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Protonated Glycine Supramolecular Systems: the need for quantum dynamics

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Abstract

IR spectroscopy is one of the most commonly employed techniques to study molecular vibrations and interactions. However, characterization of experimental IR spectra is not always straightforward. This is the case of protonated glycine supramolecular systems like Gly2H+ and (GlyH + nH2)+, whose IR spectra open questions which have still to find definitive answers even after theoretical spectroscopy investigations. Specifically, the assignment of the conformer responsible for the spectrum of the protonated glycine dimer (Gly2H+) has led to much controversy and it is still debated, while structural hypothesis formulated to explain the main experimental spectral features of (GlyH + nH2)+ systems have not been theoretically confirmed. We demonstrate that simulations must account for quantum dynamical effects in order to solve these open issues. This is achieved by means of our divide-and-conquer semiclassical initial value representation technique, which approximates the quantum dynamics of high dimensional systems with remarkable accuracy and overperforms not only the commonly employed but unfit scaled-harmonic approaches, but also pure classical dynamics simulations. Besides the specific insights concerning the two particular cases here presented, the general conclusion is that, due to the widespread presence of protonated systems in chemistry, quantum dynamics may have a prominent role and should not be totally overlooked also when dealing with large systems including biological structures.

Introduction

Protonated systems are ubiquitous in chemistry.[1] They are involved in many different processes and instances, ranging from organic reactions and intermediates to biological and interstellar-medium events. Furthermore, protonation is determinant for the chemical properties of heteroatomic compounds, such as

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† Electronic supplementary information (ESI) available: Computational setup. Geometries, harmonic frequencies and semiclassical vibrational levels of the systems investigated. Description of the theory.
amino acids. For instance, hydrolysis of amides, peptides, and proteins at biological pH is initiated and driven by the process of protonation. In general, the electronic and conformational structure of proteins as well as their dynamics are strongly influenced by protonation with the resulting three-dimensional structure playing a key role in their biological activities.

Protonated glycine compounds are pivotal examples of protonated systems because they are the smallest building blocks of more complex biological entities, and a full comprehension of their dynamics is indeed essential for a correct understanding of the stability and reactivity of many other protonated systems. For this reason, in the past, protonated glycine compounds have been the subject of extensive experimental and computational studies.[2, 3, 4, 5, 6, 7, 8, 9] However, there are some fundamental questions about these systems which are still open. Specifically: to what extent is the proton shared between the amide and the carboxylic group? Is it a static or dynamical effect? Do nuclear quantum mechanical contributions play a major or a minor role for the properties of these protonated compounds? One should expect very peculiar quantum mechanical effects when the proton is shared between nucleophilic groups either belonging to different molecules, like in the case of the glycine proton-bound dimer, or being part of the same molecule, as in protonated glycine. The main reason for this expectation is that the proton is the only ion with basically zero ionic radius and it has the lightest mass. These peculiarities are at the origin of proton mobility and reactivity, and one would expect quantum mechanical contributions to be determinant. This paper aims at providing the answers to the open questions illustrated above and at estimating the impact of quantum mechanical effects by comparing quantum and classical simulations versus available experimental results.

One popular experimental spectroscopic technique to study the vibrational features of protonated compounds is represented by infrared multiple photon dissociation (IRMPD). IRMPD provides enhanced signals of gaseous molecular ions in the infrared region once they have been trapped in the high vacuum cells of mass spectrometers.[2, 10, 11, 12, 13] However, when applied to the glycine proton-bound dimer, Gly$_2$H$^+$, IRMPD does not permit to undisputedly identify which Gly$_2$H$^+$ conformer is more representative of the IRMPD spectrum.

This open issue, which has to be solved in order to properly characterize the structural properties not only of the dimer but also of complex peptide chains, has been the topic of previous joint experimental and computational works in 2005 by MacLafferty et al.[14] and in 2007 by MacMahon et al.[15] with conclusions clearly at odds. Specifically, Gly$_2$H$^+$ has two low energy gas-phase conformers, named CS01 and CS02, plus a zwitterionic form ZW01 (see the Supplemental material for more information) which rapidly interconverts to CS01 during the dynamics. In the CS01 conformer, the two moieties making up the dimer are bound by means of a O···H$^+$N interaction, while a N···H$^+$N interaction is peculiar of CS02. According to some works, including McLaффerty’s one,[9, 14] CS02 is the most representative conformer of the experimental IRMPD spectrum, while for others, with McMahon’s paper among these,[4, 5, 15] it is CS01 that deserves recognition, so a definitive conclusion
has not been reached yet.

