\text{O}\cdots\text{H})$ is the hydrogen-bond distance and the slope α_{Hbd} was typically assumed to be 30 cm^{–1}.^{2,4} Although this simple relationship

between $\delta\bar{\nu}_I$ and $r(\text{O}\cdots\text{H})$ might be found to be of use, it was based on a linear fitting of *ab initio* calculated $\delta\bar{\nu}_I$ with respect to $r(\text{O}\cdots\text{H})$. Furthermore, the amide I mode frequency shift observed when the N–H group of a given peptide is hydrogen bonded to a water molecule cannot be explained by the same empirical formula above. Therefore, it is not possible to use the above empirical relationship to describe the amide I mode frequency shift in general for polypeptides dissolved in liquid water.

By using a variety of *ab initio* calculation methods, the NMA–water complexes have been extensively studied before.^{10–32} Guo and Karplus found that an NMA has three hydrogen bonding sites with surrounding water molecules.²⁶ Also, Torii, Tatsumi, and Tasumi performed *ab initio* vibrational analyses of NMA molecule, either when it is surrounded by a dielectric continuum or specifically hydrogen bonded to water molecules.¹⁰ They concluded that the dielectric effect alone cannot be used to explain the large low-frequency shift of the amide I band of NMA in aqueous solution, confirming the importance of specific hydrogen-bonding interactions by protic solvent molecules. Furthermore, there are a number of *ab initio* calculation studies of hydrogen-bonding strengths and conformations of NMA–water clusters. Although these previous studies show the importance of the hydration effect on the amide I vibrational frequency, there does not exist any simple model quantitatively predicting the frequency of amide I mode of a peptide when it is surrounded by solvent media such as liquid water.

In this paper, we will first present systematic *ab initio* vibrational analysis results for NMA–water clusters. Then, the theory that was developed and presented in Paper I⁹ will be used to describe the relationship between molecular structure distortion and the amide I mode frequencies of NMA– n D₂O complexes.

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II. *AB INITIO* VIBRATIONAL ANALYSES OF NMA–WATER COMPLEXES

Although there exists a vast literature on the *ab initio* calculations of NMA–water complexes, most of the previous works concerned the hydrogen bond strength and its geometry-optimized structures. In order to systematically investigate general hydration effects on the vibrational properties of amide normal modes, we will start by considering a few series of NMA–water configurations with varying intermolecular distance between the NMA and a D₂O molecule. As has been well known, the local amide I oscillator of the NMA is strongly coupled to the H₂O bending motion, so that there is more than one amide I normal modes in the NMA–*n*H₂O complexes when *n* is greater than 2. On the other hand, the mode mixing between the local amide I vibration and D₂O bending motion can be assumed to be negligible so that the amide I mode is localized on the NMA molecule.

A. *Ab initio* calculation method

All *ab initio* molecular orbital calculations were performed with the GAUSSIAN 98 program.³³ Geometry optimization and vibrational frequency analysis were carried out at the RHF/6-311++G** level. Vibrational frequencies were, as usual, corrected by multiplying the single scaling factor of 0.8929.³⁴ We shall use the same scaling factor to make a correction to the *ab initio* calculated harmonic frequency of the amide I mode. Although this single scaling factor approximation needs to be used carefully, it is believed that the general trends won't be significantly altered by this approximation as long as it is consistently used to scale the same type of normal mode frequency, i.e., amide I mode.

B. NMA hydrogen bonded to a single water molecule

Three series of *ab initio* calculations are first performed. The three hydrogen-bonding sites are denoted as A, B, and C

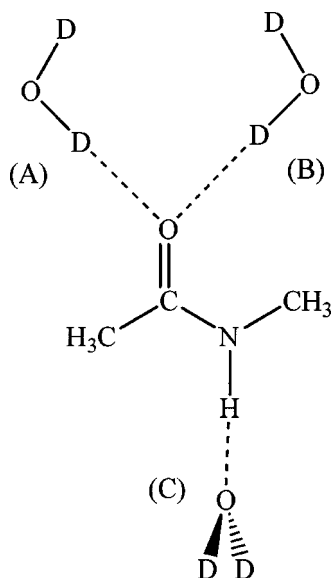


FIG. 1. The three hydrogen-bonding sites are depicted as site A, B, and C in NMA–D₂O complex.

