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Amide I modes in the *N*-methylacetamide dimer and glycine dipeptide analog: Diagonal force constants

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The local amide I mode frequency of a peptide has been found to be strongly affected by the interpeptide interaction, because the electronic and molecular structures of the peptide bond change due to the electrostatic interaction with surrounding peptides. *Ab initio* vibrational analyses of three different series of *N*-methylacetamide dimers and glycine dipeptide analog in α-helical and β-sheet conformations have been performed. It is found that the diagonal force constant shift originates from the electronic structure change of a given peptide in combination with the cubic anharmonicity of the local amide I mode. © *2003 American Institute of Physics.* [DOI: 10.1063/1.1559681]

I. INTRODUCTION

Assuming that the interpeptide interaction is well described by a dipole–dipole (DD) interaction, Krimm and coworkers proposed the so-called transition dipole coupling (TDC) theory,[1–4] where the vibrational coupling force constant between any given two local amide I modes is given by

$$C_{12}=\frac{1}{4\pi\varepsilon_0}\left(\frac{\partial\mu_1}{\partial Q_1}\right)_0\tilde{T}_{12}\left(\frac{\partial\mu_2}{\partial Q_2}\right)_0. \tag{1}$$

The dipole moments of the two peptides are denoted as μ_1 and μ_2, respectively, and the DD interaction tensor is denoted as $\tilde{T}_{12}$ defined as $\tilde{T}_{12}=(\tilde{I}-3\hat{r}\hat{r})/|\mathbf{r}|^3$. $\mathbf{r}=\mathbf{r}_1-\mathbf{r}_2$ and $\mathbf{r}_i$ $(i=1,2)$ denotes the position vectors of the two dipoles, and $\hat{r}$ denotes the unit vector along the direction of $\mathbf{r}$. The amide I vibrational coordinates of the two peptides are denoted as Q_1 and Q_2. $(\partial\mu_j/\partial Q_j)_0$ is the transition dipole moment of the jth peptide. For a dipeptide system, the corresponding Hessian matrix is therefore given as

$$\tilde{F}(\phi,\psi)=\begin{bmatrix} K_1(\phi,\psi) & C_{12}(\phi,\psi) \\ C_{12}(\phi,\psi) & K_2(\phi,\psi) \end{bmatrix}, \tag{2}$$

where the diagonal elements K_1 and K_2 are force constants of the two local amide I modes. The Ramachandran dihedral angles were denoted as ϕ and ψ. Due to the nonzero coupling force constant, two normal modes, i.e., symmetric and asymmetric amide I vibrations, are formed and their frequencies are further shifted from the zero-coupling values.

Because of the simplicity of the TDC model, it has been extensively used to describe amide I IR bands of polypeptides and even of globular proteins.[1–13] For example, Torii and Tasumi[10] and Krimm and Reisdorf, Jr.[11] used the TDC model to calculate amide I IR bands of globular proteins. Recently, the TDC model Hamiltonian was used to theoretically describe vibrational excitonic transitions involved in two-dimensional IR pump–probe and IR photon echo processes of short polypeptides and proteins.[14–18] Despite the success of the TDC model, there exist some examples proving that the model is not quantitatively reliable. As an example, Torii and Tasumi carried out *ab initio* vibrational analysis of a tripeptide, and they showed that it is impossible to simultaneously describe the coupling force constant between any two nearest-neighboring peptides as well as that between the second nearest-neighboring peptides with *a single set of TDC parameters*.[19] Recently, we carried out extensive *ab initio* calculations for a model dipeptide and compared the *ab initio* results with an extended TDC model where the diagonal Hessian matrix elements were further corrected by adding the second derivative terms from the DD interaction potential.[20] Although spectroscopic properties like IR and Raman intensities were quantitatively well described by the TDC model with properly adjusted parameters, the *ab initio* calculated center frequency, which is defined as the mean value of the symmetric and asymmetric amide I vibrational normal modes, was found to be strongly deviated from the TDC-predicted value.[20] This discrepancy between the DD interaction model and the *ab initio* calculation is mainly due to the inadequate description of the diagonal force constant for an arbitrary conformation of a given dipeptide. In this regard, the most widely used approaches to overcoming this obstacle were to modify the force field to produce best results for the spectroscopic properties. For instance, Mendelsohn and coworkers added two contributions, which are associated with the hydrogen- and valance-bond interactions, to the force field.[21] However, these ad hoc correction methods are not general nor provide a consistent picture on the origin of the frequency shift, though those methods were found to be useful for a few specific conformations.

Since the lack of any theoretical model predicting the diagonal force constants in globular proteins, Torii and Tasumi arbitrarily modified the diagonal Hessian matrix elements to make better fits of their numerically calculated amide I IR bands to experiments.[10] As far as the authors' knowledge, this important issue on the frequency shift of the amide I band, when the polypeptide forms an arbitrary con-

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formation including α-helix or β-sheet structures, still remains to be an unresolved problem.

In this paper, we attempt to tackle this problem by taking into account the anharmonicity of the local oscillators as well as the structural distortion induced by surrounding peptides. As discussed in Ref. 22 on the hydration effect on the amide I mode frequency, the electronic structure of the hydrated *N*-methylacetamide (NMA) peptide bond changes due to the perturbation of the electrostatic field created by the distributed partial charges of surrounding water molecules.[22] Then, the structural distortion combined with the cubic anharmonicity was found to be critical in describing frequency shift of the amide I mode in NMA-water clusters. We will first describe a theoretical model for the interpeptide interaction for dipeptides and peptide dimers by including molecular potential anharmonicity in Sec. II. The *ab initio* calculation results and comparisons with theory will be presented in Sec. III. The main results will be summarized in Sec. IV.

