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How Phonons Govern the Behavior of Short, Strong Hydrogen Bonds in Urea−Phosphoric Acid

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Abstract: Recent neutron diffraction data have shown that the hydrogen atom involved in the short, strong hydrogen bond in urea−phosphoric acid migrates toward the midpoint of the hydrogen bond as the temperature increases. With the help of solid state ab initio calculations and inelastic neutron scattering, we have investigated the temperature dependence of the structural and vibrational properties of the system. The potential energy surface of the proton in the short, strong hydrogen bond and the thermal population of the energy levels therein cannot account for the observed proton migration. Ab initio molecular dynamics simulations clearly reveal the migration of the proton. This molecular dynamics result was reported recently by other authors, but they only offered a tentative explanation in terms of a resonance between high-frequency vibrations, which is not supported by the calculations presented here. We explain the proton migration in terms of phonon-driven structural fluctuations and their impact on the temperature-dependent evolution of the potential energy surface of the short hydrogen-bond proton.

I. Introduction

Hydrogen bonds exhibit a wide range of structural and dynamic characteristics and play a fundamental role in many aspects of molecular science. These characteristics can be understood at a basic level in terms of a one-dimensional potential energy surface (PES). For a long hydrogen bond (donor−acceptor distance greater than ~2.6 Å), the PES is composed of two approximately harmonic potential wells, which are equally deep if the proton is equally stable in the equilibrium positions close to the donor and acceptor atoms. In the solid state, intermolecular interactions normally break this symmetry. As the hydrogen bond becomes shorter, the potential energy barrier separating them becomes lower and narrower until, for the shortest bonds (donor−acceptor distance ~2.45 Å), the potential wells merge and the single well is strongly anharmonic. Whereas long hydrogen bonds lead to weak perturbations of molecular properties, short, strong hydrogen bonds (SSHBs) can have quite different properties. SSHBs are thought to play a fundamental role in stabilizing the intermediate state of certain enzymatic reactions through a subtle modification of the local environment of the hydrogen bond.[1,2] Other implications of SSHBs in inhibitor potency of active site[3] or in stabilization of the photoactive yellow protein[4] have been shown. DNA is an example of a hydrogen-bonded molecular system which contains the genetic code of living beings. Coding depends on the base-pair sequences, but also minor chemical changes to the nucleosides, such as the methylation of cytosine, which give rise to epigenetic effects.[5] In this context, the temperature-dependent dynamics of protons in DNA hydrogen bonds and the chemical integrity of the base-pair molecules are vital to the reliability of genetic coding.[6]

Measuring hydrogen-bond-specific properties in large biomolecular systems is very difficult, and the level of quantum chemistry techniques would have to be reduced significantly when investigating such large molecular structures. Model molecular compounds are therefore required in order to identify and characterize SSHBs. Urea−phosphoric acid (UPA) is such a system which has been extensively measured by single crystal neutron diffraction as a function of temperature by Wilson and co-workers.[7,8] There are many hydrogen bonds in crystalline UPA, but only the SSHB shows novel properties, namely, the migration of the proton from a stable position at low temperature (~50 K) close to the donor urea oxygen atom to a centered

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position in the hydrogen bond at 335 K. The proton migrates by ~0.05 Å.

Recently, the same authors have published the results of ab initio molecular dynamics simulations which reproduce the measured proton migration effect with increasing temperature.[9] Understanding the proton migration mechanism from the MD simulations is not simple, and a resonance between high-frequency vibrations (1600 and 3200 cm^{-1}) was tentatively proposed as being related to proton migration. The authors suggest performing diffraction measurements on the deuterated analogue of UPA to test whether the proton migration is restricted when the vibrational resonance no longer exists. This type of work has been carried out on pyridine-3,5-carboxylic acid.[10] Proton migration is observed for both protonated and deuterated compounds, which tends to invalidate an explanation in terms of vibrational resonances.

Furthermore, the authors show the time dependence of the structural variation of the SSHB (Figure 3 in ref 9). The fastest proton motion occurring on a time scale of ~25 fs (1300 cm^{-1}) is seen at the lowest temperatures (50 K) and corresponds to the stretching vibration of the O−H bond. At higher temperature, the bond length is seen to be modulated by slower dynamics, but these were not characterized accurately in the short MD simulations (400 fs). The time dependence of the bond length indicates that lower frequency dynamics are responsible for proton migration, and these have to be identified in order to understand correctly the novel behavior of the SSHB.