In both works[14, 15] the authors employed a scaled-harmonic approach to interpret the main features of the IRMPD spectrum. In the scaled-harmonic technique,[16] first the normal mode frequencies (i.e. the purely harmonic frequencies of vibration) at the minimum geometry are calculated by diagonalizing the equilibrium nuclear Hessian matrix and taking the square roots of the Hessian eigenvalues. Then, they are scaled to account for anharmonicity and coupling between modes. Such an approach is widely employed since it is easily doable even for large size molecules. It requires calculation of just a single Hessian matrix. However, the approach remarkably neglects any dynamical and anharmonic effects that may become crucial when interactions such as hydrogen bonds dominate the interaction picture.[17] Even if several research groups have provided full sets of scaling constants for the different levels of theory and electronic basis sets employed[16, 18] as well as different scaling constants for calculations of different observables (frequency, zero point energy, enthalpy, entropy, etc.), the scaled harmonic approach is misleading for the interpretation of the glycine proton-bound dimer spectrum. Furthermore, it is generally classified as an *ab initio* method in an improper way, since an empirical tuning parameter is enforced.

### Results and Discussion

#### Protonated glycine dimer

To prove the inaccuracy and ineffectiveness of scaled-harmonic frequency estimates, following Ref. 15, we performed geometry optimizations of Gly₂H⁺ at the DFT-B3LYP level of theory with 6-311+G(d,p) basis set, followed by a scaled-harmonic analysis. In agreement with the previous studies, we found that conformer CS01 is the lowest energy conformer, while CS02 is just 2.1 kcal/mol higher in energy. Given this small difference in energy, the determination of the conformer responsible for the IRMPD spectrum in panel (a) of Fig. (1) implies the assignment and the interpretation of the spectrum in full details. By scaling all the harmonic frequencies at CS01 geometry by a factor equal to 0.96 - panel (b) -, the OH and NH stretch region is well reproduced while the mid-range one is not. Likewise, simulations based on the 0.97 factor suggested in Ref. (14) would follow a similar destiny. Conversely, if the scaling factor equal to 0.985 suggested in Ref. (15) is applied, then the stick spectrum of panel (c) is found. This scaled-harmonic spectrum mimics reasonably well the experimental peaks in the mid-range region between 1000 cm⁻¹ and 2000 cm⁻¹. However, the same scaling factor performs poorly in the H-stretching region above 3000 cm⁻¹. Since the anharmonicity parameters for each vibration are not known a priori, we conclude that it is impossible to model IR spectra on the basis of harmonic calculations, at least when different conformers are present. For these reasons, we deem that previous investigations cannot be recognized as conclusive ones.

A computational technique able to account for conformational and dynam-
Figure 1: Vibrational spectrum of Gly$_2$H$. Panel (a) is the IRMPD spectrum that has been obtained by composing figures from Refs. 15 and 14. Panel (b) and (c) report the stick harmonic spectra at DFT-B3LYP level with 6-311+G(d,p) basis set, scaled respectively by a factor of 0.96 and 0.985 (Ref. 15).
ical effects should be conveniently based on (quantum) molecular dynamics, since the dynamics allows to explore the actual Potential Energy Surface (PES) even far from the harmonic region.\cite{19, 20, 21} Such a non-local approach may be crucial for a correct interpretation of hydrogen bonding.

The quantum dynamical way to spectroscopy and frequency computation is given by the Fourier transform of the autocorrelation of the time-evolved nuclear wavepacket averaged over the quantum density matrix of vibrational states (i.e. the power spectrum)\cite{22}

\begin{equation}
I_{qm}(E) = \frac{1}{2\pi\hbar} \int_{-\infty}^{+\infty} e^{iEt/\hbar} \langle \Psi(0) | \Psi(t) \rangle \, dt.
\end{equation}

Eq.(1) includes all quantum mechanical spectroscopic information like zero point energy (ZPE), fundamental and overtone frequencies, anharmonicities and couplings, tunneling effects as well as quantum resonances between overtones and fundamentals. The classical equivalent of Eq.(1) is the Fourier transform of the velocity autocorrelation function

\begin{equation}
I_{cl}(\omega) = \frac{1}{2\pi\hbar} \int_{-\infty}^{+\infty} e^{i\omega t} \langle \mathbf{v}(0) \cdot \mathbf{v}(t) \rangle \, dt
\end{equation}

where \( \mathbf{v}(t) \) is the vector of the atomic velocities at time \( t \). Here the average is over a suitable ensemble of initial phase space configurations.\cite{6, 23, 24, 25, 26} Eq.(2) is limited to the calculation of classical fundamental frequencies, mode couplings and resonances. In other words, it accounts for the classical contribution to anharmonicity only. Anyway, both approaches are dynamical and represent a step forward with respect to single point harmonic calculations.