II. DIAGONAL HESSIAN MATRIX ELEMENTS: THEORETICAL MODEL

In this section, we will present a theoretical model for the interpeptide interaction of glycine dipeptide analog or NMA dimer. The amide I vibration of a given peptide bond has been approximated to be an oscillating dipole. However, due to the limitation of treating a peptide as a *point dipole*, we will assume that the interpeptide interaction can be described by the charge–charge interaction as was used in the theoretical description of the amide I mode frequency shift observed in NMA-nD$_2$O ($n=1-5$) complexes (see Ref. 22).

The model Hamiltonian for a dipeptide system is written as

$$H=\frac{P_1^2}{2M_1}+\frac{P_2^2}{2M_2}+V_1(Q_1)+V_2(Q_2)+V_I(Q_1,Q_2), \quad (3)$$

where

$$V_j(Q_j)=\tfrac{1}{2}k_j^0Q_j^2+\tfrac{1}{6}g_jQ_j^3+\cdots. \quad (4)$$

The force constant of the jth local amide I mode is denoted as $k_j^0=M_j\omega_j^2$. The reduced mass, angular frequency, and cubic anharmonic coefficient of the jth local amide I mode are denoted as M_j, ω_j, and g_j, respectively. Here, the interpeptide interaction $V_I(Q_1,Q_2)$ is an effective one taking into account charge–charge interaction as well as electronic polarization effects. One can Taylor-expand this effective interpeptide interaction potential with respect to the two local amide I coordinates. As discussed in Ref. 22, due to the nonzero linear force terms from the interpeptide interaction potential, the new equilibrium molecular structure differs from that of two separated peptides. More specifically, the two local coordinates become displaced by

$$\delta Q_i\cong-\frac{f_i}{k_i^0}, \quad (5)$$

where the force, which is $-f_i$, exerting on the ith local amide I mode is given as

$$f_i=\sum_j\,(\partial c_j/\partial Q_i)_0^{\mathrm{eff}}\phi_j. \quad (6)$$

Here, $(\partial c_j/\partial Q_i)_0^{\mathrm{eff}}$ is the effective vibrational transition charge of the jth site in the ith peptide group, and ϕ_j is the spatially nonuniform electrostatic potential field created by the neighboring peptide group, i.e.,

$$\phi_j=\sum_k\frac{c_k^0}{4\pi\varepsilon_0 r_{jk}}, \quad (7)$$

where c_k^0 is the effective partial charge of the kth site in the neighboring peptide group and r_{jk} is the distance between the jth site of the ith peptide and the kth site of the neighboring peptide. In the following section, we will treat the effective transition and partial charges as fitting parameters in the four-site model for glycine dipeptide and NMA dimer. Taking into account these structural changes represented by δQ_i's and potential anharmonicities of the two local modes, we obtain the Hessian matrix as

$$\tilde{F}=\begin{bmatrix}K_1(\cong k_1+g_1\delta Q_1) & C_{12}\\ C_{12} & K_2(\cong k_2+g_2\delta Q_2)\end{bmatrix}. \quad (8)$$

Note that the coordinate displacements, δQ_i, are strongly dependent on the relative orientation and distance between the two peptides. Thus, not only the off-diagonal coupling force constants but also the diagonal Hessian matrix elements change as the 3D conformation of the dipeptide changes. In Ref. 20, we did not include the anharmonicity-induced terms in Eq. (8) because the harmonic approximation to the local amide I mode was invoked.

From the above Hessian matrix, we obtain normal mode Hamiltonian

$$H=\frac{P_+^2}{2M_+}+\frac{1}{2}M_+\omega_+^2Q_+^2+\frac{P_-^2}{2M_-}+\frac{1}{2}M_-\omega_-^2Q_-^2, \quad (9)$$

where $P_\pm$ denote the conjugate momenta of $Q_\pm$. The two normal mode frequencies are given as

$$\omega_\pm=\frac{1}{\sqrt{2M_\pm}}\{(K_1+K_2)\pm\sqrt{(K_1-K_2)^2+4C_{12}^2}\}^{1/2}. \quad (10)$$

For homodipeptides and NMA dimers considered in the present paper, the frequency splitting, $\delta\tilde{\nu}(\phi,\psi)$, and center frequency, $\tilde{\nu}_{\mathrm{center}}(\phi,\psi)$, are given as

$$\delta\tilde{\nu}(\phi,\psi)\equiv\tilde{\nu}_+-\tilde{\nu}_-\cong\frac{\sqrt{(K_1-K_2)^2+4C_{12}^2}}{2\pi c\sqrt{2M(K_1+K_2)}}, \quad (11)$$

$$\begin{aligned}\tilde{\nu}_{\mathrm{center}}(\phi,\psi)&\equiv(\tilde{\nu}_++\tilde{\nu}_-)/2\\ &\cong\frac{1}{2\pi c}\sqrt{\frac{(K_1+K_2)}{2M}}\\ &\cong\tilde{\nu}_0\left\{1+\frac{g(\delta Q_1+\delta Q_2)}{4k_0}\right\},\end{aligned} \quad (12)$$

where $k_0=k_1=k_2$ and M is the reduced mass of the local amide I mode and c is the speed of light in cm/s. The amide I mode frequency of an isolated peptide is denoted as $\tilde{\nu}_0$, which will be assumed to be that of NMA.

