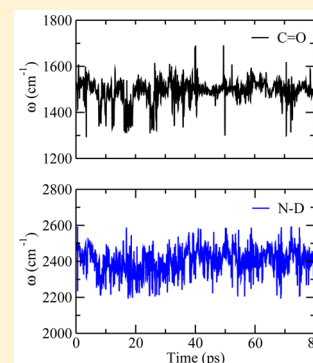


# First-Principles Simulation Study of Vibrational Spectral Diffusion and Hydrogen Bond Fluctuations in Aqueous Solution of *N*-Methylacetamide

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**ABSTRACT:** We have presented a first-principles simulation study of the vibrational spectral diffusion and hydrogen bond dynamics in an aqueous solution of *N*-methylacetamide (NMA). We have studied the spectral diffusion of local OD stretch modes of deuterated water in the first hydration shells of the carbonyl (CO) and deuterated amide (ND) modes and their relations to the dynamics of hydrogen bonds formed by water with these groups. The frequency fluctuations of the amide I and amide A modes of the solute are also investigated. It is found that the vibrational spectral diffusion of water molecules in the first hydration shell of the carbonyl oxygen of NMA proceeds with three time scales: A short-time relaxation ( $\sim 100$  fs) originating from the dynamics of NMA–water hydrogen bonds without breaking, a slower relaxation ( $\sim 3.3$  ps) arising from the breaking dynamics of NMA(CO)–water hydrogen bonds, and another longer time constant ( $\sim 14$  ps) coming from the escape dynamics of water from the first hydration shell of carbonyl oxygen. The current results show that the NMA(CO)–water hydrogen bonds have a longer lifetime than those between water molecules, although frequency calculations reveal a slightly higher stretch frequency of the water molecules in the first hydration shell of the carbonyl oxygen of NMA. An analysis of the vibrational spectral diffusion of solute modes is also presented in terms of the dynamics of solute–water hydrogen bonds. Effects of dispersion interactions on various calculated properties of the NMA–water system are also investigated in the present work.



## 1. INTRODUCTION

The single peptide unit of *N*-methylacetamide (NMA) makes it a simple commonly used model compound for studying interactions of peptide bonds with water in aqueous solutions. The behavior of NMA in water and other polar solvents has been the subject of numerous studies in recent years from both experimental and theoretical points of view.<sup>1–17</sup> The single CONH unit of NMA has been found to be predominantly planar in nature, and it favors the trans conformation over the cis one with respect to orientations of the CO and NH bonds.<sup>2</sup> Two different intermolecular hydrogen bonds that can occur in amide–water complexes are the  $\text{C}=\text{O}\cdots\text{H}-\text{O}-\text{H}$  and  $\text{N}-\text{H}\cdots\text{OH}_2$  bonds. It is generally believed that these two types of hydrogen bonds in amide–water systems play key roles for the stabilities of the secondary and tertiary structures of proteins in aqueous media. Theoretical calculations have revealed that an NMA molecule forms hydrogen bonds with three water molecules in the water-rich region.<sup>18–20</sup> The carbonyl oxygen forms typically two hydrogen bonds with two water molecules and the hydrogen of the NH group of NMA forms one hydrogen bond with a third water molecule. The characteristics of these hydrogen bonds can greatly influence the energetics, dynamics and vibrational features of both water and NMA molecules in aqueous solutions. Recent experiments have established that the frequency fluctuations of the amide I mode (mostly the CO stretching mode) can be used to capture the dynamical interactions of the solute with its surrounding water molecules.<sup>6,7</sup>

On the theoretical side, we note the work of ref 21, which used a combined quantum mechanical/molecular mechanics (QMMM) simulation method to calculate the infrared spectrum of NMA and its deuterated analog in aqueous solutions. The time-dependent infrared spectrum of the NMA–water system has also been calculated by using force-field parametrization ranging from standard point charge to more elaborate multipolar representation of the electrostatics.<sup>22</sup> The amide I frequency shift and the full width at half-maximum of the respective band have also been calculated recently by using the conventional molecular dynamics simulations in combination with ab initio calculations on NMA–water clusters,<sup>23–26</sup> and the results have been found to be close to the experimental findings.<sup>27,28</sup>

Electronic structure calculations were performed on the cluster of deuterated NMA in  $\text{D}_2\text{O}$ , and subsequently frequency maps relating the frequency of amide I mode with the electric field or the electrostatic potential were developed.<sup>23–26,29,30</sup> Using such a frequency map between the amide I frequency and electric field, a recent study<sup>26</sup> looked at the dynamics of frequency fluctuations of amide I modes of NMA in water by means of classical molecular dynamics simulations using the SPC/E model<sup>31</sup> of water. The calculated dynamics of the frequency fluctuations was found to be somewhat faster than

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that of experiments.<sup>32</sup> The objective of the present work is to investigate, from first-principles simulations, the dynamics of such vibrational spectral diffusion processes of amide I and also other solute and solvent modes in aqueous solution of NMA and to explore the roles played by the NMA–water hydrogen bonds and other dynamical modes in influencing the dynamics of such spectral diffusion processes in the aqueous solution.