Unfortunately, when dealing with high dimensional systems, purely quantum mechanical simulations based on Eq.(1) are out of reach because of the so-called curse of dimensionality problem. Furthermore, accurate and fast-to-evaluate analytical PESs are usually not available and must be replaced by more computationally expensive \textit{ab initio} “on-the-fly” calculations, whereby the dynamics can be performed (even if at a lower level of electronic theory), and which demand for a theoretical formalism that permits a convenient interface to them. Semiclassical (SC) dynamics can be interfaced to \textit{ab initio} “on-the-fly” calculations straightforwardly so we adopted it to calculate \( I_{qm}(E) \).

In a SC simulation quantum mechanical effects are reproduced by employing many entangled coherent states, which are time-evolved on top of classical trajectories. The semiclassical initial value representation (SC-IVR) approximation\cite{27, 28, 29, 30} of quantum dynamics has been proved to be reliable and robust.\cite{31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47} Recently, we developed an SC-IVR method based on a “divide-and-conquer” strategy (DC-SCIVR) to undertake the spectroscopic calculations of Eq.(1).\cite{48} The method can deal with very high dimensional molecular and supra-molecular systems, and it is very accurate when compared to available exact vibrational quantum mechanical calculations.\cite{49, 50} Specifically, our DC-SCIVR method has been tested successfully against systems up to hundreds of degrees of freedom.\cite{48} and
in particular it has been employed to study the vibrational features of the protonated water dimer, the Zundel cation. The results are very accurate (within few wavenumbers) even for the vibrational bands of the proton doublet in the region of the O–H–O stretch and associated with the proton transfer ($\approx 1000 \text{ cm}^{-1}$), when compared to exact grid-based quantum dynamics results on the same PES. The DC-SCIVR idea is to calculate the power spectrum as a sum of partial reduced-dimensionality spectra. First, full dimensional \emph{ab initio} on-the-fly classical trajectories are calculated. Then, the normal modes are divided into vibrational subspaces according to their mutual coupling,\cite{48,49,51} and the partial spectra are calculated by projecting the classical trajectory information according to the following formula \cite{48}

$$I_{qm}(E) = \left( \frac{1}{2\pi\hbar} \right)^F \int d\tilde{p}(0) d\tilde{q}(0) \frac{1}{2\pi\hbar T} \int_0^T e^{\frac{\hbar}{2} \left[ \hat{S}_t(\tilde{p}(0),\tilde{q}(0)) + Et + \hat{\phi}_t \right]} \langle \tilde{\Psi} | \tilde{p}(t), \tilde{q}(t) \rangle dt^2,$$

(3)

where $F$ is the dimensionality of the vibrational subspace, and the multi-dimensional phase-space integration is characterized by a positive-definite time-dependent integrand made of the classical action ($\hat{S}_t(\tilde{p}(0),\tilde{q}(0))$), the phase of the semiclassical prefactor ($\hat{\phi}_t$),\cite{46} and the overlap between the reference state $|\tilde{\Psi}\rangle$ and the coherent state $|\tilde{\Psi}(t),\tilde{q}(t)\rangle$. More details can be found in the SI. Fig.(2) reports the resulting DC-SCIVR power spectra, where the ZPE has been shifted to zero for better comparison with the experiments, that cannot measure ZPE values. The reported peaks are those of the vibrational modes which have the highest oscillator strengths.