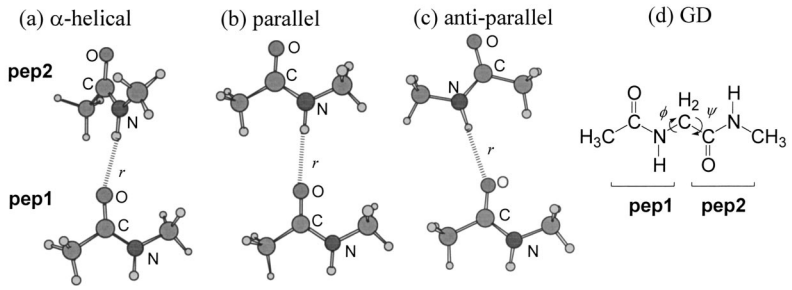

FIG. 1. Three relative orientations of two NMA molecules are depicted: (a) α-helical geometry, (b) parallel geometry, and (c) antiparallel geometry. Glycine dipeptide (GD) analog is shown in (d). Each peptide unit is denoted as pep1 or pep2 as two diagonal elements in the Hessian matrix differ.

III. *AB INITIO* VIBRATIONAL ANALYSES AND HESSIAN MATRIX RECONSTRUCTION METHOD

A. *Ab initio* vibrational analyses

In the present paper, we will consider four different systems containing two peptide groups, i.e., (a) NMA dimer in an α-helical conformation, (b) NMA dimer in a parallel β-sheet conformation, (c) NMA dimer in an antiparallel β-sheet conformation, and (d) glycine dipeptide (GD) analog [see Figs. 1(a)–1(d)]. All *ab initio* molecular orbital calculations were performed at the RHF/6-311++G** level using the GAUSSIAN 98 program.[23]

1. α-helical NMA dimers

Two *trans*-NMA molecules can be stabilized as a dimer in the gas-phase by making either one or two hydrogen bonds. We will specifically consider the case of an NMA dimer with a single hydrogen bond.[24] The relative orientations of the two NMA molecules are fixed to adopt an α-helical conformation [see Fig. 1(a)]. The two NMA molecules are then farther separated from each other along the hydrogen bond axis. For each fixed intermolecular distance, geometry optimization and vibrational analysis are performed to calculate the frequencies of symmetric ($\tilde{\nu}_s$) and asymmetric ($\tilde{\nu}_a$) amide I normal modes. Vibrational frequencies are corrected by using a single scaling factor of 0.8929.[25] In Fig. 2(a), the *ab initio* calculated $\tilde{\nu}_s$, $\tilde{\nu}_a$, and center frequency $\tilde{\nu}_{\text{center}}$ [$=(\tilde{\nu}_s+\tilde{\nu}_a)/2$] are depicted. $\tilde{\nu}_{\text{center}}$ that is directly related to the frequencies (diagonal Hessian matrix elements) of the two local amide I modes is strongly dependent on the intermolecular distance and relative orientation between the two NMA molecules. Suppose that the diagonal force constants, K_1 and K_2, are not affected by the presence of neighboring peptides and the off-diagonal coupling, such as the TDC mechanism, is solely responsible for the frequency splitting in a given dipeptide. Then, the high-frequency amide I component would shift farther up and the lower one farther down, and the center frequency $\tilde{\nu}_{\text{center}}$ is remained to be a constant. However, the *ab initio* calculation results depicted in Fig. 2(a) show that both frequencies, $\tilde{\nu}_s$ and $\tilde{\nu}_a$, shift to the lower frequencies as the two NMA's approach each other. Kubelka and Keiderling also observed the same trend, though these frequency-shifting behaviors were not explained neither quantitatively nor theoretically.[26] By using the theory discussed in Sec. II, it becomes possible to explain this frequency-shifting behavior. We will first