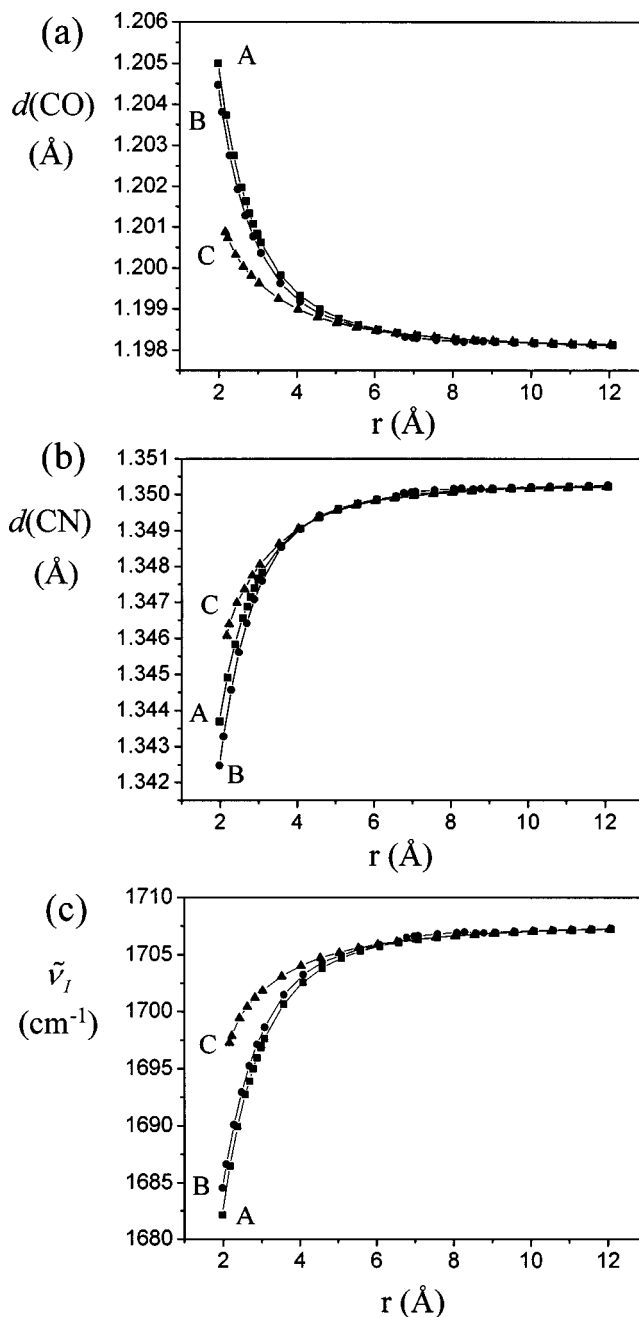


FIG. 2. For the three NMA–D₂O [(A), (B), or (C)] complexes, the C=O and C–N bond lengths (in Å) of the peptide group are plotted as a function of the intermolecular distance $r(\text{O} \cdots \text{D})$ between the NMA and water in (a) and (b), respectively. (c) $\tilde{\nu}_I$ vs r .

(see Fig. 1). We first obtain the optimized geometry of NMA–D₂O(A) complex, where the site A is occupied by a single water molecule. Then, the distance r between the hydrogen-bonding D atom of the D₂O(A) and the oxygen atom of the NMA is increased, with the relative orientations of the two molecules fixed. For each configuration with the constraints stated above, all other degrees of freedom are relaxed to find the corresponding optimized geometry, and *ab initio* vibrational analysis is performed. Similarly, for the other two sites B and C, we carried out the same series of *ab initio* calculations separately. The C=O and C–N bond lengths of the peptide group, sensitively reflecting the mo-

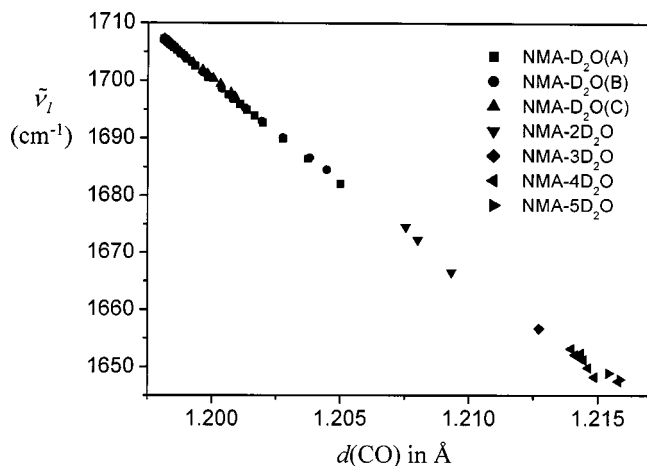


FIG. 3. $\bar{\nu}_I$ vs $d(\text{C}=\text{O})$ for all 96 NMA- $n\text{D}_2\text{O}$ ($n=1-5$) complexes.

lecular structure of the NMA- D_2O complex, are plotted as a function of r in Figs. 2(a) and 2(b), respectively. As expected, these two bond lengths vary oppositely as the water molecule approaches the NMA for all three cases. The amide I mode frequency $\bar{\nu}_I$ is then plotted as a function of r in Fig. 2(c). The hydrogen bonds at sites A and B induce strong redshift of $\bar{\nu}_I$ in comparison to that at site C. This trend was also observed by Tasumi and co-workers.¹⁰ From Figs. 2(a) and 2(b), it is clear that the surrounding water molecule can induce structural distortion of the NMA. In order to establish the relationship between the extent of molecular structure distortion and vibrational frequency shift, we plot $\bar{\nu}_I$ with respect to $d(\text{C}=\text{O})$ in Fig. 3. The linear correlation between $\bar{\nu}_I$ and $d(\text{C}=\text{O})$, regardless of the hydrogen-bonding sites, is evidently shown in Fig. 3.

C. NMA- $n\text{D}_2\text{O}$ complexes

We next carry out *ab initio* geometry optimizations and vibrational analyses for 14 NMA- $n\text{D}_2\text{O}$ ($n=2-5$) complexes shown in Fig. 4, e.g., three NMA- $2\text{D}_2\text{O}$ complexes, one NMA- $3\text{D}_2\text{O}$ complex, eight NMA- $4\text{D}_2\text{O}$ complexes, and two NMA- $5\text{D}_2\text{O}$ complexes. In Table II, the *ab initio* calculated $\bar{\nu}_I$'s are listed. Our concern here is not to find which NMA- $n\text{D}_2\text{O}$ complex is the most stable one among them but to study how the surrounding D_2O molecules affect the vibrational properties of the NMA. Therefore, the NMA- $n\text{D}_2\text{O}$ ($n=4$ and 5) clusters shown in Fig. 4 were to some extent chosen randomly. The *ab initio* calculated $\bar{\nu}_I$ values of those 14 complexes are also plotted in Fig. 3 with respect to the corresponding $d(\text{C}=\text{O})$ values. They all are on the same linear line, which indicates that regardless of the location and number of water molecules around the NMA, there is a linear relationship between $\bar{\nu}_I$ and $d(\text{C}=\text{O})$. The linear regression coefficient is 0.999. We will present a theoretical description of this phenomenon in the following section.

III. THEORETICAL ANALYSIS AND DISCUSSION

In Paper I, we showed that the spatially nonuniform electrostatic potential induces a molecular structure distortion that reflects the electronic structure change by the electrostatic potential.⁹ For NMA- $n\text{D}_2\text{O}$ complexes, the NMA molecule is exposed to the electrostatic potential of the water partial charges so that one can apply the theoretical results presented in Paper I directly to the NMA- $n\text{D}_2\text{O}$ system. For the sake of completeness, we will briefly summarize the relevant part of the theory in this section.