The reported MD simulations suggest that proton migration could be induced by fluctuations in the local molecular environment, although a causal link between structural fluctuations and proton migration has not been demonstrated. Lattice expansion is not responsible for proton migration since this is small for a hydrogen-bonded solid, and the published MD simulations were performed at different temperatures in the same unit cell. An alternative explanation is in terms of the Boltzmann population of the ground state and a low-lying vibrational energy level in the anharmonic potential well of the SSHB. Similar effects have been observed in normal hydrogen bonds, in which the two distinct proton positions, corresponding to the minima of the two-well potential, have populations that depend on temperature and the energy difference between the two tautomeric structures.[11] The form of the PES is of direct relevance to the recent paper of Morrison and co-workers since they have used a phenomenological model to interpret the structural evolution in terms of a two-well potential at low temperature and a single-well potential at high temperature. The vibrational levels and therefore indirectly the PES can be measured using spectroscopic techniques, such as Raman, IR, or inelastic neutron scattering (INS), although reliably assigning the vibrational modes for a hydrogen-bonded molecular crystal is a challenge.

Understanding vibrational spectra has, in recent years, been helped by the growing availability of quantum chemistry codes (notably based on density functional theory (DFT) methods), which perform normal-mode analysis, that is, by imposing the harmonic approximation. Although less common, solid-state DFT codes have been used in this context, which allow intermolecular interactions, including hydrogen bonds, to be incorporated.[12−14] Molecular vibrations typically calculated at the center of the Brillouin zone can then be extended over the whole Brillouin zone, including dispersion.[15−17] Once vibration frequencies and displacement vectors have been obtained from the quantum chemical calculations, the INS spectra can be easily calculated given the scattering cross-sections of the atoms and the geometry of the spectrometer. In contrast to IR and Raman techniques, INS allows direct comparison between calculated and experimental spectra and therefore a clear evaluation of the numerical model.

Vibrational spectra can also be determined from molecular dynamics simulations (MD), the vibrational density of states being the Fourier transform of the velocity autocorrelation function, and the neutron scattering functions S(Q,w) being the Fourier transform of the van Hove correlation functions.[18] Compared to normal-mode analysis (phonon calculations), MD has the advantage of not imposing the harmonic approximation and allows finite temperature to be investigated via the average kinetic energy of the atoms. The disadvantage of MD is that partial densities of states do not give as much mode-specific information as normal modes, and that the zero-point motion of atoms cannot be included in a computationally efficient way. Provided the same total energy calculation is used, phonon and MD methods will therefore give complementary information.

We have measured the vibrational spectrum of UPA using INS and performed full phonon calculations on an optimized structure of UPA, evaluating the anharmonicity of these normal modes. We have explored directly the anharmonicity of the PES of the SSHB by calculating the potential energy variation for large amplitude displacements of the proton along the hydrogen bond. MD has been validated by comparing S(Q,w) determined from a low-temperature simulation (50 K) with the results of the phonon calculations and then extended to higher temperature to further probe anharmonicity and the temperature-induced structural variations. Experimental and numerical results are reported in the following sections.

II. Structural Information

The structure of urea−phosphoric acid (1/1), $C(NH_2)_2$-$OH.PO_2(OH)_2$, was reported at a number of temperatures in the range of 150−335 K by Wilson.[7] Single-crystal, neutron diffraction was used, allowing all atomic positions to be accurately determined. UPA crystallizes in an orthorhombic structure, in the *Pbca* space group ($Z = 8$). One lower temperature structure (15 K) along with a geometry optimization using DFT calculations was also reported.[8] Figure 1 shows the SSHB in detail with atom labeling consistent with that of Wilson.

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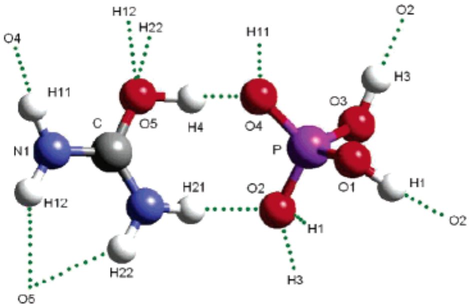

Figure 1. Urea and phosphoric acid molecules in their crystal configuration showing the SSHB O5−H4···O4.

