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Two-dimensional Infrared Spectroscopy of a Model Peptide Homodimer

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A pair of peptide groups in space, as modeled by formamide dimer, was used to evaluate vibrational coupling between the amide-I modes and the spatial behavior of the coupling using \textit{ab initio} quantum chemical calculations. It was found that the coupling between two C=O groups, which is electrostatic in nature, is still quite significant as the intermolecular distance reaches 10 Å. One- and two-dimensional infrared spectra of the dimer at several configurations were calculated using a vibrational exciton model that utilizes the \textit{ab initio} computation-obtained parameters. The distance dependence of the coupling is dramatically shown in both the 1D and 2D infrared spectral features. The results suggest that the C=O stretching modes in polypeptide can be coupled and their states can be delocalized over quite a long distance in space.

Key words: Two-dimensional infrared spectroscopy, Peptide homodimer, Vibrational coupling, Transition dipole coupling, Exciton model

I. INTRODUCTION

Recently developed two-dimensional infrared (2D IR) spectroscopy, which utilizes a four-wave mixing nonlinear process of femtosecond infrared laser pulses, has shown great potential in determining time-dependent molecular structures in condensed phase with ultrafast time resolution [1-15]. A 2D IR spectrum is obtained by carrying out a vibrational photon echo experiment [1]. It is based on the well-known three-pulse stimulated photon echo phenomenon [16,17]. The first pulse excites the molecular system and creates a vibrational coherence between the fundamental and first excited state. The second pulse, delayed by a time \( \tau \), called “coherence time”, from the first pulse, perturbs the coherence. The third pulse, which is delayed by a time \( T \), called “waiting time”, from the second pulse, is used to generate the photon echo. The occurrence of the third pulse is the beginning of the echo’s “detection time” \( t \). When scanning both \( \tau \) and \( t \) while fixing \( T \), one obtains a two-dimensional time-domain oscillatory signal. A followed double Fourier transform along \( \tau \)- and \( t \)-axis yields a two-dimensional frequency-domain signal, i.e., a 2D IR spectrum. Two frequency axes are usually named as \( \omega_c \) and \( \omega_t \), to show their connections with the corresponding delay times.

Vibrational coupling plays a key role in retrieving molecular structural information from a 2D IR spectrum. The coupling constant is directly manifested in the off-diagonal peaks in a 2D IR spectrum. The off-diagonal peaks usually appear as a pair of signals with opposite sign. Both the sign and intensity of the signals are directly related to the coupling constant. An off-diagonal signal exists only if two anharmonic vibration modes (vibrators) are coupled. In a simple system such as a dipeptide, the effect of the coupling is also manifested in the relative intensity of the linear IR (or 1D IR) peaks, as well as in the 2D IR diagonal peaks. On the other hand, the orientations of both the diagonal and off-diagonal peaks contain information about whether and how the two coupled chemical groups’ vibrations are correlated, i.e., they are molecular structural distribution indicators. Thus, multidimensional IR (including 1D and 2D) spectroscopy can be regarded as a multi-parameter structural tool.

The coupling constants can usually be evaluated by using \textit{ab initio} quantum chemical calculations for small systems and by transition dipole or transition charge density schemes proposed earlier [10,11,18-22] for large systems. Two vibrational modes are coupled when one senses change in charge distribution of the molecular system as the other is excited. It is believed that the coupling constant bears the distance and angular information of any two remote chemical groups, thus it becomes a structural parameter. Therefore it is crucial to learn how significant the coupling is as the distance increases.

Formamide is a well-known model for a mono-peptide unit. Gas-phase geometry and harmonic vibrational frequencies of formamide monomer and oligomers have been well studied by \textit{ab initio} calculations [23-27]. Structures and dynamics of liquid formamide have also been investigated using classical molecular dynamics simulations [28,29] and, recently, \textit{ab initio} molecular dynamics simulations [30,31]. The anharmonic frequencies of formamide monomer and dimer in the gas phase have also been reported [32-35]. Very recently 2D IR studies of formamide monomer and its \( ^{13}\text{C} \) and deuterium isotopomers have been reported [36-38].