The potential function of a polarizable molecule in an inhomogeneous electrostatic potential was shown to be written as

$$V(\mathbf{Q}) = V_0(\mathbf{Q}) + V_\phi(\mathbf{Q}), \quad (1)$$

where the potential function of the gas-phase molecule is as usual expanded in terms of powers of normal coordinates

$$V_0(\mathbf{Q}) = V_0(\mathbf{Q}_0) + \frac{1}{2!} \sum_j M_j \omega_j^2 Q_j^2 + \frac{1}{3!} \sum_{i,j,k} g_{ijk} Q_i Q_j Q_k + \frac{1}{4!} \sum_{i,j,k,l} \gamma_{ijkl} Q_i Q_j Q_k Q_l + \dots \quad (2)$$

Here, the equilibrium nuclear configuration of the gas-phase molecule is specified by \mathbf{Q}_0 . The reduced mass, angular frequency, and cubic and quartic anharmonic coefficients are

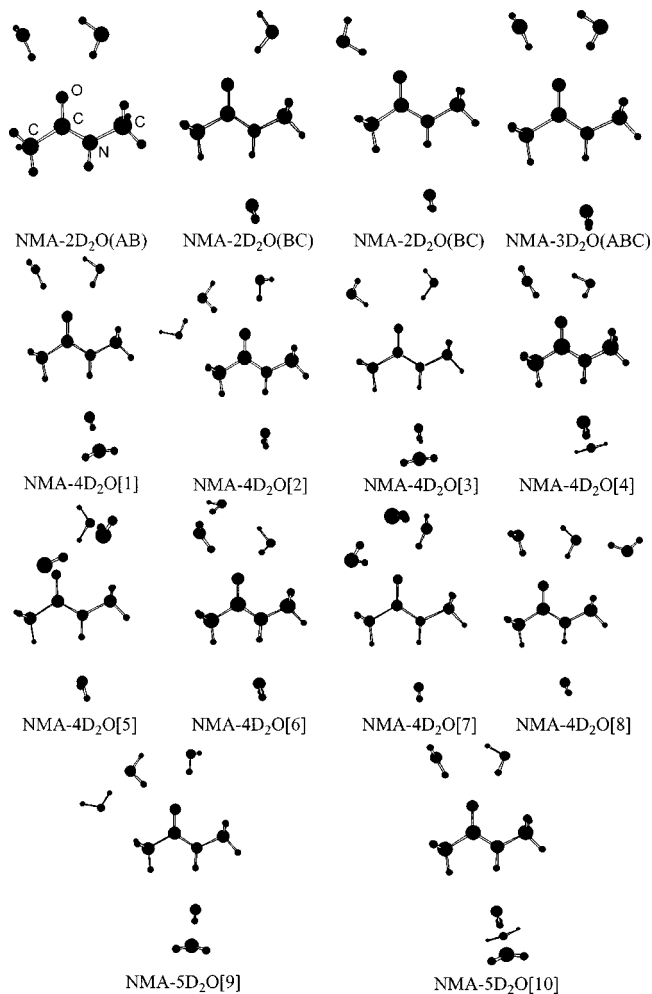


FIG. 4. Optimized geometries of a variety of NMA- $n\text{D}_2\text{O}$ ($n=2-5$) complexes calculated with the HF/6-311++G** method.

denoted as M_j , ω_j , g_{ijk} , and γ_{ijkl} , respectively. Now, using the electronic interaction Hamiltonian, $\sum_a \hat{c}_a \phi_a$ where \hat{c}_a and ϕ_a are the partial charge operator and the electrostatic potential at the site a of the target molecule, respectively, and invoking the Born–Huang adiabatic approximation, we were able to obtain the correction term, $V_\phi(\mathbf{Q})$, in Eq. (1). Noting that the partial charge of each site depends on the molecular geometry \mathbf{Q} , we found that $V_\phi(\mathbf{Q})$ can be approximately written as

$$V_\phi(\mathbf{Q}) = V_\phi(\mathbf{Q}_0) + \sum_j f_j Q_j + \frac{1}{2} \sum_{j,k} F_{jk} Q_j Q_k + \cdots, \quad (3)$$

where

$$V_\phi(\mathbf{Q}_0) = \sum_a C_a(\mathbf{Q}_0) \phi_a, \quad (4)$$

$$f_j = \left[\sum_a \left\{ \left(\frac{\partial C_a}{\partial Q_j} \right)_{\mathbf{Q}_0}^{\text{eff}} \phi_a + C_a(\mathbf{Q}_0) \left(\frac{\partial \phi_a}{\partial Q_j} \right)_{\mathbf{Q}_0} \right\} \right], \quad (5)$$

$$F_{jk} = \sum_a \left\{ \left(\frac{\partial^2 C_a}{\partial Q_j \partial Q_k} \right)_{\mathbf{Q}_0} \phi_a + 2 \left(\frac{\partial C_a}{\partial Q_j} \right)_{\mathbf{Q}_0} \left(\frac{\partial \phi_a}{\partial Q_k} \right)_{\mathbf{Q}_0} + C_a(\mathbf{Q}_0) \left(\frac{\partial^2 \phi_a}{\partial Q_j \partial Q_k} \right)_{\mathbf{Q}_0} \right\}. \quad (6)$$

Here, the partial charge of the site a when the molecule is in the electronic ground state was denoted as $C_a(\mathbf{Q})$. $(\partial C_a / \partial Q_j)_{\mathbf{Q}_0}^{\text{eff}}$ are the *effective* vibrational transition charges that include all electronic polarization effects and will be treated as fitting parameters. Typically, the electrostatic potential is a slowly varying function of Q_j , so the contributions associated with the first and second derivatives of ϕ_a will be ignored in the following discussion.