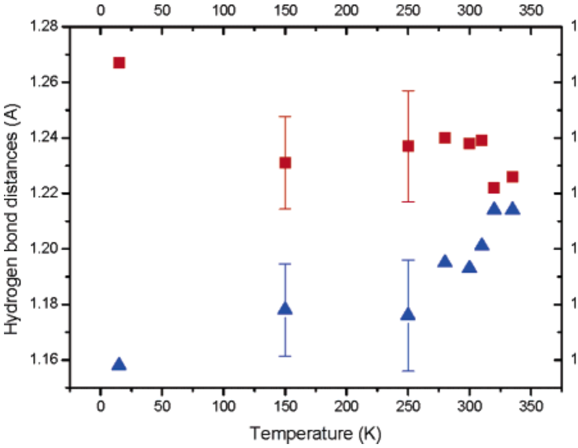

Figure 2. Proton migration as a function of temperature in the SSHB of UPA as reported in ref 10. Triangles represent the O5−H4 distance, and the squares represent the O4−H4 distance. Typical error bars are shown at 150 and 250 K.

The geometry of the SSHB O5−H4···O4 and the proton migration effect in the SSHB are shown in Figure 2.

As the basis for phonon calculations in this work, the measured structure of UPA has been optimized using the VASP DFT code.[19−22] Since the implementation of DFT in computational codes does not include long-range dispersive interactions, optimizing the atomic coordinates in the crystallographically determined unit cell can give a better description of the structure, and thereafter the dynamics of the system, than optimizing the cell parameters. This is seen to be the case here when comparing measured and calculated INS spectra (below). The measured crystal structure is very close to a potential energy minimum in the VASP calculation, with bond geometries only being slightly modified. The biggest difference occurs for the SSHB, which has an O−O length of 2.43 Å an O−H length of 1.10 Å and an OHO angle of 168.2°, compared to the corresponding experimental values of 2.40 Å, 1.16 Å, and 170.0°, respectively. The DFT calculation tends to underestimate the strength of the hydrogen bond, giving a shorter O−H distance and a longer O−O distance, so that the offset of the proton position from the middle of the hydrogen bond is about twice as big as in the measured structure. When optimizing the crystal structure in the unit cells determined experimentally at higher temperature, the most energetically stable structures (corresponding to the global minimum of the PES) retain a short O−H distance, which precludes a simple explanation of proton migration in terms of lattice expansion.

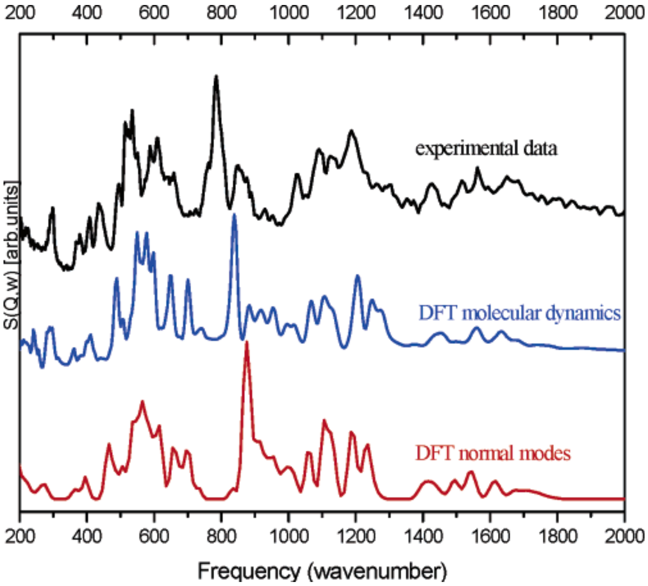

Figure 3. Comparison of measured (top) and calculated (middle, molecular dynamics; bottom, normal modes analysis) INS S(Q,w) spectra of urea−phosphoric acid.