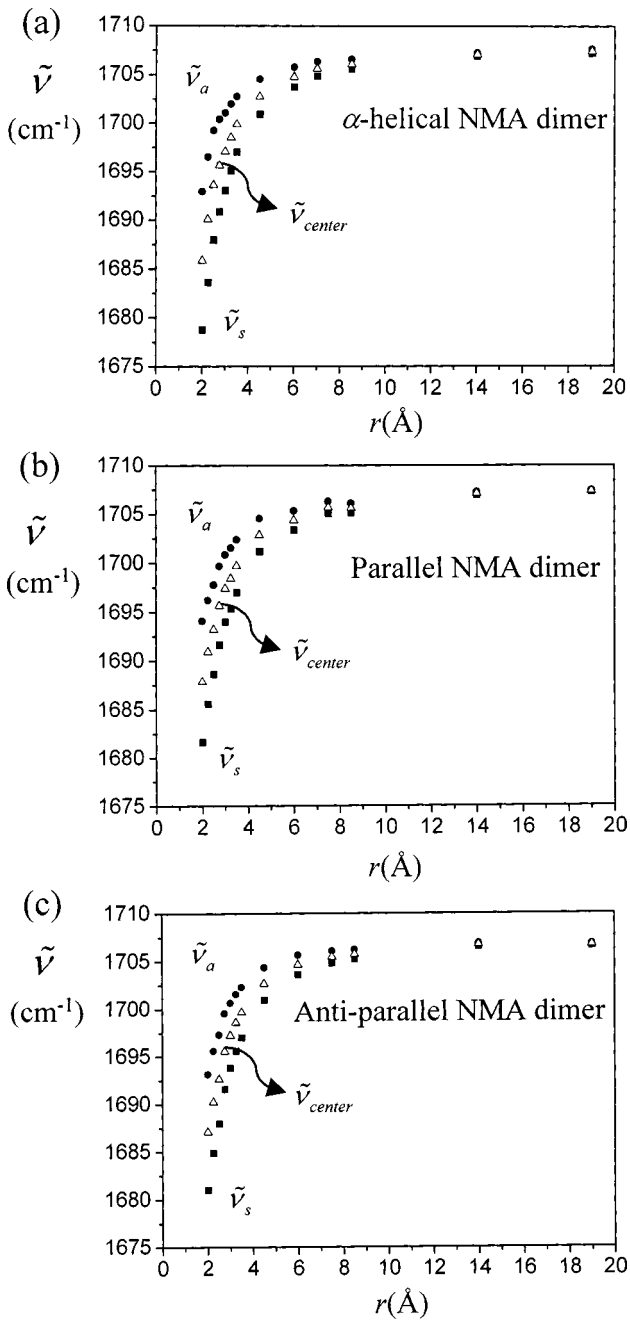

FIG. 2. *Ab initio* calculated $\tilde{\nu}_s$, $\tilde{\nu}_a$, and $\tilde{\nu}_{\text{center}}$ as functions of intermolecular distance, $r(\text{O}\cdots\text{H})$, are plotted for (a) α-helical geometry, (b) parallel geometry, and (c) antiparallel geometry of the NMA dimer.

TABLE I. Center frequency ($\tilde{\nu}_{\text{center}}$) of GD in α-helical and β-sheet regions calculated by using *ab initio* method and theoretical expression, Eq. (18). The scaling factor, 0.8929, was multiplied to the *ab initio* (RHF/6-311++G**) calculated frequency.

α helix	*Ab initio* (cm^{-1})			Theory (cm^{-1})		
$\psi\backslash\phi$	-80	-60	-40	-80	-60	-40
-40	1732.3	1727.8	1722.0	1731.9	1725.2	1715.2
-60	1737.9	1738.7	1732.8	1737.7	1733.7	1723.4
-80	1741.0	1743.9	1741.8	1738.8	1741.3	1731.4

β sheet	*Ab initio* (cm^{-1})				Theory (cm^{-1})			
$\psi\backslash\phi$	-180	-160	-140	-120	-180	-160	-140	-120
180	1706.6	1704.0	1708.6	1714.3	1700.0	1700.1	1700.1	1699.9
160	1703.6	1706.1	1703.2	1708.5	1701.0	1700.3	1700.0	1698.5
140	1706.8	1702.7	1701.4	1703.6	1703.9	1702.4	1701.0	1699.0
120	1711.4	1706.7	1703.7	1703.3	1708.6	1706.6	1704.3	1701.5
100	1717.5	1713.5	1709.4	1706.6	1714.5	1712.2	1709.5	1705.8
80	1723.0	1720.0	1715.4	1710.6	1720.6	1718.4	1715.4	1711.4
60	1725.7	1723.2	1718.2	1712.2	1725.8	1723.7	1720.9	1717.3

present a qualitative picture and the more quantitative description will be followed. As the two NMA's approach to each other, the linear force terms, $-f_1$ and $-f_2$, in this case negatively increase. Consequently, the equilibrium values of the two local amide I coordinates (or C═O bond lengths) increase (molecular structure distortion). Due to this coordinate displacement and the cubic anharmonicity that is negative, the diagonal force constants decrease as the intermolecular distance between the two NMA's decreases. This will appear as a redshift of $\tilde{\nu}_{\text{center}}$.

2. β-sheet NMA dimers

We next consider the cases when the two NMA's form either parallel or antiparallel β-sheet conformations [see Figs. 1(b) and 1(c)]. The distance between the two NMA's is increased, and the center frequency of the two amide I normal modes is calculated for each fixed intermolecular distance, $r(\text{O}\cdots\text{H})$. The *ab initio* calculated $\tilde{\nu}_{\text{center}}$, $\tilde{\nu}_s$, and $\tilde{\nu}_a$ for the two series of β-sheet NMA dimer conformations are plotted in Figs. 2(b) and 2(c), respectively. Again, the center frequency exhibits a downward shift for both cases, as r decreases. One can describe this redshifting behavior by using the same mechanism as has been done for the α-helical NMA dimers. Here, it should be mentioned that Torii *et al.* considered the geometry-optimized parallel and antiparallel NMA dimers and discussed the variations of the C═O bond lengths, C═O stretching force constants, and amide I mode frequency shifts.[27]

3. Glycine dipeptide (GD) analog

The NMA dimer systems considered above are those cases when the intermolecular electrostatic interaction energies are negative, i.e., an attractive interaction. However, in the α-helical or β-sheet polypeptides, that between two nearest neighboring peptides is typically positive, i.e., a repulsive interaction. We thus include *ab initio* calculation data of GD when its conformation is close to either α-helical ($\phi\approx-60$, $\psi\approx-60$) or β-sheet ($\phi\approx-180$, $\psi\approx180$) conformations—note that these *ab initio* data were taken from our previous report[20] and see Table I for the (ϕ,ψ) angles considered here. The *ab initio* center frequencies, $\tilde{\nu}_{\text{center}}$, for those conformations are given in the same Table I.