The present work attempts to evaluate the spatial
behavior of vibrational coupling using ab initio density functional theory (DFT) computations. A formamide dimer is chosen because it allows us to perform high level computations (e.g. geometry optimization and normal mode frequency calculation) at any given internuclear distance. Such calculations are not computationally feasible for a large molecular complex. Formamide dimer is also a good model for any two remote amide groups in space, where the intermolecular coupling is presumably electrostatic interaction in nature. In this work we evaluate the coupling between two amide-I modes (mainly the C=O stretchings) in the formamide dimer at various distance. The relative positions of the monomers are fixed so the spatial behavior of the coupling can be easily examined. The couplings were evaluated by a wave function de-mixing approach, as well as a transition dipole coupling (TDC) scheme. The 1D and 2D IR spectra were simulated for typical dimer configurations and the coupling-dependent spectral features are discussed. The coupling behavior in polar and nonpolar solvent was also examined, using a polarizable continuum solvent model.

II. METHODS

A. Normal mode frequency calculation

Full geometry optimization was carried out for the formamide dimer in gas phase using the DFT at the level of B3LYP/6-311++G**. Two intermolecular hydrogen bonds were formed between the C=O and N–H groups (see Fig.1). Partial geometry optimization was carried out by changing the intermolecular distance \( r \) from 3.7 Å to 10.5 Å (defined as the distance between the mid point of two anti-parallel C=O bonds). Harmonic normal mode frequency calculations were carried out at the same level of theory for each optimized structure. All the calculations were carried out using Gaussian 03 [39]. Partially optimized dimer structures at various \( r \) values always have \( C_2 \) symmetry, meaning that two C=O bonds are in the same plane. This implies that \( r \) is the only variable here. Such a simplified model system allows us to evaluate the coupling-distance relationship more easily.

![FIG. 1 Molecular structure of a hydrogen-bonded formamide dimer. The intermolecular distance \( r \) is defined as the distance between the mid point of two anti-parallel C=O bonds.](image)

B. Wave function de-mixing

Normal modes can be approximately decomposed into local modes. Local mode properties, including zero-order frequencies and pair-wise inter-mode couplings, can be obtained all together by the wave function de-mixing procedure [10,40] on the basis of a subset of normal modes of interest. The simplest case is a two vibrator system, in which the local modes \( q_i \) and \( q_j \) are related to two normal modes \( Q_i \) and \( Q_j \) by:

\[
\begin{pmatrix} q_i \\ q_j \end{pmatrix} = \begin{pmatrix} \cos \xi/2 & \sin \xi/2 \\ -\sin \xi/2 & \cos \xi/2 \end{pmatrix} \begin{pmatrix} Q_i \\ Q_j \end{pmatrix}
\]

where \( \xi/2 \) is the mixing angle of their local mode wave functions,

\[
\xi = \tan^{-1}\left( \frac{2|\beta_{ij}|}{v_i^0 - v_j^0} \right) \quad (0 \leq \xi < \pi)
\]

here \( \beta_{ij} \) is the coupling of two local modes with frequencies \( v_i^0 \) and \( v_j^0 \). By definition the maximum mixing occurs when \( \xi/2 = \pi/4 \). The 2-by-2 inverse matrix on the right side consists of a reduced normal mode eigenvectors. The reduced eigenvectors can be easily obtained for the amide-I modes by assuming that they are localized on the C=O stretching mode, a generally-accepted assumption for peptide oligomers. The calculations were carried using an in-house written program.

C. Transition dipole coupling

In the simplest vibrational coupling model for the amide-I modes, as proposed by Krimm et al. [41] and Tasumi et al. [19], the coupling constant is given by a simple dipole-dipole interaction term:

\[
\beta_{ij} = \frac{\vec{\mu}_i \cdot \vec{\mu}_j}{r_{ij}^3} - 3 \left( \frac{\vec{r}_{ij} \cdot \vec{\mu}_i}{r_{ij}} \right) \left( \frac{\vec{r}_{ij} \cdot \vec{\mu}_j}{r_{ij}} \right) \frac{1}{r_{ij}^5}
\]

where \( \vec{\mu}_i \) and \( \vec{\mu}_j \) are two transition dipoles and \( r_{ij} \) is the distance between the two point dipoles. The magnitude of the transition dipole was determined to be 0.33 D, and the direction of each dipole vector with respect to the C=O bond was calculated as 23°. These values were obtained from the normal mode calculations performed on a full geometry optimized formamide monomer in gas phase using the DFT at the level of B3LYP/6-311++G**. These values are quite similar to that of another mono peptide unit, trans-N-methylacetamide [42]. For the formamide monomer, the position of the dipole is placed at the center of the C=O bond. It is assumed so since the exact location of the transition dipole remains unknown in this case. There are also
other coupling schemes such as transition charge interaction with charge fluxes [43], and transition charge density derivative interactions [11]. Also it is well known that for two neighboring peptide units that are covalently bonded, ab initio calculation gives more accurate couplings than any of these electrostatic coupling schemes. This is because the through bond contribution needs to be taken into account for two nearby vibrational units. In addition, in calculating the TDC, the dielectric constant was set to 1 because this is a gas phase modeling.