III. Vibrational Spectroscopy, Normal Mode Analysis, and Molecular Dynamics Simulations

Figure 3 (upper curve) shows the INS spectrum for the fully protonated sample of UPA, measured on TOSCA at the ISIS facility (UK).[23] Often for a hydrogen-bonded system, it is straightforward to prepare partially deuterated samples, which, due to the scattering cross-section of deuterium being about 20 times smaller than that of hydrogen, allow spectral intensity from specific atoms to be attenuated or highlighted. However, in UPA, all hydrogen atoms are labile and exchange with deuterium, so no useful contrast variation could be obtained. The figure also shows two calculated spectra; the bottom curve is from the phonon calculation,[24] and the middle curve is from the MD simulation at 50 K. Both calculations are in reasonably good agreement with the experimental data in terms of the accuracy of spectral frequencies and the overall intensity distribution. The main discrepancy concerns the intense mode at 800 cm^{-1} in the data, which is found at 850 cm^{-1} in the spectrum calculated from the MD simulation and 890 cm^{-1} in the spectrum from the phonon calculation. The normal mode at 890 cm^{-1} is seen to involve essentially a wagging motion of the OH groups in the acid molecule. The discrepancy of 40 cm^{-1} between the two calculations is due to anharmonicity, and the remaining difference is due to the functional (PW91)[25] for the exchange-correlation energy and Vanderbilt-type ultrasoft pseudopotentials[26] for ion−electron interactions used in all calculations.

The mode assignment at 800 cm^{-1} is confirmed by the partial, vibrational density of states, which shows the striking differences between the normal and short hydrogen bonds that could not

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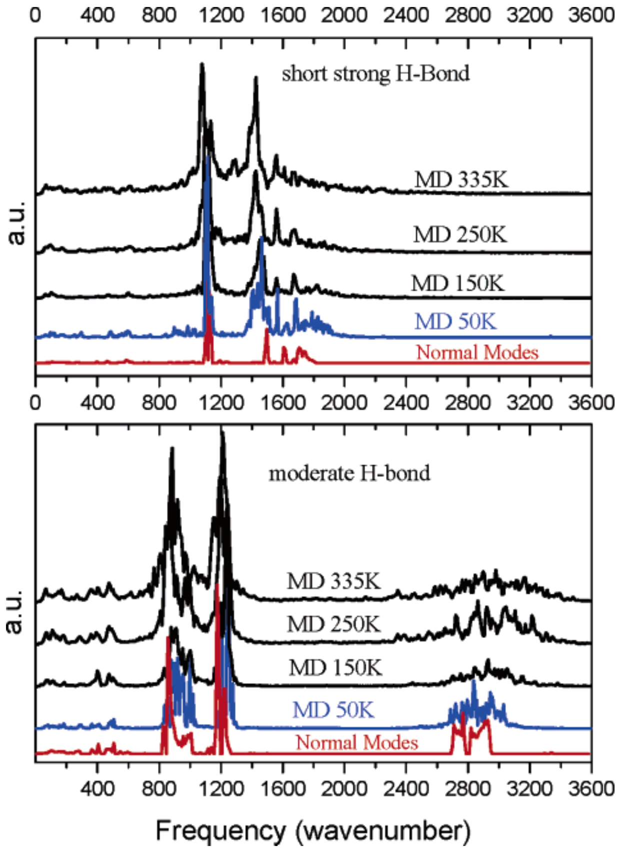

Figure 4. The vibrational density of states of the hydrogen involved in the strong H-bond O5−H4···O4 (upper panel) and of the H involved in a moderate H-bond O1−H1···O2 (lower panel). The lowest curve in each panel is derived from phonon calculations, and the upper four curves are from MD simulations.

be accessed experimentally with partially deuterated samples (Figure 4). The lower panel shows the partial density of states of the hydrogen atoms in O1−H1···O2-type bonds. The density of states extends mainly from ∼400 to 2800 cm^{-1}, the small downshift in the OH stretching frequency from above 3000 cm^{-1} being due to the weak transfer of electron density from the covalent bond to the hydrogen bond.

The upper panel shows the partial density of states for the SSHB hydrogen atom. The intensity in this case is contained in a much smaller frequency range, extending from 1100 to 1800 cm^{-1}, with the bands at 1100, 1500, and 1600 cm^{-1} involving wagging motion of the OH bond (which is strongly coupled to H−N−H bending vibrations) and the bands above 1700 cm^{-1} involving mainly stretching motion. That the lower frequency limit for the density of states is at a relatively high frequency is another indication of the significant electron transfer from the covalent to the hydrogen bond.[27,28] These assignments are consistent with the analysis of infrared and Raman results.[29] At lower frequency, the vibrational character is more difficult to describe since the vibrations of the urea and phosphoric acid molecules are strongly coupled by the SSHB and the other hydrogen bonds.