B. Hessian matrix reconstruction method

Previously, we presented a method of reconstructing Hessian matrix of dipeptide (GD) from *ab initio* calculated eigenvalues and eigenvectors by introducing the mixing angle θ,[13]

$$\begin{bmatrix} Q_S \\ Q_A \end{bmatrix} = \begin{bmatrix} \cos\theta & \sin\theta \\ -\sin\theta & \cos\theta \end{bmatrix} \begin{bmatrix} Q_1 \\ Q_2 \end{bmatrix}, \tag{13}$$

where the symmetric and antisymmetric amide I normal coordinates Q_S and Q_A are given by a linear combination of two local amide I vibrational coordinates Q_1 and Q_2. For both NMA dimers and GD, using the above Hessian matrix reconstruction method[13,28] and *ab initio* calculated symmetric and antisymmetric amide I normal mode frequencies and eigenvectors for a given GD conformation specified by the two dihedral angles (ϕ,ψ), we obtained the two local amide I mode frequencies (diagonal Hessian matrix elements) as well as the coupling constant in wave number (off-diagonal Hessian matrix elements). For the GD molecule, the two local amide I mode frequencies ($\tilde{\nu}_1$ and $\tilde{\nu}_2$) in the Ramachandran space (ϕ,ψ) are shown in Figs. 3(a) and 3(b). It should be noted that the two local amide I mode frequencies differ from each other, because the chemical environment of each peptide is different. Although this nondegeneracy nature has long been recognized, there was no theoretical model quantitatively describing this frequency difference even for a simple dipeptide molecule until recently we have attempted to describe this asymmetric nature of the two diagonal force constants found in the *ab initio* study of GD.[20]

The off-diagonal coupling force constants for GD in the entire Ramachandran space (ϕ,ψ) are also shown in Figs. 3(c) and 3(d). Although the overall shape of the contour looks similar to the previously reported one by Torii *et al.*,[19] the magnitudes are different because the asymmetric nature of the two diagonal force constants are correctly considered in the present paper.