In the current work, we have carried out a first-principles simulation study of the vibrational spectral diffusion and hydrogen-bond fluctuations in an aqueous solution of NMA at room temperature. We have used the methods of *ab initio* molecular dynamics<sup>33,34</sup> and wavelet analysis<sup>35–38</sup> for the generation of dynamical trajectories and subsequent calculation of fluctuating vibrational frequencies. The *ab initio* simulations have been conducted by using the well-known BLYP<sup>39,40</sup> functional and also by using its dispersion-corrected version, known as the BLYP-D functional. It may be noted that in the BLYP-D functional the dispersion corrections are incorporated to the BLYP functional<sup>39,40</sup> empirically by using the scheme of Grimme.<sup>41–43</sup> The use of the BLYP-D functional allows us to look at the effects of dispersion interactions on various equilibrium and dynamical properties of the NMA–water solution. After the simulation trajectories are generated and the time-series analyses are carried out, the dynamics of vibrational spectral diffusion is investigated by calculating the frequency time correlation function and also through the so-called hole dynamics calculations<sup>38,44</sup> of the OD stretch modes of water and also of the amide I (CO) and amide A (ND) modes of deuterated NMA. The spectral diffusion results are analyzed in terms of the solute–water hydrogen bond fluctuations and escape dynamics of water from the solute hydration shells. In addition to the dynamics of frequency and hydrogen bond fluctuations, we have also looked at some of the relevant structural quantities such as solute–water atom–atom radial distribution functions and hydrogen-bonding properties of different polar sites of the solute.

We have organized the rest of the paper as follows. In Section 2, we have presented the details of the present *ab initio* molecular dynamics simulations. In Sections 3 and 4, we have presented the results of solute–water structural distribution functions and frequency calculations. The results of the dynamics of vibrational spectral diffusion of water and solute modes are presented in Sections 5 and 6, respectively. The results of the dynamics of solute–water hydrogen bonds are presented in Section 7. We conclude the paper in Section 8 with a brief summary of the main results of the current study.

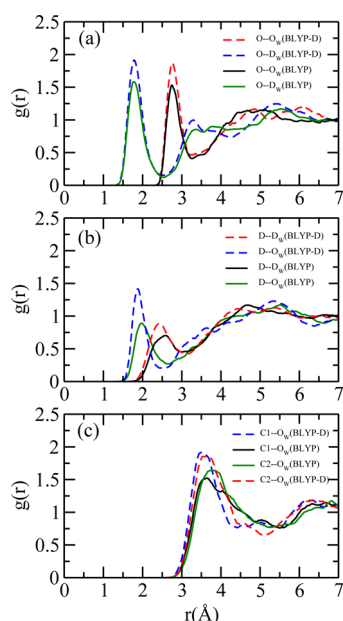
## 2. SIMULATION DETAILS

The *ab initio* molecular dynamics simulations have been carried out by using the Car–Parrinello method<sup>33,34</sup> and the CPMD code.<sup>45</sup> The simulation system contains one *N*-methylacetamide and 107 water molecules in a cubic box with the edge length of 14.8 Å. The size of the box is determined from the experimental density of the solution at 300 K.<sup>46</sup> Periodic boundary conditions were applied in all three dimensions, and the electronic structure of the extended system was calculated by using the density functional theory within Kohn–Sham<sup>47</sup> (KS) formulation. The KS orbitals were represented using a basis set of plane waves. The core electrons were treated through Troullier–Martins<sup>48</sup> pseudopotentials and the plane wave expansion of the KS orbitals was truncated at 70 Ry. The electronic orbitals were assigned a fictitious mass of  $\mu = 800$  au and the dynamical equations of motion were integrated by

using a time step of 5 au (0.125 fs). The deuterium mass was assigned to all the hydrogen atoms. Our choice of deuterated NMA and D<sub>2</sub>O in place of H<sub>2</sub>O also ensured that the electronic adiabaticity and energy conservation were maintained during the simulations. We employed the well-known BLYP<sup>39,40</sup> functional in the electronic structure calculations. Apart from using the BLYP functional, we also carried out an additional simulation using the dispersion-corrected BLYP-D density functional to look at the possible effects of dispersion interactions in our calculated structural and dynamical properties. We note that the BLYP-D functional includes dispersion corrections to the pure BLYP functional,<sup>39,40</sup> as introduced by Grimme.<sup>41,42</sup> We prepared the initial configurations through classical molecular dynamics simulations using the empirical SPC/E potential for water<sup>31</sup> and OPLS-AA potential for NMA.<sup>49</sup> Subsequently, we equilibrated each system through *ab initio* molecular dynamics for 15 ps in canonical ensemble. After equilibration, we ran the BLYP system for another 80 ps in microcanonical ensemble for calculations of various equilibrium and dynamical properties. For simulation with the dispersion-corrected BLYP-D functional, the length of the simulation trajectory in the production phase was 50 ps. We note that the run lengths and size of the current simulations are significantly longer than those of the existing *ab initio* simulations of NMA–water system.<sup>50</sup> Subsequently, we carried out a time series analysis of the coordinates and momenta of OD bonds of D<sub>2</sub>O and also of CO and ND bonds of NMA to calculate their stretch frequencies. Specifically, we used the wavelet method<sup>36</sup> of time series analysis in our frequency calculations. The details of this method have been discussed elsewhere in the context of frequency fluctuations in aqueous systems,<sup>38,51–54</sup> and here the method is extended to calculate the time-dependent stretch frequencies of CO and ND modes of NMA in addition to calculations of OD stretch frequencies of water.