A. Distortion of the molecular structure: Q_I mode displacement in NMA– $n\text{D}_2\text{O}$ complexes

Due to the existence of the first-order expansion terms, $\sum_j f_j Q_j$, in the total potential function, Eq. (3), the new equilibrium geometry of the molecule surrounded by other solvent molecules differs from that of the gas-phase molecule. More specifically, the amide I mode coordinate at the new equilibrium structure of NMA in a given NMA– $n\text{D}_2\text{O}$ complex is displaced by δQ_I , which was found to be⁹

$$\delta Q_I = -\frac{f_I}{M_I(\omega_I^0)^2} = -\frac{1}{M_I(\omega_I^0)^2} \sum_a \left(\frac{\partial C_a}{\partial Q_I} \right)_{\mathbf{Q}_0}^{\text{eff}} \phi_a, \quad (7)$$

where the reduced mass and angular frequency of the amide I mode of the gas-phase NMA are denoted as M_I and ω_I^0 , respectively. Here, δQ_I represents the magnitude of the molecular structure distortion, which is induced by the electrostatic interaction of the NMA with the surrounding water molecules, projected onto the amide I coordinate. For NMA– $n\text{D}_2\text{O}$ complexes, δQ_I is given as

$$\delta Q_I = -\frac{1}{M_I(\omega_I^0)^2} \sum_a \left[\left(\frac{\partial C_a}{\partial Q_I} \right)_{\mathbf{Q}_0}^{\text{eff}} \left(\sum_{m,b} \frac{C_{b(m)}^{\text{D}_2\text{O}}}{4\pi\epsilon_0 r_{ab(m)}} \right) \right], \quad (8)$$

where $C_{b(m)}^{\text{D}_2\text{O}}$ is the partial charge of the b site of the m th water molecule and $r_{ab(m)}$ is the distance between the a site of the NMA and the b site of the m th water molecule. Equation (8) explains why the molecular structure, particularly the equilibrium amide I coordinate value, changes as the NMA is solvated by water molecules (or any other polar solvent molecules).

B. Amide I mode frequency shift

The frequency shift induced by the electrostatic solute–solvent interaction was mainly ascribed to the combination of the intrinsic anharmonicity of the gas-phase potential function and structural distortion.⁹ Thus, we have

$$\tilde{\nu}_I \cong \tilde{\nu}_I^0 + \frac{g_I}{4\pi c M_I \omega_I^0} \delta Q_I, \quad (9)$$

where δQ_I was given in Eq. (8), $g_I = (\partial^3 V_0 / \partial Q_I^3)_{\mathbf{Q}_0}$, c is the speed of light in cm/s. In order to obtain Eq. (9), we assumed that the off-diagonal cubic anharmonicity contributions are negligibly small in comparison to the diagonal one. The quartic anharmonicity contribution was ignored because its contribution to $\tilde{\nu}_I$ is quadratically dependent on δQ_I [or $d(\text{C}=\text{O})$], whereas $\tilde{\nu}_I$ was found to be almost linearly proportional to $d(\text{C}=\text{O})$ (see Fig. 3). Also, the contribution associated with the second derivatives of the partial charges with respect to Q_I , which is the second term in Eq. (72) of Paper I, was ignored.³⁵ By assuming that δQ_I is linearly proportional to $\delta d(\text{C}=\text{O})$ as

$$\delta Q_I = \beta \delta d(\text{C}=\text{O}), \quad (10)$$

where the proportionality constant β is, roughly speaking, an averaged weight of the $\text{C}=\text{O}$ stretch internal coordinate in the amide I coordinate, Eq. (9) with (10) can be used to theoretically describe the linear relationship shown in Fig. 3. From the linear regression analysis, we find that the slope is given as

$$\frac{g_I \beta}{4\pi c M_I \omega_I^0} = -3431.2 \text{ cm}^{-1}/\text{\AA}. \quad (11)$$

The reduced mass and frequency of the NMA amide I mode are calculated to be 0.716 amu and 1707.1 cm^{-1} , respectively. The cubic anharmonic coefficient g_I can be numerically calculated by using a finite-difference method. Using the same basis set, we found that the g_I value is $-1.105 \times 10^{13} \text{ Kg}/(\text{m} \cdot \text{s}^2)$. Combining these results, the proportionality constant β is estimated to be 0.55. The amide I coordinate displacements, δQ_I , of all 96 complexes were not directly calculated from the optimized molecular structures, because the amide I mode of an isolated NMA molecule is not precisely identical to that of the other NMA– $n\text{D}_2\text{O}$ complexes. In other words, the eigenvector elements of the amide I mode depend on which NMA– $n\text{D}_2\text{O}$ complex is under consideration. However, the $\text{C}=\text{O}$ bond length can be easily measured from all 96 optimized structures without any ambiguity. Thus, the proportionality constant β acts like a bridge connecting $d(\text{C}=\text{O})$ that can be straightforwardly calculated with any *ab initio* method with δQ_I that cannot be easily determined.

Before we close this subsection, we compare the *ab initio* calculated cubic anharmonic coefficient with the experimentally measured one. For a weakly anharmonic oscillator, the vibrational transition frequency from $|n-1\rangle$ to $|n\rangle$ is given as $\nu_{n,n-1} = \nu_0(1 - nA)$, where $A = 5\hbar g^2/24M^3\omega_0^5$. The fundamental transition frequency is $\omega_{1,0} = \omega_0(1 - A)$, and the transition frequency from $|1\rangle$ to $|2\rangle$ is $\omega_{2,1} = \omega_0(1 - 2A)$. Therefore, due to the cubic anharmonicity, the difference between the overtone transition frequency and twice of the fundamental transition frequency is ω_0A . This quantity was recently measured by Hamm and co-workers, who employed a two-dimensional pump-probe method and was estimated to be 16 cm^{-1} .² By using the *ab initio* calculated reduced mass, angular frequency, and cubic anharmonic coefficient of the amide I mode given above, we find that A is 0.025. Thus, the cubic-anharmonicity-induced frequency shift of the overtone band is about $42.7 (=1707 \times 0.025)\text{ cm}^{-1}$. The quantitative difference between experiment and *ab initio* result on the overtone frequency shift might originate from the following approximations and complications: (i) ignorance of the quartic anharmonicity contribution; (ii) errors associated with the finite-difference method for the calculation of the cubic anharmonic coefficient; (iii) limited basis set; (iv) ignorance of the electron correlation effects on the calculation of the potential energy surface; and (v) solvation effects on the molecular cubic anharmonic coefficient. Although our *ab initio* calculated g_I value appears to be larger than the experimentally measured one, we will use this *ab initio* calculated g_I value throughout this paper for the sake of internal consistency.