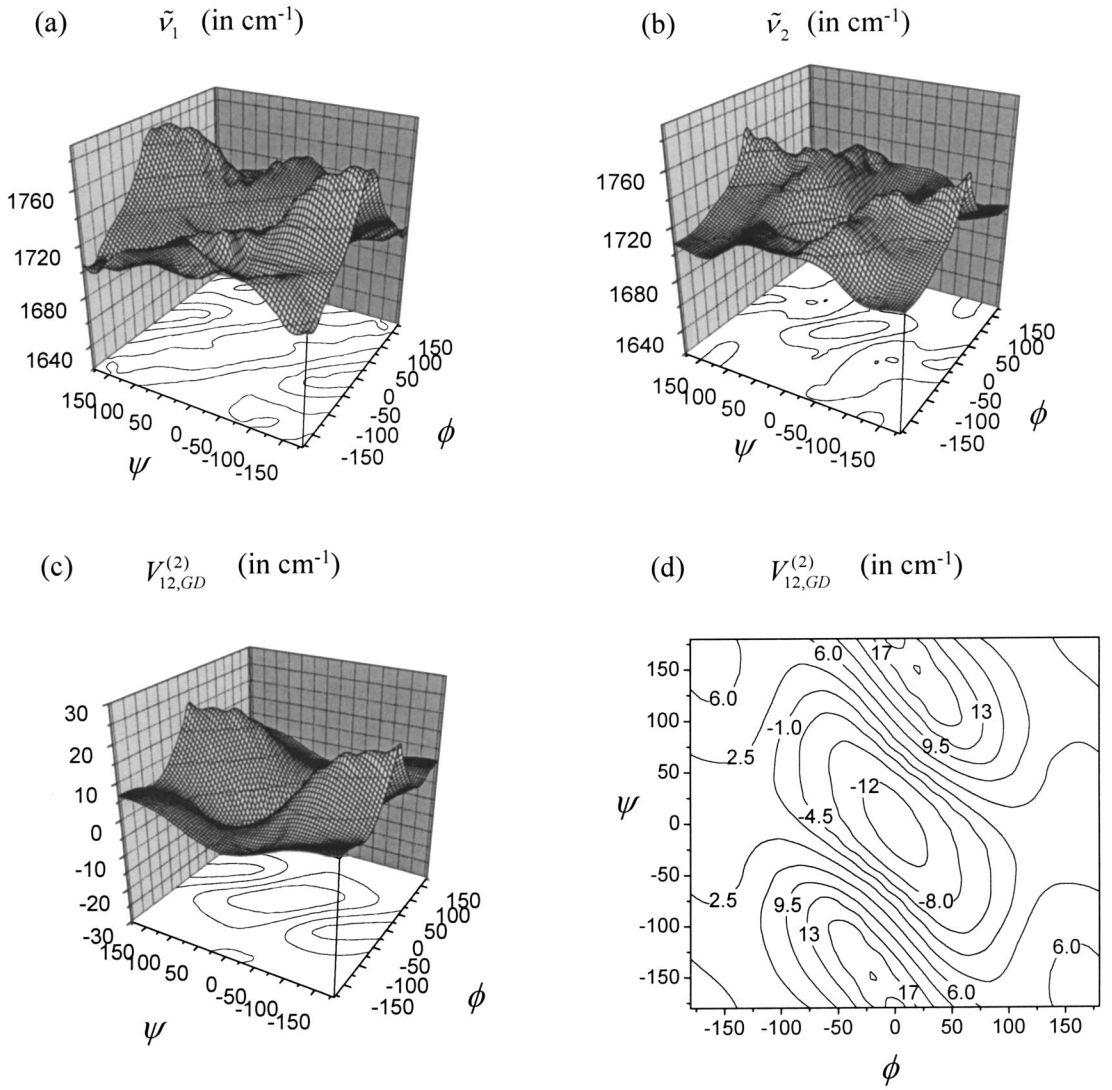

FIG. 3. The diagonal Hessian matrix element $\tilde{\nu}_1$ and $\tilde{\nu}_2$ are plotted in the full Ramachandran space for dipeptide (GDA) in (a) and (b), respectively. Also, the Ramachandran surface of the off-diagonal coupling constant in cm^{-1} is shown in (c) and (d).

C. Relationship between the C═O bond length and the local amide I mode frequency

Recently, we found that the amide I mode frequency of each NMA-nD$_2$O complex is linearly proportional to the C═O bond length displacement, δd_{CO}, i.e.,

$$\tilde{\nu}_I \propto \delta d_{\mathrm{CO}}, \tag{14}$$

where $\delta d_{\mathrm{CO}} = d_{\mathrm{CO}} - d_{\mathrm{CO}}^{\mathrm{NMA}}$, and d_{CO} and $d_{\mathrm{CO}}^{\mathrm{NMA}}$ are the C═O bond length of the NMA in an NMA-nD$_2$O complex and that of the gas-phase NMA, respectively.[22] However, there are no existing reports showing that the same linear relationship holds for polypeptides, although the linear relationship between the C═O stretching force constant and C═O bond length was observed and reported before for a few NMA-water complexes,[29] and for NMA dimers and trimers.[27] Due to the electrostatic interaction between two neighboring peptide groups, each of the C═O bond lengths differs from that of an isolated peptide bond due to the structural distortion induced by the neighboring peptides. We thus define δd_{CO} as the deviation of the CO bond length from that of the isolated peptide bond (1.1981 Å for the gas-phase NMA). In Fig. 4, the local amide I mode frequency shifts obtained from the Hessian matrix reconstruction method ($\delta\tilde{\nu} = \tilde{\nu} - \tilde{\nu}^{\mathrm{NMA}}$, $\tilde{\nu}^{\mathrm{NMA}} = 1707$ cm^{-1}) are plotted with respect to the measured δd_{CO} (Å) values obtained from the geometry-optimized structures. The linear relationship between $\delta\tilde{\nu}$ and δd_{CO} is evident.

Regardless of the existence of a covalent bond between two peptide bonds—note that the NMA dimer has no covalent bond between the two whereas in GD the two peptide bonds are connected to each other via a methylene group—the entire data points are on the same linear line with slope of -4390 cm^{-1}/Å. This result suggests that the covalent bond effect on the relationship between the structural distortion reflected by the C═O bond length change and $\tilde{\nu}$ does not originate from the so-called through-bond (mechanical) effect when the GD conformation is close to an α helix or β sheet (see Table I).

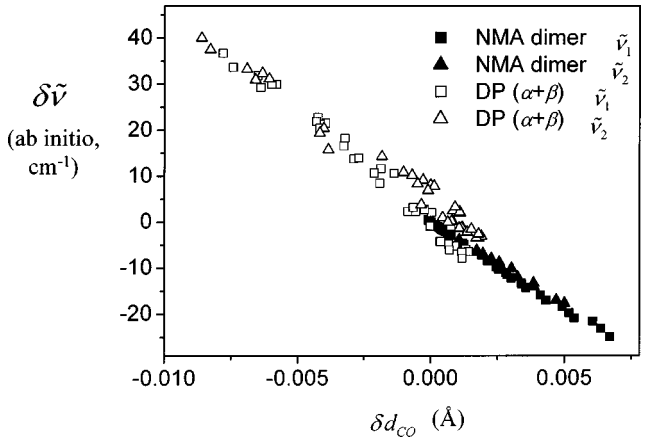

FIG. 4. The local amide I mode frequency shift $\delta\tilde{\nu}$ is plotted as a function of δd_{CO} for all NMA dimers and α-helical and β-sheet GD's.

D. Comparison with the *ab initio* results: Determination of the partial and transition charges

In Sec. II, we showed that the diagonal and off-diagonal Hessian matrix elements can be estimated by using the *effective* partial and transition charges of a single peptide group. In Ref. 22, in order to describe the effective electrostatic potential in the NMA-water system, we used a multivariate least square regression method to determine the transition charges of the six sites in an NMA. The two methyl groups in the NMA were treated as a united atom so that the total number of interacting sites was assumed to be six, i.e., O(═C), C(═O), N, H(–N), CH_3(N), and CH_3(C). However, one cannot directly use this six-site model for the peptide group in a given polypeptide such as GD, because each peptide cannot be simply replaced with an NMA. Therefore, we newly performed a multivariate least square regression analysis by assuming that the number of interacting sites of a given peptide bond is reduced to four, i.e., O(═C), C(═O), N, and H(–N). For the same 96 different NMA-$n$$D_2O$ complexes considered in Ref. 22, the amide I mode frequency is assumed to be written as

$$\tilde{\nu}-\tilde{\nu}_0=\sum_{j=1}^{4} l_j\phi_j, \tag{15}$$

where the linear expansion constants are defined as

$$l_j=-\frac{g_I}{4\pi c M_I^2(\omega_I^0)^3}(\partial c_j/\partial Q)_0^{\mathrm{eff}}. \tag{16}$$