D. Spectral simulations using the exciton model

Because of the unique property of the amide-I modes in peptides, namely the relatively localized wave functions and isolated frequencies, which implies that the modes do not mix heavily with other types of modes, the classical Frenkel exciton model [44] is applicable in this case. The vibrational exciton model was developed based on force field calculations of model peptide [41] and evaluation of FTIR spectral of several sized proteins [19]. The calculation of the linear IR and 2D IR requires diagonalizing the one- and two-exciton Hamiltonian matrices [42]. The Hamiltonian matrix takes a set of local model frequencies as its diagonal elements, while the off-diagonal elements are pairwise coupling constants, both having the units of energy. We assume a non-degenerate zero-order frequency picture for the two amide units in the dimer configuration. The assumption is generally reasonable since in a given polypeptide chain, it is common to find two local mode frequencies unequal, as shown in a recent study [45]. Two local mode frequencies are set to be 1715 and 1740 cm$^{-1}$. This mimics a pair of isotopically labeled amide units, for example, one has $^{13}$C$=^{18}$O and the other has $^{13}$C$=^{16}$O. A recent study [9] has shown that a pair of such amide units would have a non-zero frequency separation, typically ranging from 20 cm$^{-1}$ to 25 cm$^{-1}$. In this regard, our model deals with a case in which two modes are isotopically labeled and thus singled out of a large collection of modes. This is especially useful in revealing detailed interactions between two selected regions in a molecular complex.

Ab initio calculated couplings are used in spectral simulation via the exciton model. The simulation procedures of both 1D IR and 2D IR have been described in detail [10]. Briefly, the linear IR spectrum can be obtained by computing the quantity:

$$S(\omega) = \sum_{k} \left| \bar{\rho}_{k0}^{(k)} \right|^2 \frac{\gamma_k/\pi}{\gamma_k^2 + (\omega - \omega_k)^2} M$$

(4)

where $\bar{\rho}_{k0}^{(k)}$ is the transition dipole of the $v=0\rightarrow v=1$ transition of the $k$th Eigen mode. The parameter $\gamma_k$ models the homogeneous linewidths for each of the Eigen states. We set $\gamma_k=4.0$ cm$^{-1}$ throughout the work.

The 2D IR spectra consists of two parts: $S(\pm\omega_r, \omega_t)$ which corresponds to the rephasing (with $-\omega_r$) and non-rephasing (with $+\omega_r$). The rephasing signal is collected when $\tau$ is negative (the first pulse appears on sample first), whereas the non-rephasing signal is obtained with time $\tau>0$ (the second pulse appears on sample first). All the Liouville pathways at $T=0$ [46] need to be fully considered in writing out the analytical formula in the frequency-domain. We set the lower case $k$ indices to be the whole set of $N$ one-exciton states and $K$ to be the set of $N(N+1)/2$ two-exciton states at roughly twice the frequency, where $N=2$ for the formamide dimer. Therefore the overtone and combinations can be labeled by $K$ ($K=k+k'$). General expressions for 2D IR spectra in a Bloch limit can be written as:

$$S(-\omega_r, \omega_t) =$$

$$= 4 \sum_{k,k',K} \left[ -i(-\omega_{k0} - \omega_r) - \gamma_{k0} \right] \left[ i(\omega_{k0} - \omega_t) + \gamma_{k0} \right]$$

$$- 2 \sum_{k,k',K} \left[ -i(-\omega_{k'0} - \omega_r) - \gamma_{k'0} \right] \left[ i(\omega_{k'0} - \omega_t) + \gamma_{k'0} \right]$$

$$+ \sum_{k,k'} \left[ -i(\omega_{k0} - \omega_r) - \gamma_{k0} \right] \left[ i(\omega_{k0} - \omega_t) + \gamma_{k0} \right]$$