## 3. SOLUTE–WATER STRUCTURAL CORRELATIONS AND HYDROGEN BONDS

In Figure 1, we have shown the NMA–water atom–atom partial radial distribution functions for both the BLYP and BLYP-D functionals. We note that the hydrophilic interaction between NMA and water is primarily through the hydrogen bonds between carbonyl oxygen of NMA and hydrogen of its nearest water and also between the hydrogen of NH group of NMA and the oxygen of its nearest water. On the contrary, the hydrophobic interaction between the NMA and water can be captured through the structural correlations between methyl carbon of water and oxygen of water molecules in its neighborhood. In view of this, we have calculated the radial distribution functions corresponding to the O(NMA)–H(Water), H(NMA)–O(Water), and C(NMA)–O(Water) correlations, and the results are shown in Figure 1a–c, respectively. In this Figure, and also in the subsequent Figures, we have shown the results for both BLYP and BLYP-D functionals. We have also calculated the number of hydrogen bonds that the NMA molecule makes with water through its carbonyl oxygen and amide hydrogen atoms, and the results are shown in Table 1. The existence of a hydrogen bond is determined by using a geometrical criterion where the NMA–water pair is taken to be hydrogen bonded if the distance between the carbonyl oxygen of NMA and hydrogen of its nearest water is less than the cutoff value  $R_{c1}$  or the distance between the amide hydrogen of NMA and oxygen of its nearest



**Figure 1.** Atom–atom radial distribution functions for (a) O(NMA)–O<sub>w</sub> and O(NMA)–D<sub>w</sub>, (b) D(NMA)–O<sub>w</sub> and D(NMA)–H<sub>w</sub>, where D(NMA) is the hydrogen (with deuterium mass) of the ND group of NMA, and (c) C1(NMA)–O<sub>w</sub> and C2(NMA)–O<sub>w</sub>, where C1 and C2 are the terminal carbon atoms adjacent to the carbonyl oxygen and amide nitrogen, respectively. O<sub>w</sub> and D<sub>w</sub> represent the oxygen and deuterium atoms of a D<sub>2</sub>O molecule.

**Table 1.** Average Numbers of NMA Carbonyl Oxygen–water and Amide Hydrogen–water Hydrogen Bonds for the BLYP and BLYP-D Functionals

functional	number of NMA(O)–water HBs	number of NMA(D)–water HBs
BLYP	2.38 ± 0.15	0.98 ± 0.055
BLYP-D	2.60 ± 0.11	1.01 ± 0.057

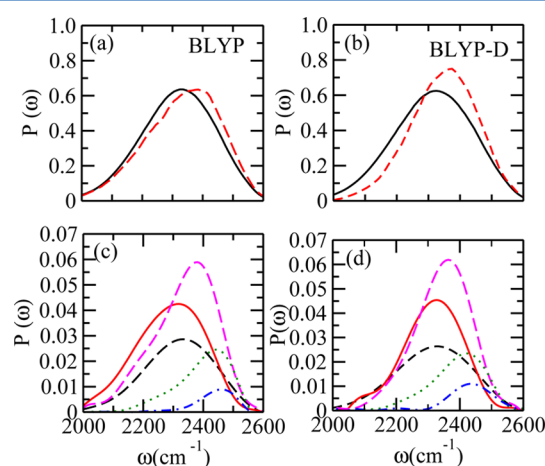
water is less than the cutoff value  $R_{c2}$ . The values of  $R_{c1}$  and  $R_{c2}$  are, respectively, 2.5 and 2.6 Å, which correspond to the location of the first minimum of the corresponding atom–atom radial distribution functions. The numbers of hydrogen bonds per carbonyl oxygen and amide hydrogen of the NMA molecule are found to be 2.38 (2.60) and 0.98 (1.01), respectively, for the BLYP (BLYP-D) functional. It is found that the hydrogen bonding takes place in higher number through the carbonyl oxygen of NMA, while the amide hydrogen forms one hydrogen bond with a water molecule in its surroundings.

In the following sections, we will be particularly interested in the frequency fluctuations and hydrogen-bond dynamics of those water molecules that are hydrogen bonded to the CO or ND groups. These water molecules are referred to as the first hydration shell water around carbonyl oxygen or amide hydrogen. It may be noted that the full hydration shell of the NMA solute extends well beyond its first hydration layer, as can be seen from the structural features present beyond the first peaks of all the solute–water correlations shown in Figure 1. Recent terahertz spectroscopic studies of Havenith and coworkers<sup>55–57</sup> on aqueous solutions of biomolecular solutes like glucose, lactose, trehalose, and helix bundle protein  $\lambda_{8–85}$  have also shown that the hydration layer around these solutes extends well beyond 5 Å from the surface of the solutes, which

means the number of water molecules in the entire hydration layer of a solute is much more than the number of water molecules that constitute the first hydration layer in the immediate vicinity of the solute. Because in the present study we are particularly interested only in the first hydration layer of water molecules around the carbonyl oxygen or the amide hydrogen rather than the full hydration shell of the entire NMA solute, we have referred to these water molecules as “first hydration shell” rather than “hydration shell” water in the following sections.

#### 4. VIBRATIONAL FREQUENCIES OF WATER IN THE VICINITY OF NMA

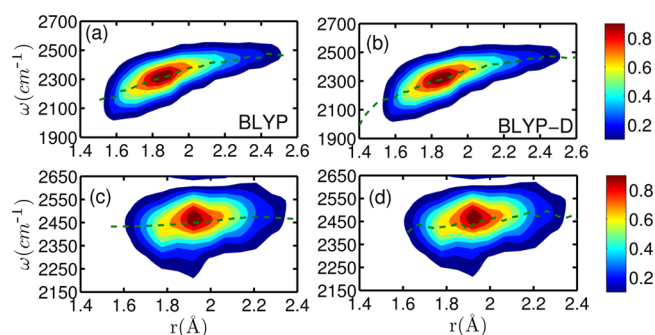
In an aqueous solution of NMA, the stretch frequencies of water OD modes fluctuate due to fluctuations in the associated hydrogen bonds with NMA or with other water molecules. In Figure 2a, we have shown the distribution of stretch frequencies