The electrostatic potential at the jth site of the NMA is given by

$$\phi_j=\left(\sum_{m,k}\frac{c_{k(m)}^{\mathrm{D_2O}}}{4\pi\varepsilon_0 r_{jk(m)}}\right), \tag{17}$$

where the partial charge of the kth site of the mth D_2O molecule is denoted as $c_{k(m)}^{\mathrm{D_2O}}$ and $r_{jk(m)}$ is the distance between the jth site of the NMA and the kth site of the mth D_2O molecule. Assuming that the NMA is electrically neutral, we have $\Sigma_{j=1}^{4} l_j=0$. Using the *ab initio* vibrational analysis results of 96 NMA-$n$$D_2O$ complexes and the multivariate least square regression analysis with the linear relationship given in Eq. (15), one can determine the four expansion coefficients, l_j (in e, $j=1-4$), which are summarized in Table II—here the dimension of the electrostatic potential was converted into cm^{-1}/e so that the parameters, l_j, are in e. By inserting the reduced mass (8.716 amu), angular frequency (1707.1 cm^{-1}), and cubic anharmonic coefficient $[-1.105\times10^{14}\ \mathrm{kg/(m\,s^2)}]$ of the amide I mode of NMA into Eq. (16), the four effective transition charges, $(\partial c_j/\partial Q)_0^{\mathrm{eff}}$, are determined and listed in Table II.

TABLE II. Effective partial (in e) and transition charges (in e/Å) of the gas-phase NMA. Also, the multivariate least square fitting parameters, l_j (in e), are given.

NMA	$c_j^{(0)}$	l_j	$(\partial c_j/\partial Q)_0^{\mathrm{eff}}$
O (C═O)	−0.837	−0.00554	−0.660
C (C═O)	0.492	0.00160	0.190
N	0.529	0.00479	0.572
H (N–H)	−0.184	−0.00086	−0.102

Next, we will use the same transition charges for each peptide in a dipeptide molecule and in an NMA dimer to quantitatively calculate both the diagonal force constants and the off-diagonal coupling constants. Then, it is necessary to optimize the four effective partial charges of the peptide—note that one can use the partial charges such as Mulliken or Chelpg but because the number of sites is four (not twelve) it is not straightforward to use these conventional partial charges. By modifying Eq. (15), the mth local amide I mode frequency of a given tripeptide can be recast in the form

$$\tilde{\nu}_m=\tilde{\nu}_0+\sum_{j=1}^{4} l_{j(m)}\sum_{n\neq m}\phi_{j(n)} \quad (\text{for } m=1,2), \tag{18}$$

where

$$l_{j(m)}=-\frac{g_I}{4\pi c M_I^2(\omega_I^0)^3}(\partial c_{j(m)}/\partial Q_m)_0^{\mathrm{eff}}, \tag{19}$$

$$\phi_{j(n)}=\frac{1}{4\pi\varepsilon_0}\sum_{k(n)}\frac{c_{k(n)}^{(0)}}{r_{j(m),k(n)}}. \tag{20}$$

We will assume that the cubic anharmonic coefficients, reduced masses, and angular frequencies of the two local amide I modes are the same with those of NMA. Then, totally 152 local amide I mode frequencies obtained from the NMA dimer (39 conformations×2 peptide units) and GD (37 conformations×2 peptide units) are used to determine the best set of partial charges $c_k^{(0)}$ (for $k=1-4$) of the four sites. In Table II, the four effective partial charges are listed.

Since the transition and partial charges of the four sites representing a single peptide group were all determined, we now calculate the diagonal Hessian matrix elements. For the NMA dimers and GD, the theoretically predicted local amide I mode frequencies are calculated and compared with the *ab initio* frequencies obtained by using the Hessian reconstruction method (see Fig. 5). In Fig. 5, the linear line of which slope equals 1 is drawn for a comparison. The agreement between $\tilde{\nu}_{\mathrm{theory}}$ and $\tilde{\nu}_{ab\ initio}$ is acceptable.

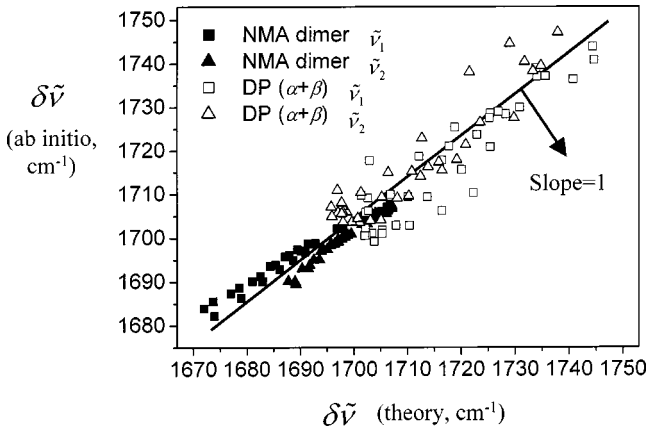

FIG. 5. The theoretically predicted local amide I mode frequency shifts [by Eq. (18)] are plotted with respect to the *ab initio* frequency shifts obtained by the Hessian reconstruction method for all NMA dimers and GD conformations in α-helical and β-sheet regions. The linear line with slope of 1 is also plotted.