$$- 2 \sum_{k,k',K} \left[ -i(\omega_{k'0} - \omega_r) - \gamma_{k'0} \right] \left[ i(\omega_{k'0} - \omega_t) + \gamma_{k'0} \right]$$

$$+ \sum_{k} \left[ -i(\omega_{k0} - \omega_r) - \gamma_{k0} \right] \left[ i(\omega_{k'0} - \omega_t) + \gamma_{k'0} \right]$$

$$- 2 \sum_{k,k',K} \left[ -i(\omega_{k'0} - \omega_r) - \gamma_{k'0} \right] \left[ i(\omega_{k'0} - \omega_t) + \gamma_{k'0} \right]$$

(5)

where the numerators are the orientation factors, written for a given sequence of laboratory fixed pulse polarizations $\hat{a}$ to $\hat{d}$ and molecule frame transition dipole directions given by the indices. $\omega_{k0}$ is the center frequency of the $|0\rangle\rightarrow|k\rangle$ transition, with the transition dipole $\hat{m}_{k0}$. The $\gamma_{kk'}$ are the homogeneous widths of the individual transitions at $\omega_{kk'}$, and chosen to be equal for all the $|0\rangle\rightarrow|k\rangle$ and $|k\rangle\rightarrow|k\rangle$ transitions. An ensemble average of Eqs.(4)-(6) over the resonance frequencies was carried out to simulate the inhomogeneous broadening using uncorrelated Gaussian functions ($\sigma=7$ cm$^{-1}$). This was realized by applying diagonal disorder over an ensemble (averaging over 5000 shots). The diagonal anharmonicity of the amide-I mode is set to 16 cm$^{-1}$,
a value that is supported by gas-phase DFT calculations (17.5 cm$^{-1}$) [40]. The 2D IR correlation spectra are obtained by adding the equally weighted rephasing spectrum $S(-\omega_r, \omega_t)$ and non-rephasing spectrum $S(+\omega_r, \omega_t)$. All the spectra are in (zzzz) polarization conditions, in which three input laser pulses and the generated photon echo signal are in vertical polarization.

III. RESULTS AND DISCUSSION

A. Spatial behavior of intermolecular vibrational coupling

Figure 2 shows the intermolecular distance dependence of the DFT-computed amide-I normal mode frequencies, their differences, and the mixing angles in the formamide dimer obtained by the wave function de-mixing approach. Fully optimized dimer has C$_2$ symmetry, both hydrogen bonds have an O···H distance equal to 1.887 Å, and two normal mode frequencies are $\omega_i=1741.0$ cm$^{-1}$ (IR inactive) and $\omega_j=1771.4$ cm$^{-1}$ (IR active). The distance between the midpoint of the C=O bonds is $r=3.67$ Å. As $r$ increases, the difference between the two normal mode frequencies drops, and approaches zero at $r=10.59$ Å. However, the wave function mixing angle remains essentially unchanged ($\xi/2\approx45^\circ$) as $r$ changes. This suggests that even though the intermolecular distance increases, the wave functions of the two modes are still highly mixed, indicating that the modes are delocalized over a long distance. Here, because the mixing angle $\xi/2$ is nearly 45$^\circ$ in all cases, we have $\tan\xi=+\infty$ and $v_0^0-v_0^j=0$ as $r$ changes, meaning a fully degenerate local mode picture.

Figure 3 shows the vibrational coupling constants between two amide-I modes in the formamide dimer. Strong distance dependence is observed in ab initio calculated couplings. The shorter the $r$, the stronger the coupling is, whereas at larger $r$, the coupling becomes weaker. The results show that the coupling is still significant ($-0.52$ cm$^{-1}$) at $r=10.5$ Å. As a comparison, the TDC was also calculated for each dimer configuration and the result is also plotted in Fig.3. It shows that indeed the coupling is electrostatic in nature when two monomers are far separated ($r>6.0$ Å), however, there is still some difference between two curves at shorter $r$ values, suggesting that the coupling contains certain degree of through bond effect. This implies that the hydrogen bond in the formamide dimer may behave like a covalent bond in this case.