**Figure 2.** (a,b) Distributions of the stretch frequencies of OD modes in the first hydration shell of carbonyl oxygen of NMA (dashed curve) and other water molecules beyond the first hydration shell (solid curve). (c,d) Frequency distributions of the first hydration shell OD modes around carbonyl oxygen for different values of the hydrogen bond angle  $\phi$ . The solid, dashed, dotted, and the dashed-dotted curves are for OD groups with hydrogen bond angle of  $5 \pm 5$ ,  $15 \pm 5$ ,  $25 \pm 5$ , and  $35 \pm 5^\circ$ . The distribution at the top is averaged over all OD groups. The results shown in (a) and (c) are for BLYP and those in (b) and (d) are for the BLYP-D functional.

of OD modes present in the bulk and the first hydration shell of the carbonyl oxygen of NMA. Results are also shown for OD stretch frequencies averaged over all water molecules. The first hydration shell considered here is that of the CO oxygen so that it consists of mainly those water molecules which are hydrogen bonded with the carbonyl oxygen of NMA. The dependence of the frequency distribution of OD modes in the first hydration shell of the carbonyl oxygen on hydrogen bond angle is shown in Figure 2b. In Figure 3, we have shown the mutual probability of observing a particular OD frequency of water for a given (a) D (of water)–O (of NMA) and (b) D (of NMA)–O (water) distance. Results are shown for both the BLYP and BLYP-D functionals. It is clear from the width of the distributions that a single frequency cannot be assigned to a single hydrogen bond distance; however, on average, as shown by the dashed lines in the Figures (a) and (b), the OD covalent frequency increases to some extent with an increase in the associated hydrogen bond distance for water molecules





**Figure 3.** (a,b) Joint probability distribution of OD frequency and O(NMA)–D(water) hydrogen bond distance for the first hydration shell water around the carbonyl oxygen of NMA. (c,d) Similar joint probability distribution of the OD frequency and D(NMA)–O(water) distance for hydration shell water around the ND group, where D is the amide hydrogen (with deuterium mass) of NMA. The contour levels of different fractions of the maximum values are coded in different color. The results (a) and (c) are for BLYP and those of (b) and (d) are for the BLYP-D functional.

hydrogen bonded to the carbonyl oxygen of NMA. The average OD frequency of water in the first hydration shell of the carbonyl oxygen of NMA is found to be 2341 (2346)  $\text{cm}^{-1}$  for the BLYP (BLYP-D) functional. The stretch frequency of water OD modes in the hydration shell of the ND group of NMA is found to be 2459 (2465)  $\text{cm}^{-1}$ . These frequency results also mean that the carbonyl group of NMA forms stronger hydrogen bonds with water than ND group, which is consistent with the structural results shown in Figure 1. Also, considering the slightly higher average frequency of the OD modes that are hydrogen bonded to the carbonyl oxygen than that of bulk water molecules that are hydrogen bonded to other water molecules, it may be concluded that the NMA–water hydrogen bonds are slightly weaker than the corresponding water–water hydrogen bonds. We have also calculated the power spectrum of the velocity correlation of D atoms of water molecules present in the first hydration shell of NMA carbonyl oxygen and also in the bulk (results not shown). It is found that the peak position of the OD stretch of water in the first hydration shell of carbonyl oxygen is slightly blue-shifted compared with that of the bulk molecules, which is consistent with the frequency distributions shown in Figure 2. This blue shift of the OD frequencies in the first hydration shell can again be attributed to slightly weaker hydrogen bonds that are formed between the carbonyl oxygen of NMA and hydrogens of nearest water molecules. We have also performed a quantum-chemical calculation of an NMA–water dimer complex. Here we have considered two complexes where water is hydrogen bonded with the carbonyl oxygen for the first case and with the amide hydrogen in another one. The hydrogen bond energy for CO–water and ND–water was found to be  $-9.795$  and  $-7.184$  kcal/mol, respectively. We have used the B3LYP/6-31g(d,p) method for the calculations by using the GAUSSIAN03 program.<sup>58</sup> These results also show that the hydrogen bond between carbonyl CO–water is relatively stronger than the amide NH–water hydrogen bond.

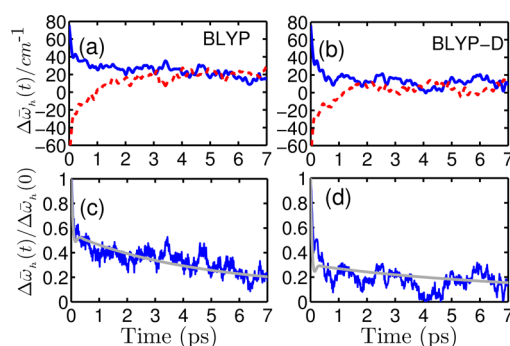
## 5. VIBRATIONAL SPECTRAL DIFFUSION OF OD STRETCH MODES OF HYDRATION SHELL WATER