E. Center frequency of the GD analog: Ramachandran surface

We next quantitatively test the validity of the above empirical relationship, Eq. (18). For the entire Ramachandran space, we reported an *ab initio* calculated $\tilde{\nu}_{\text{center}}(\phi,\psi)$ surface and present it again in Fig. 6(a) for the sake of comparison. In Fig. 6(b), the theoretically predicted $\tilde{\nu}_{\text{center}}(\phi,\psi)$ surface using Eq. (18) is plotted. The overall shapes of the two surfaces are quantitatively similar to each other, meaning that the diagonal force constant predicted by using the empirical relationship developed in the present paper is quantitatively acceptable in the region where the steric effect is not critical. Those conformations having strong steric interaction between the two peptide groups, e.g., GD conformations around ($\phi\approx 0$, $\psi\approx 180$), are however energetically unstable so that their population in realistic polypeptides is relatively small. The above result is important because, as far as the authors' knowledge, there does not exist a simple theoretical model that is capable of predicting diagonal force constants of polypeptides when the orientation of each peptide and the interpeptide distance are arbitrarily given. In order to further test the validity of the empirical relationship considered in the present paper, it will be interesting to study isotopic substitution effects on the amide I normal mode frequencies of polypeptides.[26,27,30–33]

IV. SUMMARY

We performed extensive *ab initio* vibrational analyses for three series of dimer systems consisting of two *trans*-NMA molecules varying the intermolecular distance, i.e., α-helical, parallel, and antiparallel β-sheet conformations. Using the Hessian matrix reconstruction method, the local amide I mode frequencies of each peptide and the coupling constants were obtained for a number of NMA dimer and GD conformations. Thus obtained local amide I mode frequency is found to be linearly proportional to δd_{CO}. For the NMA–NMA dimers, we found that the center frequency of two amide I normal modes exhibits a strong red shift, as the intermolecular distance between the two NMA's decreases. We found that the physical origin of this low-frequency shift lies in the electronic as well as molecular structure changes of a given peptide, which is induced by the effective electrostatic interaction with the neighboring peptide group. It was shown that the present theory can also be used to describe the frequency shift of the amide I modes of the model dipeptide (GD), on the basis of the comparative investigation of the *ab initio* calculated $\tilde{\nu}_{\text{center}}(\phi,\psi)$ with theoretically predicted $\tilde{\nu}_{\text{center}}(\phi,\psi)$. The result shows that a significant improvement in terms of explaining the frequency-shifting behavior of the amide I modes in dipeptide was achieved in the present paper. It is also believed that the amide I mode frequency shifting pattern when a polypeptide forms either α-helix or β-sheet conformation can be described by using the present theory. Furthermore, it becomes possible to predict the diagonal force constant change of the local amide I modes of polypeptides and proteins, which is the subject currently under investigation.

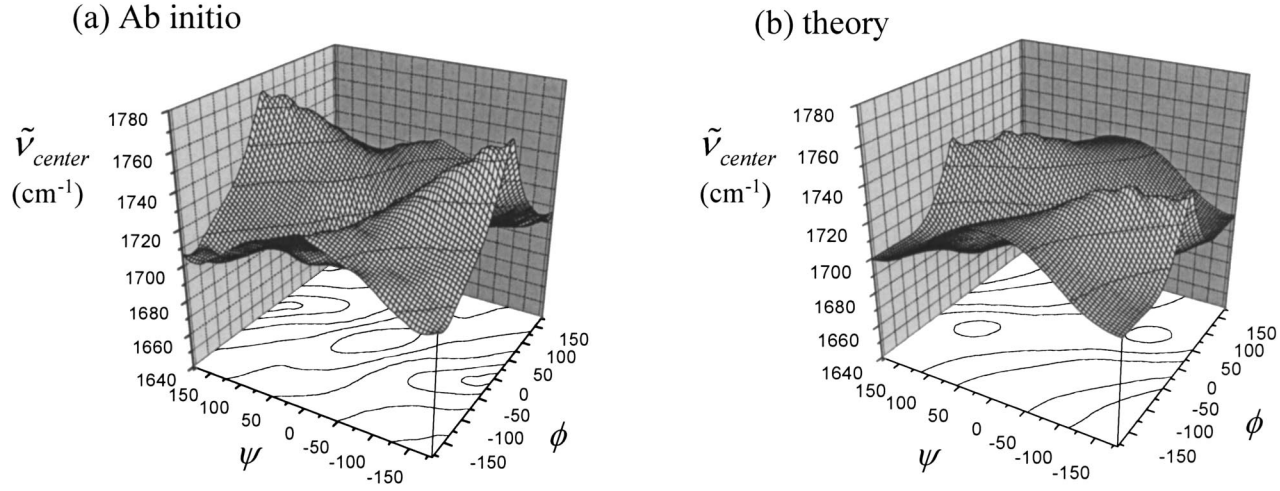

FIG. 6. The *ab initio* calculated $\tilde{\nu}_{\text{center}}(\phi,\psi)$ and theoretically predicted $\tilde{\nu}_{\text{center}}(\phi,\psi)$ are plotted in (a) and (b), respectively. (a) Was taken from Ref. 20.

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