C. Multivariate least-square fitting analysis: Effective transition charges of six sites

We next develop a general approach to the prediction of the amide I mode frequency of NMA in any arbitrary NMA-water clusters or in liquid water. For a given NMA-water configuration, it is possible to determine the electrostatic potential field at each site, ϕ_a . In the present paper, we will treat the two methyl groups as a united atom so that the number of sites is six and they are O, C, N, H, CH₃(N), and CH₃(C)—note that the sum of the partial charges of C and three H atoms is assigned to the partial charge of the C atom in a given methyl group. Now, it is necessary to quantitatively determine the *effective* six transition charges $(\partial C_a/\partial Q_I)_{Q_0}^{\text{eff}}$. We will treat the six transition charges as adjustable parameters. In Table I, the CHELPG partial charges³⁶ of water are listed.

Equation (9) is now re-expressed as a linear curve in the six-dimensional space constructed by the six electrostatic potentials, i.e.,

$$\tilde{\nu}_I - \tilde{\nu}_I^0 = \sum_{a=1}^6 l_a \phi_a, \quad (12)$$

where the expansion constants are defined as

$$l_a = -\frac{g_I}{4\pi c M_I^2 (\omega_I^0)^3} \left(\frac{\partial C_a}{\partial Q_I} \right)_{Q_0}^{\text{eff}}. \quad (13)$$

TABLE I. Six fitting parameters l_a (in e), the corresponding effective transition charges for NMA, and CHELPG charges (in e) of isolated water molecules are listed. Optimized geometry was obtained with the HF/6-311 + G** level calculation. The effective transition charge $(\partial C_a/\partial Q_I)_{Q_0}^{\text{eff}}$ is in $e/\text{\AA}$.

NMA	l_a	$(\partial C_a/\partial Q_I)_{Q_0}$	Water	Charges
O (C=O)	-0.0054	-0.647	O	-0.824
C (C=O)	0.0003	0.036	H	0.412
N	0.0064	0.767		
H (N-H)	-0.0014	-0.168		
CH ₃ (N)	-0.0011	-0.132		
CH ₃ (C)	0.0012	0.144		

From the optimized molecular structures of 96 NMA- $n\text{H}_2\text{O}$ complexes, the electrostatic potentials ϕ_a ($a=1-6$) are calculated. Therefore, one can use a multivariate least-square regression method to obtain six parameters that are linearly proportional to the six transition charges $(\partial C_a/\partial Q_I)_{Q_0}^{\text{eff}}$. Here, it should be noted that all parameters, l_a ($a=1-6$), are not independent because of the charge neutrality condition, i.e., $\sum_a C_a = 0$ and $\sum_a (\partial C_a/\partial Q_I)_{Q_0}^{\text{eff}} = 0$. That is to say, $\sum_a l_a = 0$. Therefore, without loss of any generality, we assume that $l_6 = -\sum_{a=1}^5 l_a$. With this constraint regarding the number of independent parameters, Eq. (12) can be rewritten as

$$\tilde{\nu}_I - \tilde{\nu}_I^0 = \sum_{a=1}^5 l_a (\phi_a - \phi_6). \quad (14)$$

Note that the dimension is now reduced to five instead of six. Performing the multivariate least-square regression analysis solves the following linear equation:

$$\mathbf{I} = \tilde{\mathbf{M}}^{-1} \mathbf{y}, \quad (15)$$

where \mathbf{I} is a column vector of $\{l_a (a=1 \sim 5)\}$, and

$$\tilde{\mathbf{M}}_{jk} = \sum_n (\phi_j^{(n)} - \phi_6^{(n)}) (\phi_k^{(n)} - \phi_6^{(n)}), \quad (16)$$

$$y_j = \sum_n (\phi_j^{(n)} - \phi_6^{(n)}) (\tilde{\nu}_I^{(n)} - \tilde{\nu}_I^0).$$

The summation over n is over all *ab initio* calculation data for 96 NMA- $n\text{H}_2\text{O}$ complexes. Now, the above analysis provides us the values of the six parameters, l_a ($a=1-6$), and inserting *ab initio* calculated g_I , reduced mass, and angular frequency into Eq. (13) we determined the six effective transition charges $(\partial C_a/\partial Q_I)_{Q_0}^{\text{eff}}$, in $e/\text{\AA}$ (see Table I). Since we have converted the dimension of ϕ_a into cm^{-1}/e , the parameters, l_a , are in e . By using thus-determined $(\partial C_a/\partial Q_I)_{Q_0}^{\text{eff}}$ values, we plot the *ab initio* calculated $\tilde{\nu}_I$ (*ab initio*) with respect to $\sum_{a=1}^6 l_a \phi_a$ to emphasize the fitting quality (see Fig. 5 and Table II). The empirical relationship in Eq. (12) is found to be successful in describing the amide I mode frequency shift of NMA hydrated by a single water molecule as well as those of 14 NMA- $n\text{D}_2\text{O}$ ($n=2-5$) complexes.