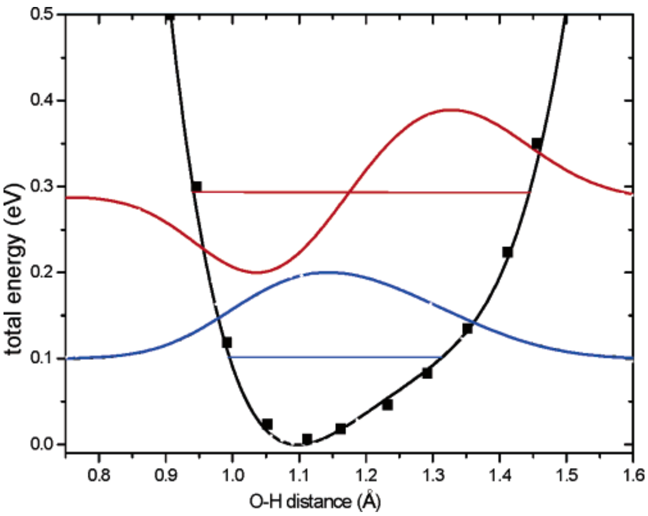

Figure 5. Potential energy well, vibrational energy levels, and wave functions of the hydrogen atom in the SSHB. The wave functions represent the fundamental state $n = 0$ (lower curve) and the first excited state $n = 1$ (upper curve) in the anharmonic potential energy well; the vibrational energy is 1525 cm^{-1}.

As for S(Q,w) (Figure 3), there is reasonably good agreement between the densities of states obtained from the phonon calculation and MD simulation (lower two curves in each panel of Figure 4). From this comparison, anharmonicity is most apparent for the SSHB for the mode at 1400 cm^{-1}. However, the anharmonicity is not apparent in S(Q,w) because it includes the signal from all atoms, in particular, from the urea NH_2 groups in the 1400−1500 cm^{-1} range. The temperature dependence of the densities of states does not reveal any further, significant anharmonic effects, especially for the normal hydrogen bonds.

IV. Anharmonicity: Mapping the PES

Anharmonicity is a recurring theme in studies of systems with SSHBs.[30] In addition to the analysis in the preceding section, the anharmonicity of the normal modes can be investigated by calculating the PES for structures obtained by applying normal mode displacements to the equilibrium structure. The maximum amplitude of the displacements should induce an increase in potential energy equivalent to the corresponding vibrational frequency (for example, ∼2 times the vibrational energy). We have analyzed every normal mode for UPA in the frequency range from 900 to 2000 cm^{-1} in this way, fitting each 1D slice of the PES along the normal coordinate with a 4th-order polynomial and using the fit parameters in a perturbative correction to the harmonic frequency. The biggest anharmonic correction was less than 1.2% of the harmonic frequency.

A common way to evaluate anharmonicity is to calculate eigen energies and functions in the 1D slice of the PES of the O5−H4 stretching displacement along the SSHB, the potential energy variation being determined from the variation in the crystal energy as a function of the position of the H4 proton. From the low-temperature structure, the calculated potential energy well is broad and asymmetric with a single minimum close to the O5 atom (Figure 5). It is not a two-well potential. The energy levels and wave functions in this potential energy well have been obtained from a numerical solution of Schroed-

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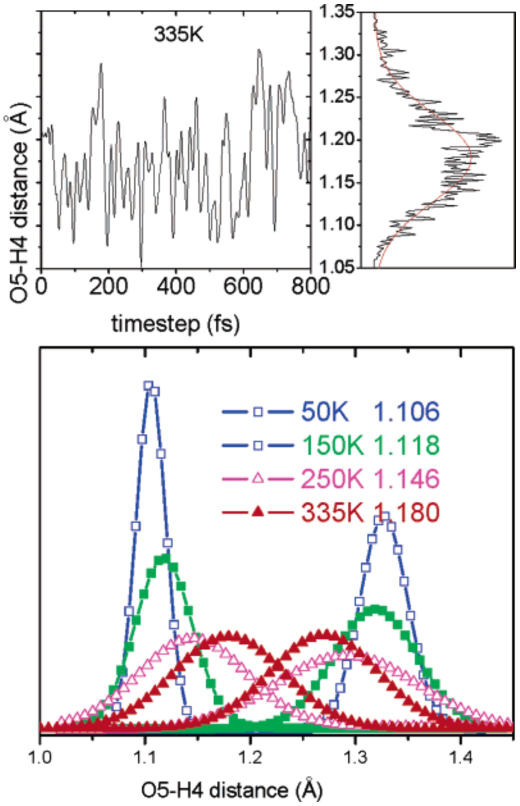