We now look at the dynamics of frequency fluctuations, also called vibrational spectral diffusion, of OD stretch of water and also of amide I and amide A modes of NMA. In this section, we

focus on the frequency fluctuations of OD stretch of water in the first hydration shell of the carbonyl oxygen of NMA. We have investigated the dynamics of spectral diffusion by performing the so-called hole dynamics calculations<sup>38,44</sup> where the dynamics of a frequency hole, that is created by the removal of a bunch of OD modes of selected frequencies from the entire OD band for the first hydration shell water, is followed until the equilibrium is reached. The time evolution of this initially created nonequilibrium distribution is closely related to the time evolution of the pump–probe signals of time dependent infrared spectroscopic experiments that are designed to study the vibrational spectral diffusion in hydrogen-bonded liquids. It is assumed that at time  $t = 0$ , a Gaussian frequency hole is created in the equilibrium distribution of the following form<sup>38,44</sup>

$$P_h(\omega, 0) = P_{eq}(\omega) e^{-(\omega - \omega_p)^2 / 2\sigma^2} \quad (1)$$

where  $\omega_p$  is central frequency of the Gaussian distribution and  $P_{eq}(\omega)$  is the equilibrium distribution of all the OD frequencies present in the hydration shell. The initial distribution of the remaining frequencies is equal to  $P_{eq}(\omega) - P_h(\omega, 0)$ . Here we have calculated the time evolution of the nonequilibrium distributions of  $P_r(\omega, t)$  and  $P_h(\omega, t)$  for a large set of system trajectories reflecting the initial distributions  $P_r(\omega, 0)$  and  $P_h(\omega, 0)$  of hydration shell water in the vicinity of the CO group of NMA. We have also calculated the time dependence of the average frequencies of the remaining and hole modes of hydration shell water from the temporal evolution of the respective frequency distributions. We created the hole in two different frequency regions in our calculations of the spectral diffusion: One centered at the lower (red) frequency side at  $\omega_p = \bar{\omega} - 100 \text{ cm}^{-1}$  and another centered at the higher (blue) frequency side at  $\omega_p = \bar{\omega} + 100 \text{ cm}^{-1}$ , where  $\bar{\omega}$  is the average frequency of all the OD modes present in the hydration shell. Following our previous work on water and methanol,<sup>38,59</sup> we employed a Metropolis Monte Carlo like algorithm<sup>60</sup> using a Gaussian distribution to create the holes in red or blue side. This exercise is carried out for different initial times along the simulation trajectory for the hydration shell water. In Figure 4, we have shown the temporal evolution of the average hole frequencies when the hole is created at the higher frequency



**Figure 4.** Time variation of the (a) and (b) average frequency shifts of hole modes after excitation in blue (solid curve) and in red (dashed) sides of those OD modes that are present inside the first hydration shell of carbonyl oxygen of NMA. (c,d) Frequency shift results normalized by the initial frequency shifts for blue excitations are shown. The gray curve corresponds to the fit by eq 2. The results of (a) and (c) are for BLYP and those of (b) and (d) are for the BLYP-D functional.

**Table 2.** Relaxation Times (in ps) and Their Weights in the Vibrational Spectral Diffusion of OD Modes of Water in the First Hydration Shell of CO Oxygen of NMA for the BLYP (BLYP-D) Functional<sup>a</sup>

qty	excitation	$\tau_0$	$\tau_1$	$\tau_2$	$\omega_s$	$a_0$	$a_1$
$\Delta\omega_h(t)$	blue	0.11(0.10)	3.4(3.2)	14.6(14.1)	81.5(81.6)	0.49(0.70)	0.28(0.10)
$\Delta\omega_r(t)$	red	0.10(0.10)	3.9(3.6)	16.0(15.0)	118.9(78.9)	0.28(0.51)	0.39(0.20)

<sup>a</sup>Frequency is expressed in  $\text{cm}^{-1}$ .

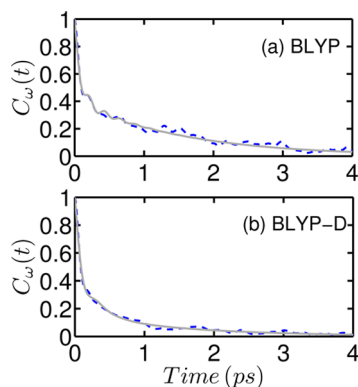
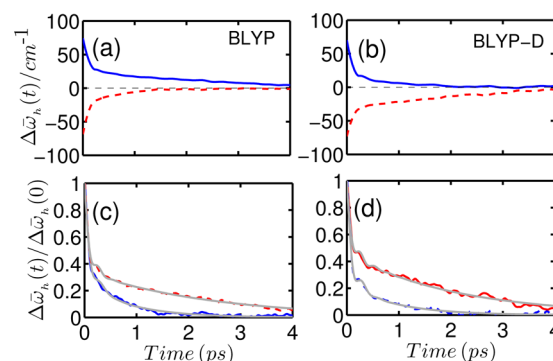
(blue) and also at the lower frequency (red) sides. The Figure also includes results of the decay of normalized frequency shifts.

When the hole is created in the higher frequency (blue) region, the average hole frequency shifts toward the lower frequency side with time until the average equilibrium value is attained. The average frequency of the remaining modes shifts toward the blue side with time as the hole in the blue region is filled gradually, and finally the distribution adopts a nearly symmetric shape around the average frequency  $\omega^-$ , that is, around  $\Delta\omega = 0$ . It is also clear from Figure 4 that an opposite behavior is found when the hole is created in the red side. We fitted the decay of the average frequencies of the hole and remaining modes to the function<sup>38,44,61</sup>

$$f(t) = a_0 \cos \omega_s t e^{-t/\tau_0} + a_1 e^{-t/\tau_1} + (1 - a_0 - a_1) e^{-t/\tau_2} \quad (2)$$

and the results of the relaxation times and weights are included in Table 2 for both the BLYP and BLYP-D functionals. The weak oscillation at the short time is likely due to the underdamped motion of the hydrogen-bonded OD groups. The two longer time scales arise from solute-water hydrogen bond dynamics and escape dynamics of water molecules from the first hydration shell of the carbonyl oxygen of the solute, as will be discussed in the later part of this paper.