The above results discussed in this section provide a way to explain a couple of puzzling observations made in this

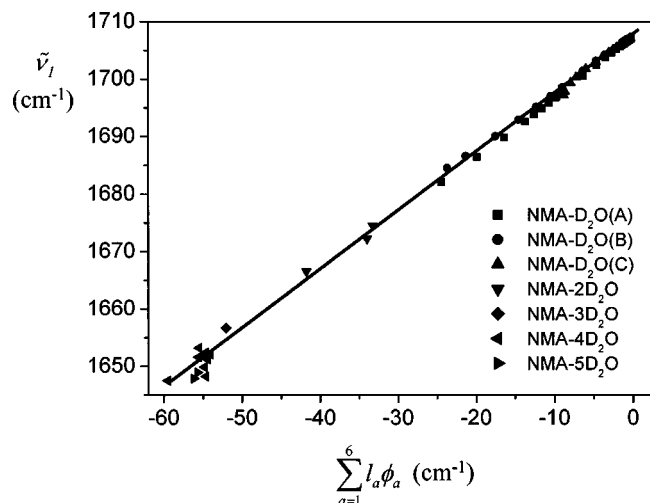


FIG. 5. For all NMA- n D₂O complexes (for $n=1-5$), the amide I mode frequencies are plotted with respect to the theoretically calculated $\sum_{a=1}^6 l_a \phi_a$ given in Eq. (12). The linear fitting is shown as a solid line on the top of the data points.

paper and reported by other workers. The first is that, as found by Torii *et al.*,¹⁰ the amide I mode frequency shift by hydrogen-bonded water molecules to the NMA is additive. To be more specific, the amide I mode frequency shift of the NMA-3H₂O(ABC) is almost equal to the sum of amide I mode frequency shifts of NMA-H₂O(A), NMA-H₂O(B), and NMA-H₂O(C). From Eqs. (9) with (8), the electrostatic potential field at the site a , ϕ_a , of the NMA is given by a sum of contributions from each water molecule. Due to this additive nature of the electrostatic potential, both δQ_I and $(\bar{\nu}_I - \bar{\nu}_I^0)$ can be written as a sum of components, each associated with a different water molecule. Also, the excellent fitting quality shown in Fig. 5 suggests that the many-body effect and polarizable nature of the surrounding water molecules might not be the dominant factors in the low-

TABLE II. *Ab initio* calculated amide I mode frequencies of various NMA-water complexes, and those calculated by using Eq. (12) and parameters presented in Table I.

	<i>Ab initio</i> (cm ⁻¹)	Theory (cm ⁻¹)
NMA-D ₂ O(A) ^a	1682.1	1682.6
NMA-D ₂ O(B) ^a	1684.5	1683.4
NMA-D ₂ O(C) ^a	1697.3	1698.3
NMA-2D ₂ O (AB)	1674.5	1673.9
NMA-2D ₂ O (AC)	1666.6	1665.4
NMA-2D ₂ O (BC)	1672.2	1673.1
NMA-3D ₂ O(ABC)	1656.7	1655.1
NMA-4D ₂ O[1]	1653.2	1651.6
NMA-4D ₂ O[2]	1652.4	1652.5
NMA-4D ₂ O[3]	1647.5	1647.6
NMA-4D ₂ O[4]	1651.6	1651.6
NMA-4D ₂ O[5]	1649.8	1652.3
NMA-4D ₂ O[6]	1648.2	1652.5
NMA-4D ₂ O[7]	1652.1	1653.0
NMA-4D ₂ O[8]	1651.2	1652.7
NMA-5D ₂ O[9]	1647.8	1650.9
NMA-5D ₂ O[10]	1648.9	1651.4

^aThe structures of these NMA-D₂O(A, B, or C) complexes are fully optimized ones.

frequency shift of the amide I mode in NMA-water complexes. As a matter of fact, one can use a polarizable model for the partial charges of each water molecule. For instance, the charge-response-kernel theory developed by Kato and co-workers³⁷ can be used to rewrite the partial charge of the b site of the m th water molecule as $C_{b(m)}^{H_2O} = C_b^{H_2O} + \sum_{b,c} K_{bc}^{H_2O} \phi_{c(m)}$, where the partial charge and the charge-response kernel of the gas-phase water molecule were denoted as $C_b^{H_2O}$ and $K_{bc}^{H_2O}$, respectively, and $\phi_{c(m)}$ is the electrostatic potential at the c site of the m th water molecule, which is created by all other molecules including NMA and other neighboring water molecules. Thus, the partial charges $C_{b(m)}^{H_2O}$ are to be calculated self-consistently. If the many-body effect is notably large, the amide I mode frequency shift cannot be approximated by a sum of contributions, each separately associated with one of the water molecules. However, this is not the case we found in the *ab initio* calculations.

The second puzzle was the site independence of the correlation between $\bar{\nu}_I$ and $d(\text{CO})$ shown in Fig. 3. For the two sites A and B (see Fig. 1), a single water molecule can directly form a hydrogen bond to the same carbonyl oxygen atom, so that one can expect the same correlation patterns for both cases. However, the site C is distinctively different from the other two sites. The oxygen atom of D₂O is hydrogen bonded to the H atom of the H-N (NMA) group. Nevertheless, the *ab initio* data (filled triangles in Fig. 3) are exactly on the same linear line. This may appear to be puzzling at first sight, if the local hydrogen-bond structure is only taken into account. However, noting that the water molecule at site C contributes to the structural distortion of the NMA via its electrostatic potential field at the NMA, and that the distortion amplitude is directly proportional to the amide I mode frequency shift [Eq. (9)], we can suggest that all water molecules regardless of their locations and orientations around the peptide should be treated on an equal footing. Therefore, as will be mentioned in Sec. IV, the empirical relationship in Eq. (12) can be used to predict the amide I mode frequency of the NMA dissolved in liquid water.