A peak by peak comparison between the semiclassical spectra of the two possible conformers shown in panel (a) and (c) in Fig.(2) and the experimental one which appears in the mid panel (b) shows clearly that in panel (a) all the experimental vibrational features are faithfully reproduced, differently from the case of panel (c) where the agreement is not as good. By looking at the actual calculated frequencies for each peak, a mean absolute error from the experimental peaks of 14 cm$^{-1}$ is associated to the spectrum of conformer CS01 in panel (a), while a deviation of 32 cm$^{-1}$ characterizes the spectrum of conformer CS02 in panel (c). This discrepancy in the mean absolute error values is pretty significant and conclusive even upon weighing in the typical accuracy of semiclassical calculations.\cite{49} More specifically, in the fingerprint region, the two carbonyl stretching frequencies (violet and orange lines) are degenerate in the case of the CS02 conformer, while they are not for CS01, in agreement with the experimental spectrum. Furthermore, the two vibrational peaks around 1500 cm$^{-1}$, corresponding to the fundamentals for the OH hydrogen-bonded bending (blue profile) and the umbrella inversion mode (green line), are well reproduced in panel (a), while panel (c) shows more elaborated vibrational coupling features. Similar considerations are valid also for the symmetric NH stretch and the free OH stretch in the high frequency region, with the spectrum in panel (a) better resembling the experimental profile. We stress out that our assignment of
Figure 2: DC-SCIVR power spectra for conformer CS01 in panel (a) and CS02 in panel (c) of Gly$_2$H$^+$. Panel (b) is the experimental IRMPD spectrum. Starting from the left, the red continuous line is for the free OH bending mode, the blue one is the OH hydrogen-bonded bending, the green line is for the umbrella inversion mode, the violet and the orange ones are both carbonyl stretchings, the cyan line is for the NH symmetric stretch and, finally, the magenta one is for the free OH stretch.
the experimental spectrum to conformer CS01 has been obtained without any tuning parameter and in a fully ab initio way. Furthermore, no ad-hoc frequency scaling factor nor fitting procedures have been applied to the calculated spectra here reported. From our simulations we note that there are numerous peaks in the frequency domain between the fingerprint peaks and the NH and OH stretching region which have not been detected by the experiments. These peaks belong to mode overtones and combinations of them, and are consequently experimentally much less intense. Finally, energetics calculations for both conformers have been performed at a quantum level by adding ZPE values to the classical minimum, i.e. the bottom of the well, and CS01 has been found to be about 2.5 kcal/mol more stable than CS02 revealing that the conformer that we identified as the major contributor to the experimental IR spectrum is also the (quantum mechanical) global minimum.

Despite the success of the semiclassical simulations presented above, one key methodological question remains open. In fact, if on one hand quantum effects are hallmarks of spectroscopy, on the other hand for systems of dimensionality similar or bigger than Gly$_2$H$^+$ it could be argued that a classical picture be enough to describe with sufficient accuracy the spectral features of at least fundamental transitions. This would require much less effort since a semiclassical simulation is significantly more computationally intense than a classical one. Eq.(2) requests to calculate at each time step the cartesian velocities $v(t)$ of the nuclei only. Instead, in Eq.(3), the calculation of $I_{pm}(E)$ in semiclassical approximation implies to evaluate not only the position and the velocities of the nuclei at each time step, but also the nuclear Hessian (for evolution of the phase term). This is about an order of magnitude more expensive in terms of computational efforts.

**Protonated glycine tagged by hydrogen molecules**

To point out clearly the importance of quantum mechanical effects in vibrational spectra influenced by proton dynamics, we consider that, recently, Mason, Williams and Rizzo published a series of very interesting IRMPD spectra, where protonated glycine, GlyH$^+$, was tagged by an increasing and controlled number of hydrogen molecules.[3] We focus particularly on two of these investigations. The first one regards protonated glycine solvated by a single hydrogen molecule (GlyH + H$_2$)$^+$, while in the other instance three H$_2$ molecules are involved (GlyH + 3H$_2$)$^+$. The minimum geometries of these systems are reported in Fig.(3).

This figure suggests that panel a) is characterized by a strong hydrogen bond interaction between one of the amide hydrogens and the carbonylic oxygen atom of the carboxylic acid group, while in panel b) the presence of the three hydrogen molecules may suppress the hydrogen bond interaction by inducing a reorientation of the amide group. In panel a) the H···O distance at the minimum geometry is about 1.90 Å, while in panel b) the distance is equal to 2.52 Å. This last distance is still shorter than the sum of hydrogen and oxygen van der Walls radii (2.72 Å), which is considered, as a rule of thumb, the limit
for hydrogen bonding.

To check out whether the hydrogen bond is lifted or not by virtue of the H₂ tagging process and if quantum mechanical effects play any relevant role for this kind of interaction, we will first perform ab initio “on-the-fly” DC-SCIVR simulations using the DFT-B3LYP level of theory and employing the aVDZ basis set, and then compare with the experimental spectra. Fig.(4) reports the IRMPD and simulated spectra for (GlyH + H₂)⁺.