The results previously presented are for water in the first hydration shell of carbonyl oxygen only. It would also be interesting to look at the vibrational spectral diffusion of all OD modes because the dynamical response in an experimental situation captures contributions from all water molecules that fall in the experimental frequency domain. For all OD modes, we have investigated the spectral diffusion first through frequency time correlation and then through the hole dynamics calculations. In Figure 5, we have shown the results of the frequency time correlation and, in Figure 6, we have shown the dynamics of average frequencies of the hole modes after

**Figure 5.** Time correlation function of the OD fluctuating frequencies averaged over all water molecules. The blue dashed curve represents the simulation results and the gray curve represents the fit by using eq 2. The results of (a) and (b) are for BLYP and BLYP-D functionals, respectively.**Figure 6.** (a,b) Variation of the average frequency shifts of the hole modes after excitations in the blue and red sides when all water molecules are considered in the calculations. The corresponding results after normalization by the initial frequency shifts are shown in (c) and (d). In both Figures, the blue solid and red dashed curves correspond to excitations in the blue and red sides, respectively. The gray solid curves in (c) and (d) represent the fits by the function of eq 2. Results of (a) and (c) are for BLYP and those of (b) and (d) are for the BLYP-D functional.

creation of a hole in the higher (blue) and also lower (red) sides of the frequency distribution at time  $t = 0$ . Overall, the temporal decay of the frequency correlation is found to be similar to that of the normalized frequency shifts of the hole and remaining modes. We fitted the decay of the frequency correlation and average frequency shifts to the function of eq 2, and the results of the relaxation times and weights are included in Table 3. In general, a fast decay at short times followed by a slower decay extended up to a few picosecond is found with the slower time scale ranging around 1 to 2 ps. Clearly, the very slow relaxation time of  $\sim 15$  ps that was found when the spectral diffusion dynamics was calculated exclusively for the first hydration shell water around carbonyl oxygen is missing when such calculations are done for all water molecules. Similar results were also found in previous studies of water containing halide ions.<sup>51,62–64</sup> As discussed later, the third slower time scale originates from the escape dynamics of water from the first hydration shell of the carbonyl oxygen to the rest of the solvent. When calculations are done for all water molecules, the contribution of such escape dynamical mode is minimal because of very small fraction of the total number of water molecules residing in the hydration shell of the polar group of interest, that is, the carbonyl oxygen of NMA.

## 6. FREQUENCY FLUCTUATIONS OF THE AMIDE I AND AMIDE A MODES OF NMA IN WATER

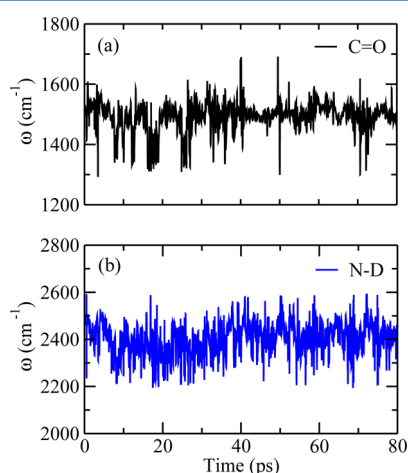
We have also looked at the dynamics of frequency fluctuations of certain vibrational modes of the solute, namely, its amide I and amide A modes by using a time-series method similar to that used for calculations of the fluctuating OD frequencies. In particular, it is noted from previous studies<sup>65</sup> that the amide I mode of NMA is mostly CO stretch, and that of amide A is mostly NH stretch (with deuterium mass for hydrogen in the

**Table 3.** Results for the Vibrational Spectral Diffusion of OD Modes Averaged over All Water Molecules for the BLYP (BLYP-D) Functional<sup>a</sup>

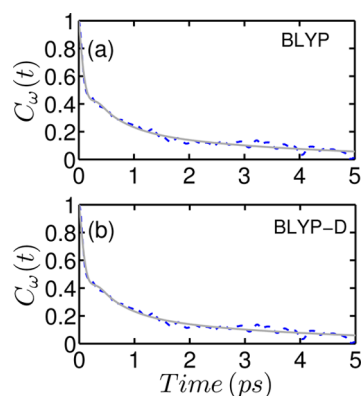
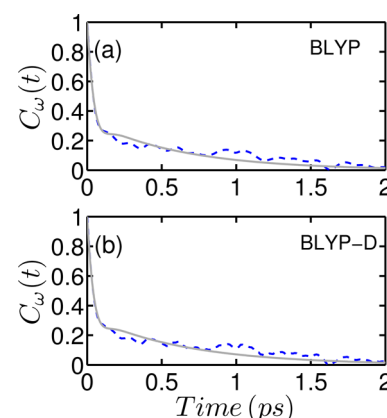
quantity	excitation	$\tau_0$	$\tau_1$	$\tau_2$	$\omega_s$	$a_0$	$a_1$
$C_\omega(t)$		0.31(0.11)	0.10(0.21)	1.56(1.42)	145.6(132.3)	0.07(0.29)	0.52(0.48)
$\Delta\omega_h^-(t)$	blue	0.12(0.13)	0.17(0.14)	1.42(0.93)	86.17(97.9)	0.28(0.26)	0.47(0.51)
$\Delta\omega_r^-(t)$	blue	0.13(0.14)	0.13(0.12)	2.50(2.02)	99.11(95.6)	0.15(0.19)	0.45(0.40)
$\Delta\omega_h^-(t)$	red	0.14(0.20)	0.12(0.11)	2.71(2.11)	109.3(116.4)	0.17(0.10)	0.49(0.44)
$\Delta\omega_r^-(t)$	red	0.13(0.12)	0.13(0.13)	1.34(0.87)	104.2(116.6)	0.24(0.13)	0.56(0.62)