In Sec. I, we briefly mentioned an empirical relationship used by many workers, i.e., $\delta\bar{\nu}_I = -\alpha_{\text{H}_{\text{yd}}} \{2.6 - r(\text{O} \cdots \text{H})\}$, where $\alpha_{\text{H}_{\text{yd}}}$ was obtained by finding the best fit between experimental and modeled spectra.³⁸ Within this model, the amide I mode frequency shift is solely dependent on the intermolecular distance between the two atoms directly participating in the hydrogen bond. From Fig. 2(c), we can estimate $\alpha_{\text{H}_{\text{yd}}}$ values for the three different sites. Despite the fact that it is a highly simplified one with just a single adjustable parameter, $\alpha_{\text{H}_{\text{yd}}}$, we have found that $\alpha_{\text{H}_{\text{yd}}}$ is strongly site dependent—note that the initial slopes of the three curves differ from one another. Furthermore, if the relative orientation of the hydrogen-bonding water molecule deviates from the optimized geometry of the NMA-H₂O complex, $\alpha_{\text{H}_{\text{yd}}}$ value should be readjusted. This means that just one parameter value for $\alpha_{\text{H}_{\text{yd}}}$ cannot be used to generally predict $\delta\bar{\nu}_I$ for peptides solvated by water or any other associating liquids. On the other hand, the empirical relationship in Eq. (9) with (8) takes into account the dependence of $\delta\bar{\nu}_I$

on the orientation and distance of solvent molecule, though our theoretical model needs six adjustable parameters, i.e., β value and five transition charges. Despite the fact that the number of parameters required is relatively large, as shown in this paper, one needs at least this many parameters to describe the amide I mode frequency shifting behavior in general.

Before we close this section, there is one more issue that needs to be discussed. One might suggest that the charge transfer from the donor (NMA in our case) to the acceptor (water molecule) might be responsible for the low-frequency shift of the amide I mode. If the electron density around the carbonyl bond decreases due to the charge transfer from the C=O to water molecule, the C=O bond strength would be weakened a bit, and consequently the force constant and frequency of the amide I mode decrease. In order to study the charge-transfer effect, we calculated the net charge of the NMA as water molecule approaches it using both CHELPG and Mulliken population analyses. The results indicate that the extent of charge transfer from NMA to water at the A site is fairly different from that at the B site, whereas the hydration effect on the amide I mode frequency shift for the two sites A and B was found to be almost identical [see Fig. 2(c)]. Also, the extent of total charge transfer from the NMA to water was found to be very small (less than 0.07e). These observations suggest that it is possible to rule out the intermolecular charge-transfer mechanism for the amide I mode frequency shift, at least for those NMA- n D₂O complexes studied in the present paper.

IV. SUMMARY AND A FEW CONCLUDING REMARKS

We have carried out extensive *ab initio* calculations for a number of NMA-water complexes. For NMA- n D₂O (for $n = 1-5$) complexes, regardless of the locations and orientations of the surrounding water molecules, the amide I mode frequency was found to be linearly proportional to the hydration-induced displacement of the C=O bond length. Basically, the electrostatic potential created by the surrounding water molecules induces a distortion of the electronic structure of the NMA molecule. Then, the molecular structure accordingly changes to accommodate the electronic structure distortion, which is in turn observed by the increment of the C=O bond length when D₂O molecules are hydrogen bonded to the NMA. Due to this molecular structure distortion and nonzero cubic anharmonicity of the amide I mode, the amide I mode frequency shifts when the NMA is hydrated by a few water molecules were successfully explained. By using the *ab initio* calculated cubic anharmonic coefficient and the multivariate least-square regression analysis method, we determined the six effective transition charges $(\partial C_a / \partial Q_I)_{Q_0}^{\text{eff}}$. Although we have only considered a model peptide molecule, NMA, the same theoretical result is believed to be applicable to quantitatively predict the frequency shift of the amide I modes of polypeptides in aqueous solution.

An immediate application of the present theory is to study vibrational frequency shift of the amide I mode of NMA in liquid water. Molecular dynamics simulation can

provide information on the pair correlation functions of the H and O atoms of surrounding water molecules around the NMA. By using the pair distribution function as $g_{aH}(r_{aH})$ ($g_{aO}(r_{aO})$), where r_{aH} (r_{aO}) is the distance between the a site of the NMA and H (O) atom of the solvent H₂O molecules around it, the ensemble averaged values, $\langle \phi_a \rangle$, for all six sites over the distribution of water molecules, can be calculated as

$$\langle \phi_a \rangle = (4\pi\epsilon_0)^{-1} \left\{ C_{\text{O}}^{\text{H}_2\text{O}} \left\langle \frac{1}{r_{a\text{O}}} \right\rangle + C_{\text{H}}^{\text{H}_2\text{O}} \left\langle \frac{1}{r_{a\text{H}}} \right\rangle \right\}, \quad (17)$$

where $C_{\text{O}}^{\text{H}_2\text{O}}$ and $C_{\text{H}}^{\text{H}_2\text{O}}$ are the partial charges of the oxygen and hydrogen atoms of the gas-phase water molecule, respectively. The ensemble averaged values of $\langle 1/r_{aH} \rangle$ and $\langle 1/r_{aO} \rangle$ can be expressed as integrals over the pair correlation functions, $g_{aH}(r_{aH})$ and $g_{aO}(r_{aO})$, respectively. Therefore, once the pair correlation functions are determined from the MD (MC) simulation, the ensemble averaged amide I mode frequency can be calculated by using the expression in Eq. (9), i.e.,

$$\langle \tilde{\nu}_I \rangle \cong \tilde{\nu}_I^0 + \langle \tilde{\nu}_I^{(1)} \rangle,$$

where

$$\begin{aligned} \langle \tilde{\nu}_I^{(1)} \rangle &\equiv \frac{g_I}{4\pi c M_I \omega_I^0} \langle \delta Q_I \rangle \\ &= - \frac{g_I}{4\pi c M_I^2 (\omega_I^0)^3} \sum_a \left[\left(\frac{\partial C_a}{\partial Q_I} \right)_{Q_0}^{\text{eff}} \langle \phi_a \rangle \right]. \end{aligned} \quad (18)$$

Currently, we are carrying out this MD simulation of the aqueous NMA solution to obtain the 12 pair correlation functions to calculate the ensemble averaged frequency shift of the amide I mode in liquid water, and the result will be quantitatively compared with the experiment.