Figure 6. The upper panels show (left) the O5−H4 distance extracted from part (0.8 ps of a total of 2 ps) of the MD simulation at 335 K and (right) a histogram representation of the whole trajectory and a Gaussian fit. The lower panel shows the Gaussian fits to the O5−H4 and the O4−H4 data from the MD simulations at four temperatures.

inger's equation, assuming the oscillator mass to be that of a proton, giving a vibrational frequency of 1525 cm^{-1}, compared to ∼1700 cm^{-1} in Figure 4 (upper panel). However, phonon calculations show clearly that the O5−H4 stretch is not a normal mode, which has two consequences; the effective oscillator mass is not simply that of the proton, and the spatial exploration of the anharmonic potential energy well by any normal mode is limited. Accordingly, a harmonic analysis of the potential energy well close to the minimum (±0.05 Å) gives a vibrational frequency of 1555 cm^{-1}, compared to 1525 cm^{-1}.

Mapping a 1D slice of the PES, as in Figure 5, does show that there cannot be excited vibrational energy levels associated with the SSHB that could be populated at room temperature and therefore explain the observed proton migration. While quantifying the vibrational energies in the PES depends on the oscillator mass, the partial density of states for the SSHB proton (Figure 4, upper panel) shows that these range between 1700 and 1800 cm^{-1}, that is, between 2400 and 2500 K.

V. Structural Analysis of UPA as a Function of Temperature

Having ruled out proton migration arising from simple lattice expansion or from the population of energy levels in the PES of the SSHB, the relevant structural information has to be sought in the MD simulations as a function of temperature. From the atomic trajectories, a histogram of the O5−H4 distance can be constructed at each temperature. Figure 6 shows Gaussian fits to these histograms. The average O−H bond length increases from 1.1 to 1.18 Å in going from 50 to 335 K, and the full width of the distribution increases by a factor of ∼4. This temperature-dependent evolution is in reasonably good agreement with the experimental observations, the corresponding values being 1.16 and 1.21 Å, and the recently published MD results. Since the O−O distance in the SSHB is slightly longer and the OH bond is slightly shorter in our calculations than in the measured structure, the proton does not quite reach the middle of the hydrogen bond, by 0.04 Å, at a temperature of 335 K. Increasing the temperature in the MD simulation does not allow the proton to migrate further. The lack of zero-point motion in MD simulations, which, according to phonon calculations, contributes ∼25% of the mean square displacement of the H4 proton at 335 K, is also responsible for the reduced amplitude of the calculated proton migration. So having eliminated an explanation in terms of the static PES of the hydrogen bond, MD reveals the mechanism of the proton migration to be fluctuations of the molecular environment, although the amplitude of the effect is underestimated.

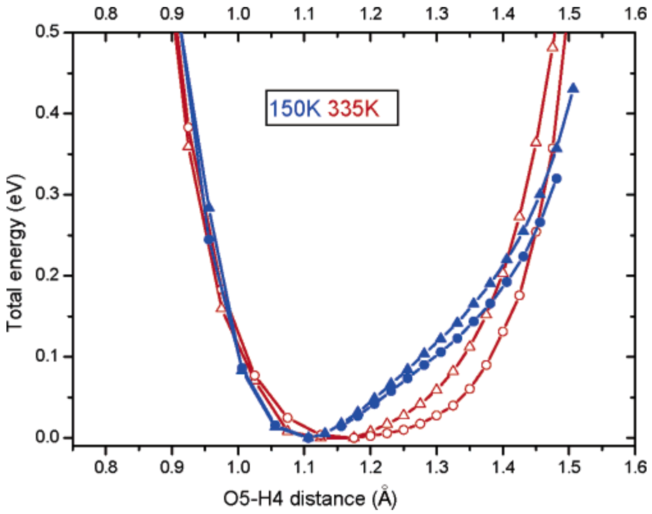

Figure 7. The potential energy wells for the O5−H4 stretching displacement at 150 (filled symbols) and 335 K (open symbols) temperatures for the crystal structures with the minimum (triangles) and maximum (circles) separations of the urea and phosphoric acid molecules.

Additional understanding of the proton migration mechanism can be obtained by combining structures from MD simulations with methods for mapping the PES. By monitoring the distance of C−P between the urea carbon atom and the acid phosphor atom during the MD simulations, crystal structures (symmetry *P*1) have been extracted which correspond to the maximum and the minimum of the C−P distance. For each of these structures, the 1D slice of the PES, like the one shown in Figure 5, has been calculated (see Figure 7). At 150 K, the two PES's are similar and resemble the one determined from the equilibrium structure (Figure 5). At 335 K, there are bigger differences between the two PES's due to the thermal fluctuations and, more importantly, both PES are relatively flat-bottomed compared to the lower temperature PES's. This shape of the PES allows the proton to spend more time closer to the acid oxygen, while, for the PES, for the maximum C−P distance, the potential energy minimum is actually shifted by ∼0.07 Å away from the urea molecule.