<sup>a</sup>Time constants are expressed in ps and the frequency in  $\text{cm}^{-1}$ .

present case). In view of this, we have calculated the fluctuations of stretch modes of CO and ND modes of NMA through time series analysis and assigned them to the frequency fluctuations of the amide I and amide A modes, respectively. The results of these frequency fluctuations are shown in Figure 7, and the corresponding frequency time correlations are shown

**Figure 7.** Frequency fluctuations of (a) amide I (CO) and (b) amide A (ND) modes of the NMA molecule along the simulation trajectory. Results shown in this Figure are for the BLYP functional.

in Figures 8 and 9. We have used the same fitting function as given in eq 2 for these frequency correlations also, and the results of the relaxation times and weights are included in Table 4. The average frequencies of the amide I (CO) and amide A (ND) modes are found to be 1481 (1490)  $\text{cm}^{-1}$  and 2367

**Figure 8.** Time correlation function of amide I (CO) fluctuating frequencies of the NMA molecule in water. The gray line represents the fit by using eq 2. Results of (a) and (b) are for the BLYP and BLYP-D functionals, respectively.**Figure 9.** Time correlation function of amide A (ND) fluctuating frequencies of the NMA molecule in water. The gray line represents the fit by using eq 2. Results of (a) and (b) are for the BLYP and BLYP-D functionals, respectively.

(2375)  $\text{cm}^{-1}$ , respectively, for the BLYP (BLYP-D) functional. Similar to the decay of the OD frequency correlations, here also a short time decay followed by a slower decay extended to a few picoseconds is found for both of the frequency correlations. In general, the decay of the CO frequency correlation is found to be slower than that of the ND frequency correlation, which can be attributed to the relatively stronger hydrogen bonds between the CO group and water molecules in its vicinity. The slower time scales of the spectral diffusion of these two modes are found to be 3.65 (3.30) and 0.63 (0.51) ps, respectively, for the BLYP (BLYP-D) functional.

For the amide I mode, the current results of 3.3 and 3.65 ps for the BLYP-D and BLYP functionals can be compared with the corresponding experimental value of 1.6 ps reported in ref 32. Previous simulation studies<sup>23,25,26,30,66</sup> using empirical force fields for NMA and water found time scales of 0.75 to 0.83 ps for the slower component of the amide I frequency fluctuations of NMA in water. Thus, while the current study predicts a relatively slower relaxation of the amide I vibrational frequency fluctuations, the existing force-field-based computational studies predicted a faster relaxation compared with the experimental results. It may be noted that the frequency of the amide I mode in water fluctuates primarily due to fluctuations in the surrounding solvent. The faster relaxation predicted in the previous simulation studies of refs 23, 25, 26, 30, and 66 likely arises from the classical force fields used in those studies such as the SPC/E model of water, which is known to predict a faster dynamics of hydrogen bond fluctuations than found in experiments<sup>67–69</sup> in real water at room temperature. The relatively slower dynamics of the amide I frequency fluctuations found in the current ab initio simulation study may arise from a combination of factors such as the density functional used in



**Table 4. Time Constants (in ps) of the Vibrational Spectral Diffusion of Amide I (CO) and Amide A (ND) Modes of NMA for the BLYP (BLYP-D) Functional**

mode	$\tau_0$	$\tau_1$	$\tau_2$	$\omega_s$	$a_0$	$a_1$
mode I	0.20(0.70)	0.10(0.10)	3.65(3.30)	60.1(108.1)	0.25(0.10)	0.48(0.70)
mode A	0.05(0.04)	0.03(0.02)	0.63(0.51)	94.6(92.2)	0.60(0.50)	0.10(0.10)

the current study, basis set cutoff, system size, and so on. We also note that the use of dispersion corrections improved the dynamics in the right direction, which is consistent with the findings of other ab initio studies of pure water and aqueous solutions, where such dispersion-corrected BLYP or other density functionals were used.<sup>70–73</sup>

## 7. NMA–WATER HYDROGEN BOND AND ESCAPE DYNAMICS OF WATER FROM THE FIRST HYDRATION SHELL OF CARBONYL OXYGEN

We have calculated the dynamics of NMA–water hydrogen bonds using the so-called population time correlation function approach.<sup>74–87</sup> We define two hydrogen-bond population variables,  $h(t)$  and  $H(t)$ , where  $h(t)$  is unity when a particular NMA–water pair is hydrogen bonded at time  $t$  and it is zero otherwise. The variable  $H(t) = 1$  if the NMA–water pair remains continuously hydrogen bonded from time  $t = 0$  to  $t$ , and it is zero otherwise. Subsequently, we calculate the continuous hydrogen bond time correlation function  $S_{HB}(t) = \langle h(0)H(t) \rangle / \langle h(0)^2 \rangle$ , where  $\langle \dots \rangle$  denotes an average over all NMA–water pairs. Clearly,  $S_{HB}(t)$  describes the probability that an initially hydrogen-bonded NMA–water pair remains bonded at all times up to  $t$ . The associated integrated relaxation time  $\tau_{HB}$  measures the average lifetime of a hydrogen bond between the two molecules. Once the correlation function is calculated, we obtained the average hydrogen bond lifetime by integrating the continuous probability function  $S_{HB}(t)$ . We have calculated the dynamics separately for two kinds of solute–water hydrogen bonds: CO(NMA)–D(Water) and ND(NMA)–O(Water). We have also calculated the dynamics averaged over all hydrogen bonds. In all our calculations, we have used a geometric definition of hydrogen bonds as previously introduced in Section 3. The results of our hydrogen-bond dynamics calculations are summarized in Table 5. In this Table,