B. Linear IR spectra

To examine the effect of the distance-dependent coupling on linear IR spectra, 1D IR spectra were simulated at three $r$ values: 3.67, 7.13, and 10.09 Å. The corresponding coupling constants are $-15.21$, $-1.94$, and $-0.60$ cm$^{-1}$, respectively. The simulated 1D IR spectra are given in Fig.4. Dramatic effects of the coupling are seen on the linear IR spectra. These effects include the IR peak position and relative peak intensity. For $r=3.67$ Å, two peaks are widely separated (1707.8 vs. 1747.2 cm$^{-1}$), and the high-frequency transition is much stronger than the low frequency one. For $r=7.13$ Å, the peak separation becomes smaller (1714.9 vs. 1740.1 cm$^{-1}$), and it becomes even smaller at...
C. 2D IR spectra

2D IR spectra not only show the result of coupling (the diagonal signals), but also show the signal directly related to the coupling constant (the off-diagonal signals). The linear IR spectra, on the other hand, only show spectral features as a result of coupling; in this sense, a linear IR spectrum may be regarded as a “projection” of the inter-mode interactions. In other words, the coupling parameter itself is not directly manifested in a linear IR spectrum. The coupling constant can only be characterized quantitatively from the off-diagonal signals in a 2D IR spectrum. We first examine a 2D IR “stick spectrum” in the case of $r=7.13$ Å, which is shown in Fig.5. The spectrum was obtained by giving zero homogeneous line width while averaging over the inhomogeneous ensembles. Such a spectrum is extremely useful in understanding the framework of the 2D spectrum. It can be seen that the diagonal peaks form two narrowed lines, representing the $|0\rangle \rightarrow |1\rangle$ (right line) and $|1\rangle \rightarrow |2\rangle$ (left line). The diagonal signals are elongated along the diagonal due to the inhomogeneous averaging effect. The off-diagonal signals, on the contrary, show as scattered dots because each of the two vibrators has its own diagonal frequency distribution, and the two distributions were assumed to be uncorrelated.

The simulated 2D IR spectra with appropriate line broadening parameters at the three $r$ values (3.67, 7.13, and 10.09 Å) are shown in Fig.6 as 3D contour plots. The signs of the 2D IR signals are labeled on the left column (panels (a), (d), and (g)) as examples. These three spectra are the real part of the rephasing, non-rephasing and absorptive spectra at $r=3.67$ Å respectively. In the rephasing spectrum (panel-(a)), a pair of diagonal peaks with $-\omega_r=1747.2$ cm$^{-1}$, are present and correspond to the high-frequency component in the 1D IR spectrum (Fig.4(a)). The one that sits more closely on the diagonal has a positive sign and belongs to the $|0\rangle \rightarrow |1\rangle$ transition (similar to the 1D IR). The diagonal peak that usually appears on the left side of the diagonal and has a minus sign, resulted from the $|1\rangle \rightarrow |2\rangle$ transition, which is beyond the scope of the 1D IR. The frequency separation of the pair-wise $|0\rangle \rightarrow |1\rangle$ and $|1\rangle \rightarrow |2\rangle$ parallel to the $\omega_r$-axis is determined by the diagonal anharmonicity of the vibrator. The diagonal signals at $-\omega_r=1747.2$ cm$^{-1}$ are much stronger than those at $-\omega_r=1707.8$ cm$^{-1}$, in agreement with the 1D IR results. In addition, the diagonal signal is elongated diagonally and line-narrowed anti-diagonally in panel-(a). The line-narrowing feature is directly associated with the rephasing process of the echo signal, suggesting that indeed it is a “rephasing” 2D spectrum. The off-diagonal signals usually appear on both sides of the diagonal line, nevertheless it is usually asymmetrical. In panel-(a) two pairs of the off-diagonal signals are clearly shown, indicating a strong coupling between two vibrators in this case. The apparent peak separation of the two off-diagonal signals along the $\omega_r$-axis, although directly related to the coupling constant, is a measure of the off-diagonal anharmonicity, which is
FIG. 6 Simulated 2D IR spectra of the formamide dimer system. (panels (a), (d) and (g)) \( r = 3.67 \) Å, panels (b), (e), and (h) for \( r = 7.13 \) Å, panels (c), (f), (i) for \( r = 10.09 \) Å. The top row (panels (a) to (c)) shows the rephasing 2D IR spectra, the middle row (panels (d) to (f)) shows the non-rephasing 2D IR spectra, and the bottom row shows the pure absorptive 2D IR spectra (panels (g) to (i)).