The high-temperature structure, with the proton shifted toward the center of the hydrogen bond, is stabilized by vibrational entropy, that is, by the low-frequency lattice vibrations that are activated up to 335 K. A time-independent potential energy well

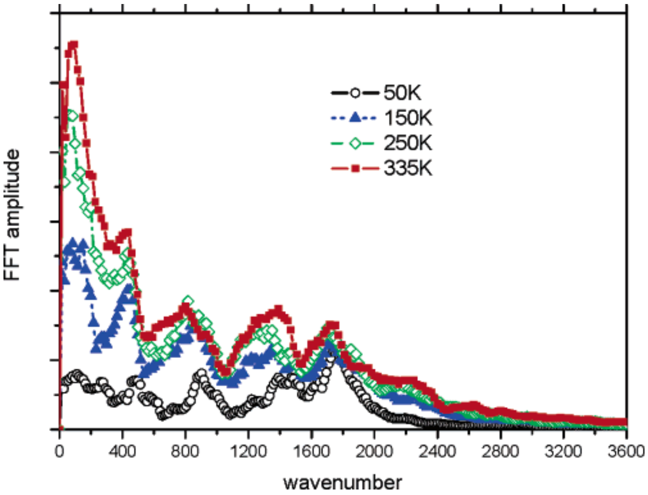

Figure 8. The FFT amplitude of the O5−H4 bond length variation at four temperatures.

can be obtained from the time-averaged crystal structure and is similar to the average of the two, high-temperature potential energy wells in Figure 7. The proton is shifted by ∼0.06 Å away from the urea oxygen atom. At any temperature, fluctuations in the potential energy well tend to broaden the distribution of proton positions. Figure 7 shows directly the change in the average potential energy well and its time-dependent modulation for the SSHB due to thermal fluctuations and therefore the mechanism for proton migration.

The final question concerns the characteristics of the dynamics that induce proton migration. Since this effect occurs continuously in the temperature range from 50 to 335 K, the lattice vibrations (phonons) of the crystal are expected to be responsible. The frequencies that modulate the O5−H4 bond length can be found from the Fourier transform (FT) of the time dependence of the bond length variation. Figure 8 shows the amplitude of the FT, which therefore displays the amplitude of the oscillations as a function of frequency. This figure clearly reveals that the lowest frequency modes (∼50−200 cm^{-1}), that is, the phonons, give rise to the strongest modulation of the O5−H4 bond length. We note that the amplitude of the FT tends to zero at zero frequency since the long wavelength acoustic phonons do not modulate the local structure.

Dynamic properties of hydrogen bonds can be influenced by specific vibrational modes. For example, in benzoic acid dimers, proton transfer is enhanced by a small number of modes and, in particular, the intradimer stretch.[13] In UPA, up to 200 cm^{-1}, there are 80 normal modes. If any of these modes in particular were involved in the modulation of the potential energy well, a well-defined peak could be expected in the FT's of Figure 8 (the MD trajectories are sufficiently long and the frequency resolution is good enough, see for example Figure 4). Figure 8 therefore suggests that many modes are involved in the modulation of the potential energy well. Inspection of the modes (eigenvectors) reveals a certain similarity in that they tend to involve molecular rotations which solicit several hydrogen bonds, reflecting the complex 3D hydrogen-bond network in UPA. This situation is more complicated than benzoic acid, which can be considered as an isolated dimer with only one type of hydrogen bond.