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- ¹P. Hamm, M. Lim, W. F. DeGrado, and R. M. Hochstrasser, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 2036 (1999).
- ²P. Hamm, M. Lim, and R. M. Hochstrasser, *J. Phys. Chem. B* **102**, 6123 (1998).
- ³S. Woutersen and P. Hamm, *J. Phys. Chem. B* **104**, 11316 (2000).
- ⁴C. Scheurer, A. Piryatinski, and S. Mukamel, *J. Am. Chem. Soc.* **123**, 3114 (2001).
- ⁵P. Hamm, M. Lim, W. F. DeGrado, and R. M. Hochstrasser, *J. Phys. Chem. A* **103**, 10049 (1999); *J. Chem. Phys.* **112**, 1907 (2000).
- ⁶M. Cho, *Advances in Multi-Photon Processes and Spectroscopy*, edited by S. H. Lin, A. A. Villaes, and Y. Fujimura (World Scientific, Singapore, 1999).
- ⁷M. Cho, *PhysChemComm.* **5**, 40 (2002).
- ⁸G. Eaton, C. R. Symons, and P. P. Rastogi, *J. Chem. Soc., Faraday Trans.* **85**, 3257 (1991).
- ⁹M. Cho, *J. Chem. Phys.* **118**, 3480 (2003). This is the companion Paper I on the correlation between electronic and molecular structure distortions and vibrational properties. I. Adiabatic approximations.
- ¹⁰H. Torii, T. Tatsumi, and M. Tasumi, *J. Raman Spectrosc.* **29**, 537 (1998).
- ¹¹N. Mirkin and S. Krimm, *J. Am. Chem. Soc.* **113**, 9742 (1991).
- ¹²N. Mirkin and S. Krimm, *J. Mol. Struct.* **242**, 143 (1991).
- ¹³N. Mirkin and S. Krimm, *J. Mol. Struct.* **377**, 219 (1996).
- ¹⁴L. M. Markham and B. S. Hudson, *J. Phys. Chem.* **100**, 2731 (1996).
- ¹⁵N. A. Besley and J. Hirst, *J. Phys. Chem. A* **102**, 10791 (1998).

- ¹⁶H. Torii, T. Tatsumi, T. Kanazawa, and M. Tasumi, *J. Phys. Chem. B* **102**, 309 (1998).
- ¹⁷G. J. Kearley, M. R. Johnson, M. Plazanet, and E. J. Suard, *Chem. Phys.* **115**, 2614 (2001).
- ¹⁸H. Torii and M. Tasumi, *Int. J. Quantum Chem.* **70**, 241 (1998).
- ¹⁹W. A. Herrebout, K. Clou, and H. O. Desseyn, *J. Phys. Chem. A* **105**, 4865 (2001).
- ²⁰D. A. Dixon, K. D. Dobbs, and J. J. Valentini, *J. Phys. Chem.* **98**, 13435 (1994).
- ²¹S. Haseler, G. Poglitsch, G. Bechtold, and W. L. Peticolas, *J. Chem. Phys.* **84**, 1046 (1986).
- ²²Y. Wang, R. Purello, S. Georgiu, and T. G. Spiro, *J. Am. Chem. Soc.* **113**, 6368 (1991).
- ²³X. G. Chen, R. Schweitzer-Stenner, S. Krimm, N. G. Mirkin, and S. A. Asher, *J. Am. Chem. Soc.* **166**, 11141 (1994).
- ²⁴X. G. Chen, R. Schweitzer-Stenner, S. A. Asher, N. G. Mirkin, and S. Krimm, *J. Phys. Chem.* **99**, 3074 (1995).
- ²⁵X. G. Chen, S. A. Asher, R. Schweitzer-Stenner, N. G. Mirkin, and S. Krimm, *J. Am. Chem. Soc.* **117**, 2884 (1995).
- ²⁶H. Guo and M. Karplus, *J. Phys. Chem.* **96**, 7273 (1992).
- ²⁷H. Guo and M. Karplus, *J. Phys. Chem.* **98**, 7104 (1994).
- ²⁸D. A. Dixon, K. D. Dobbs, and J. J. Valentini, *J. Phys. Chem.* **98**, 13435 (1994).
- ²⁹W.-G. Han and S. Suhai, *J. Phys. Chem.* **100**, 3942 (1996).
- ³⁰B. Kallies and R. Mitzner, *J. Chem. Soc., Perkin Trans. 2* **2**, 1403 (1996).
- ³¹J. Kubelka and T. A. Keiderling, *J. Phys. Chem. A* **105**, 10922 (2001).
- ³²M. Buck and M. Karplus, *J. Phys. Chem. B* **105**, 11000 (2001).
- ³³M. J. Frisch, G. W. Trucks, H. B. Schlegel *et al.*, GAUSSIAN 98, Revision A.7, Gaussian, Inc., Pittsburgh, PA, 1998.
- ³⁴J. A. Pople, A. P. Scott, M. W. Wong, and L. Radom, *Isr. J. Chem.* **33**, 345 (1994).
- ³⁵Preliminary *ab initio* calculated $(\partial^2 C_a / \partial Q_I^2)_{Q_0}$ values by using a finite-difference method were used to numerically estimate the second term on the right-hand side of Eq. (72) in Paper I (Ref. 9). It is found that this contribution (less than 2 cm^{-1}) is an order of magnitude smaller than $(g_I/4\pi c M_I \omega_I^0) \delta Q_I$ in Eq. (9).
- ³⁶M. W. Wong, M. Frisch, and K. B. Wiberg, *J. Am. Chem. Soc.* **113**, 4776 (1991).
- ³⁷A. Morita and S. Kato, *J. Am. Chem. Soc.* **119**, 4021 (1997).
- ³⁸ α_{Hyd} was estimated to be 30 cm^{-1} in Ref. 2 by finding the best fit between experimental and modeled spectra. The fact that hydrogen bonding causes a redshift of monomeric frequency was discussed in the following papers: S. Krimm and W. C. Reisdorf, Jr., *Faraday Discuss.* **99**, 181 (1994); N. G. Mirkin and S. Krimm, *J. Am. Chem. Soc.* **113**, 9742 (1991); and H. Torii, T. Tatsumi, and M. Tasumi, *Mikrochim. Acta, Suppl.* **14**, 531 (1997).