the transition energy difference between the sum of two fundamental transitions (\( |0\rangle \rightarrow |1\rangle \)) and that of the combination band of the two modes. The non-phasing 2D IR spectrum shown in panel-(d), bears similar information about the transition energies. However, no line-narrowing is observed in a non-rephasing 2D spectrum, indicating the “non-rephasing” nature of the signal. It should be noted that in both the rephasing and non-rephasing 2D spectra, the diagonal and off-diagonal signals usually show strong tailing effect (dispersions). To get rid of these tails, a pure absorptive spectrum is obtained by adding equal amounts of the rephasing and non-rephasing spectra, and the result is shown in panel-(g) in this case. The absorptive spectrum retains the line-narrowing feature of the rephasing spectra and yet the dispersive patterns are removed. Such representation is also very common in two-dimensional nuclear magnetic resonance (2D NMR) [47]. The line-narrowing feature of the diagonal signal is a manifestation of the line broadening parameters used in our simulations employing the Bloch dynamics. In the Bloch picture, one assumes a clear time separation between the fast motions (motional narrowing) and a slow inhomogeneous broadening (static). The Bloch picture has been proven to be a reasonable approximation for the amide-I modes of peptide in solution phase [9,12,48]. On one hand, the elongation along diagonal is due to the contributions from \( \gamma \) and \( \sigma \), the homogeneous and inhomogeneous broadenings; on the other hand, the narrowed width along the anti-diagonal direction is only \( \gamma \)-dependent.
TABLE I Solvent effect on the amide-I vibrational coupling in the formamide dimer. The values in the parentheses are the intermolecular distance \( r \). The couplings are in cm\(^{-1}\) and the distances are in Å.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Vibrational coupling (( r ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vacuum</td>
<td>-11.61 (4.22)</td>
</tr>
<tr>
<td>CCl(_4)</td>
<td>-9.23 (4.24)</td>
</tr>
<tr>
<td>Water</td>
<td>-1.89 (4.23)</td>
</tr>
</tbody>
</table>

With the information at hand, we now turn to discuss the 2D IR spectral feature as a function of the coupling. As coupling changes from -15.21 cm\(^{-1}\) to -1.94 cm\(^{-1}\) and further to -0.60 cm\(^{-1}\), the 2D IR spectra shown in Fig.6 change substantially. These changes are manifested in all three types of 2D spectra. First, it is interesting to notice the change of the diagonal peaks. The profile of the totally four diagonal peaks change from the left column to the right ones, mainly in the relative intensity. This is especially clear in Fig.6 panels (g), (h), and (i) where the dispersive tails are not present. The variation of the diagonal signal as a function of the coupling is also shown in the rephasing and non-rephasing spectra (top two rows of panels). However, it should be pointed out that the apparent diagonal width is not sensitive to the coupling, but rather to the spectral line broadening parameters. Since the same set of parameters is used in all simulations, i.e., \( \gamma = 4 \) cm\(^{-1}\) and \( \sigma = 7 \) cm\(^{-1}\), it is not expected that any large changes be observed in the diagonal width. Second, the profile of the off-diagonal signals show a dramatic change as the coupling strength varies: in Fig.6 panel-(g), pair-appearing cross peaks are clearly shown; however, they become less significant in Fig.6 panel-(h) and further decreased in Fig.6 panel-(i), directly indicating the weakening of the coupling between the two vibrators. In addition, as shown in Fig.6, there are some extra cross peak-like signals shown in both the rephasing and non-rephasing spectra, marked as “\( x \)”, but not in the absorptive spectra. Care should be taken in assigning these signals. They appear due to the tailing and twisting effects in the rephasing and non-rephasing spectra, and their peak positions are not always in agreement with those of the diagonals peaks, and thus they are not real cross peaks. Simulations with the coupling being “turned off” support this argument (data not shown). In fact, Figure 6 panels (g), (h), and (i) clearly demonstrate already that it is the absorptive 2D IR spectra that show the coupling-sensitive cross peaks. However, a more quantitative characterization of the cross peaks would require further analysis, such as taking a slice along the \( \omega_t \)-axis to cut through both the diagonal and off-diagonal signal at the same time. Such an analysis has been performed previously in the 2D IR study of the alanine dimer [12].