VI. Discussion

Similar MD simulations were recently reported by Morrison and co-workers.[9] While their simulations were long enough to reproduce the proton migration with temperature, they were too short to obtain adequate resolution in the frequency spectra that they extracted. Their resolution was of the order of 100 cm^{-1}, whereas we have improved this by a factor of 10 or more. Furthermore, they have taken the Fourier transform of the forces acting on the atoms, whereas the physically relevant quantity is the vibrational density of states, which is obtained from the velocity autocorrelation function. Their tentative explanation of proton migration being driven by a resonance between one- and two-phonon excitations of different vibrations is therefore highly speculative since, first, there are many possible such resonances, and second, the density of states for the modes they cite at ∼1600 cm^{-1} is very weak (see Figure 4). Furthermore, if these vibrations were responsible for the significant changes in the hydrogen bond geometry, jumps in the proton position would occur on a time scale shorter than 25 fs, corresponding to the approximate O5−H4 stretch frequency, whereas Figure 2 of ref 9 and Figure 6 in this article show that these jumps occur on a longer time scale. These slower dynamics are quantified in the Fourier transform of the O5−H4 bond length and are seen to correspond mainly to the lattice vibrations in the 50−200 cm^{-1} frequency range.

The work presented in this paper also shows that the phenomenological model used in ref 9 to interpret the MD results is not appropriate in the stated form. The authors talk about a transition from a two-well potential to a single-well potential, whereas we have clearly shown that the PES always has a single minimum and that proton migration is due to rather subtle changes in the average PES induced by the fluctuating environment.

VII. Conclusion

With a view to understanding the proton migration in the SSHB in UPA, we have calculated and measured, directly and indirectly, the PES that governs the proton dynamics. INS has been used to measure the vibrational modes of UPA at 20 K. Characteristics of the PES are obtained from solid-state DFT calculations that are validated by comparing calculated spectra with the measured spectrum. On the basis of this comparison, the phonon calculation, based on the harmonic approximation, can be seen to give a good description of the vibrational modes in UPA. Further analysis reveals clear differences in terms of vibrational modes, between the SSHB and the other, normal hydrogen bonds. The normal hydrogen bonds have modes that cover a much larger spectral range, from 800 cm^{-1} for wagging modes to 2500 cm^{-1} for stretching modes. In contrast, the SSHB proton participates in modes that are concentrated between 1100 and 1800 cm^{-1}, revealing a significant transfer of electron density from the covalent bond to the hydrogen bond. Since there is generally a strong vibrational density of states in the spectral range up to ∼2000 cm^{-1}, there is a strong mixing of the SSHB vibrations with other molecular vibrations.

The first and simplest step in the analysis of the PES (and in the determination of the phonons) of UPA is to find the global minimum, which corresponds to the low-temperature crystal structure. Taking the measured unit cell at any temperature, or the unit cell optimized by DFT, gives a short O−H bond length of 1.1 Å. Proton transfer in UPA is not a simple consequence of lattice expansion.

The DFT calculations are also used to map out the 1D slice of the PES of the proton in the SSHB in the O5−O4 direction. As expected, the potential energy well is strongly anharmonic, but this does not show up clearly in the vibrational spectroscopy because the mixed character of the normal modes means that only a limited spatial range of the PES is explored. Vibrational energy levels in the potential energy well have been calculated in the harmonic approximation and taking into account the anharmonicity. Although the excited-state wave function in the anharmonic potential has the center of gravity of the corresponding probability distribution shifted toward the center of the hydrogen bond, the excited state is at least 2400 K in energy above the ground state and cannot be populated at room temperature.

Molecular dynamics simulations using the same DFT code, VASP, also give a vibrational spectrum that is in good agreement with the INS spectrum. MD is not restricted to the harmonic approximation and shows that anharmonicity does not significantly affect the vibrational modes in UPA. Analyzing the time and temperature dependence of the molecular geometries from the MD trajectories shows clearly that the proton migration is due to thermal fluctuations of the molecular environment induced by the lattice vibrations. The high-temperature structure is stabilized by vibrational entropy, and the resulting time-averaged PES has a minimum that shifts toward the center of the hydrogen bond and the shape becomes more “flat-bottomed”, which also favors proton migration. Time-dependent fluctuations broaden the distribution of proton positions about the average value. MD simulations under-estimate slightly the extent of proton transfer, which is due to the under-estimated hydrogen-bond strength and to the protons being treated as classical particles.

This combined neutron scattering and DFT modeling work demonstrates clearly that the properties of short hydrogen bonds can be modified by the thermal fluctuations of the local molecular environment, that is, by phonons in the case of a molecular crystal, such as UPA. Temperature, weak interatomic interactions, and local structure collectively govern the reactivity of SSHB. Changing any of these parameters can therefore modify the properties of the SSHB and the processes that they mediate, such as enzymatic reactions and inhibitor potency.

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Supporting Information Available: Sample preparation, inelastic neutron scattering, numerical simulations. This material is available free of charge via the Internet at http://pubs.acs.org.

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