**Table 5. Results for Average Lifetimes (in ps) of NMA–water Hydrogen Bonds and Also the Residence Times (in ps) of Water in the First Hydration Shells of Carbonyl Oxygen and Amide Hydrogen of NMA for the BLYP (BLYP-D) Functional**

quantity	NMA(O)–water HBs	NMA(H)–water HBs	all HBs
$\tau_{HB}$	3.45(2.90)	0.76(0.41)	2.10(1.90)
$\tau_R$	16.06(11.50)	3.78(3.40)	

we have included the hydrogen-bond lifetime for both types of solute–water hydrogen bonds for both the BLYP and BLYP-D functionals. The value of  $\tau_{HB}$ , as found from the integration of the continuous correlation of  $S_{HB}(t)$ , is found to be 3.45 (2.90) ps for the carbonyl oxygen–water hydrogen bonds and 0.76 (0.41) ps for amide hydrogen–water hydrogen bonds for the BLYP (BLYP-D) functional. The hydrogen-bond lifetime of water–water hydrogen bonds outside the first solvation shell of the carbonyl oxygen or amide hydrogen of NMA is found to be  $\sim 2.10$  (1.90) ps for BLYP (BLYP-D), which can be compared with the corresponding pure water hydrogen-bond lifetime of

about 2 ps previously found for the BLYP functional.<sup>38</sup> In addition to the solute–water hydrogen-bond lifetimes, we have also calculated the residence time of water molecules in the solute hydration shell. Specifically, we have calculated the probability that a water molecule, which was in the first hydration shell of the carbonyl oxygen or amide hydrogen of NMA at time  $t = 0$ , remains continuously in the same hydration shell up to time  $t$  subject to an allowance time  $t^*$ . The associated integrated relaxation time  $\tau_R$  gives the average residence time of water molecules in the first hydration shell of the respective atoms of the solute. We calculated the residence time  $\tau_R$  by explicit integration of the residence probability function from simulations until 10 ps and by calculating the integral for the tail part from fitted exponential functions. Following previous work,<sup>88</sup> we have taken the allowance time to be 2 ps and found a value of 16.0 (11.5) ps for the residence time of water molecules in the first hydration shell of carbonyl oxygen of NMA for the BLYP (BLYP-D) functional. The residence time of water in the hydration shell of amide hydrogen of NMA is found to be 3.78 (3.40) for the BLYP (BLYP-D) functional. The above results for the hydrogen-bond and residence dynamics of water in the first hydration shell seem to suggest that the two slower relaxation times of the spectral diffusion of water molecules in the first hydration shell of the carbonyl oxygen of NMA arise from the dynamics of solute–water hydrogen bonds and escape of water molecules from the respective first hydration shell of the solute.

## 8. CONCLUSIONS

In this work, we have presented a first-principles theoretical study of the vibrational spectral diffusion and hydrogen bond fluctuations in aqueous solution of *N*-methylacetamide. Our calculations are based on ab initio molecular dynamics simulations for trajectory generation and time series analysis using the wavelet method for calculations of fluctuating frequencies. The ab initio simulations have been performed using two density functionals: BLYP<sup>39,40</sup> and its dispersion-corrected version BLYP-D.<sup>41–43</sup> In addition to the dynamics of hydrogen-bond fluctuations and vibrational spectral diffusion of various solute and solvent modes, we have also looked at some of the relevant equilibrium quantities such as solute–water pair correlations and hydrogen-bonding properties.

Our calculations reveal that the carbonyl oxygen of deuterated NMA forms stronger hydrogen bonds with water than the deuterated hydrogen of its ND group. On average, the carbonyl oxygen and amide hydrogen are found to form 2.4 (2.7) and 1.0 (1.01) number of hydrogen bonds with water for the BLYP (BLYP-D) functional. The average frequency of OD modes in the first hydration shell of carbonyl oxygen of NMA is found to be slightly higher than that of bulk water molecules, which means the NMA(CO)–water hydrogen bonds are slightly weaker than water–water hydrogen bonds on average. On the dynamical side, the vibrational spectral diffusion of the OD stretch modes of water and also the amide I (CO) and amide A (ND) modes of NMA are investigated through hole-dynamics and frequency correlation function calculations. The

vibrational spectral diffusion of OD modes in the first hydration shell of carbonyl oxygen are found to have a very fast time scale of  $\sim 100$  fs and two slower time scales of  $\sim 3$  and  $\sim 14$  ps. The time scale of  $\sim 3$  ps can be assigned to the lifetime of NMA(CO)–water hydrogen bonds, and that of  $\sim 14$  ps is attributed to the escape dynamics of water from the first hydration shell of the carbonyl oxygen of NMA; however, this slow time scale of  $\sim 15$  ps is found to be absent when the spectral diffusion is calculated over all water molecules, which is likely due to the very small weight that the first hydration shell water around the carbonyl oxygen makes to the overall spectral diffusion of all water molecules. The slower component of the vibrational spectral diffusion of all water molecules is found to be  $\sim 1.6$  ps, which can be compared with the time scale of  $\sim 2$  ps found for pure water in our previous study.<sup>38</sup> In addition to the stretch frequencies of OD modes, we have also looked at the fluctuating frequencies of amide I (CO) and amide A (ND) modes of NMA. The spectral diffusion of these two modes is found to occur with time scales of 3.65 (3.3) and 0.63 (0.51) ps, respectively, for the BLYP (BLYP-D) functional. The faster time scale of spectral diffusion of the amide A mode can be attributed to the relatively weaker NMA–water hydrogen bonds that are formed through the amide hydrogen of NMA and oxygen of a water molecule in its vicinity.

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### Notes

The authors declare no competing financial interest.

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