The above results suggest that 2D IR signals are extremely sensitive to the strength of the coupling. Since the coupling can be expressed as a function of the distance and relative angle between any two transition dipoles (TDC picture), it is expected that 2D IR can be used to obtain the geometric relationship between any two chemical groups, therefore providing molecular structural information. Since the through-space coupling, either inter- or intramolecular, could be still significant at long distances (\( r \geq 10 \) Å), 2D IR can be used to follow chemical reactions, protein foldings, and solute-solvent interactions in real time. For this, a nonequilibrium initiation technique needs to be combined with 2D IR technique. Further, these results suggest that the vibrational coupling effect may be somewhat advantageous over the well-known nuclei Overhauser effect in obtaining geometric parameters of chemical groups, because the latter is only effective up to approximately 4 Å [47].

D. Solvent effect on the coupling

Although our simulations were performed using the gas-phase coupling parameters, we examine the solvent effect on the coupling constant in this section, since we are interested in studying condensed phase molecular complexes. The calculation performed in Table I is just the beginning of our exploration. It is known that peptide may have different conformations in solution than in gas phase, implying that the coupling constant is solvent-dependent. For the homo-dimer, it was found that the conformation does not change much in vacuum or in the presence of a solvent at a give \( r \) value, however, solvent may still affect the coupling via the so-called “screening effect”. To this end, we have optimized the dimer structure in several \( r \) values, in either water or carbon tetrachloride. The integral equation formalism version of the polarizable continuum method (IEF-PCM) [49] was used to include the solvent effect. The IEF-PCM scheme has recently been used to evaluate vibrational couplings in various dipeptides in solution [22]. These calculations were performed using the IEF-PCM solvent model, by knowing that the solvent model does not predict the structural aspect of the solvent, such as the ability to form a solute-solvent hydrogen bond. In this scheme, the solute molecule is assumed to be hosted in a “cavity” in the environment of a polarizable continuum dielectric. The solute is then treated quantum mechanically whereas the solvent polarization is described in terms of an induced surface charge on such a cavity. Such a solvent surface charge could change the molecular structure and the wave func-
tion of the solute. All the calculations were performed using Gaussian 03.

Table I summarizes the calculated coupling constants for several $r$ values. It shows that in CCl$_4$ the coupling constants drop only moderately from its gas-phase values, whereas in water large decreases are observed. Since we found that the optimized structure of the dimer at a given $r$ value shows subtle difference in vacuum, in water, and in CCl$_4$, the change of the coupling is not due to conformation, but rather can be understood in terms of the nature of the coupling and the polarity of solvent. The dimer is only hydrogen-bonded at shorter $r$ distance, so the C=O/C=O coupling is electrostatic in nature and is therefore subjected to an electrostatic screening effect of the solvent. CCl$_4$ is a nonpolar solvent and it is expected that solute in CCl$_4$ is somewhat gas-phase like, so the coupling is being less “screened” by the solvent molecules. On the contrary, water is a polar solvent and may exert a large solvent screening effect on the interaction between two monomers because the coupling is dominated by electrostatic interactions. This also means that the dielectric constant should not be set to 1 if we really want to perform spectral simulations in the presence of a solvent. As for the large drop of the couplings in water, care should be taken to compare the actual values. At this point, the accuracy of the IEF-PCM solvent model in predicting the couplings is not yet known. The IEF-PCM scheme might have overestimated the change of the coupling in this case. A more reasonable way of evaluating the solvent effect is to perform calculations in the presence of solvent clusters, or in the presence of solvent point charges. Such calculations can be done on the basis of the molecular dynamics simulations and \textit{ab initio} computations. These issues are being currently investigated in our group.

IV. CONCLUSION

It is of great interest to obtain a molecular-level understanding of couplings and their manifestation in 2D IR experiments. In this work the distance-dependence of the vibrational coupling in the formamide dimer was examined. It was found that the two amide-I modes are coupled and their wave functions are delocalized over a quite long intermolecular distance (10 Å). The coupling is mainly electrostatic in nature at longer distances; however, a through-bond effect is shown when two monomers are close to one another and forming hydrogen bonds. The simulated 1D and 2D IR spectra show clear signatures of the distance-dependent couplings. The results suggest that 2D IR is very sensitive to the geometric relationship between two remote chemical groups. Taking advantage of femtosecond laser technologies, 2D IR can be used to obtain a detailed picture of two interacting groups in a given molecular complex in real time. It thus may become a powerful analytical tool in monitoring equilibrium and non-equilibrium molecular structural evolution in condensed phases.

V. ACKNOWLEDGMENTS

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