The experimental results are reproduced in spectrum b), where the amide N-H stretch involved in the intramolecular hydrogen bond is located between 2950 and 3000 cm⁻¹ and labeled as NHₐ, while NH₉ and NHc indicate the free NH stretching peaks. The signal at 3546 cm⁻¹ corresponds to the free OH stretch. Upon adoption of a scaling coefficient equal to 0.96 to match the harmonic OH frequency (at MP2 level of theory with aVDZ basis set) with the experimental OH band, also the NH₉ and NHc peaks are reproduced quite well, while NHₐ is off by about 117 cm⁻¹, as shown by the stick spectrum on the top panel of Fig.(4).[3] Moving to classical simulations, we calculated the classical spectrum, I₉, by means of Eq.(2) and report it in panel c) separately for each mode for a better comparison with the experiment. The main spectroscopic features are reproduced, even if the signal corresponding to the NHₐ and NH₉ bands is quite broad. Finally, in the semiclassical spectrum of panel d), calculated with Eq.(3), the fundamental bands are faithfully reproduced, with the addition of overtones that are too weak to be detected in the experiment and that are missing in the classical and scaled-harmonic simulations. In general,
Figure 4: (GlyH + H₂)⁺ spectra. In a) the scaled-harmonic stick spectrum is presented; Panel b) reports the experimental IRMPD spectrum; c) is the I_cl classical spectrum according to Eq. (2), and d) is the I_qm semiclassical spectrum from Eq (1). In the experimental spectrum, the label NHa is for the hydrogen bonded NH stretching frequencies, while NHb and NHc indicate the unbound ones. OH labels the homonymous stretching frequency. Numerical values of the frequencies are reported in the SI.
the simulated peaks are broader than the experimental ones because, on one hand, experiments are performed at very low temperature (a few K) and rotations are hindered or even blocked, while, on the other hand, in the simulations the dynamics is propagated only for a short time (less than 1 ps) before the Fourier transform is undertaken, and every mode (including internal rotators) is given an amount of energy according to its contribution to the ZPE and let free to evolve without any artificial constraints. Furthermore, the dynamics of the hydrogen bonding may contribute to the broadening of the NH stretching bands as shown by Gaigeot and coworkers by applying finite temperature classical molecular dynamics to small protonated peptides, such as Ala2H+ and Ala3H+[6, 7, 25].

We now turn to the other system, i.e. (GlyH + 3H2)++, reported in panel b) of Fig.(3). Fig.(5) shows the spectra corresponding to those presented in Fig.(4) but this time for this bigger system. One may think that hydrogen molecules do not interact significantly with GlyH+ and that it is possible to obtain in good approximation the IRMPD signal of the isolated molecule. However, there are clear differences between the experimental spectra of Figures (4) and (5). One of them is represented by the blue shifted NHa peak. As usual, scaled-harmonic calculations are shown as a stick spectrum in panel (a) of Fig.(5) and they miss to account correctly for the anharmonicity of the NHa stretch motion. Once more, the scaling of harmonic frequencies brings us to a dead end. A classical approach based on Eq. (2) is not helpful in this circumstance as demonstrated by the set of spectra in panel (c) of Fig.(5) that clearly show classical mechanics overestimating the NHa stretch frequency. We believe that this is due to the fact that the intramolecular hydrogen bond and the dynamics of the involved proton have a prevalent quantum nature. In other words, a scaled-harmonic or classical dynamics approach lead to the wrong conclusion that the intramolecular hydrogen bond is broken in presence of 3H2 molecules interacting with GlyH+. Conversely, a semiclassical simulation based on Eq.(1), reported in panel d), reproduces faithfully all the vibrational features of the IRMPD spectrum also in this case, including the strong anharmonicity of the NHa stretch and the consequent red shift, thus confirming that the hydrogen bond interaction is only weakened and not completely broken, even in presence of three H2 molecules coordinated to the amide group.

Another key difference between Figures (4) and (5) lies on the appearance of a second OH stretch band, located at 3491 cm−1, and labeled as OHr. Masson et al.[3] suggested that this band is given by a configuration where one of the three H2 molecules interacts with the carboxylic group. Indeed, the peak is red-shifted by about 55 cm−1 with respect to the free OH stretch (the OHb band). This would mean that the experimental spectrum b) of Fig.(5) is actually originated by two different conformers. To validate the previous conformational hypothesis we consider a configuration with a single H2 molecule tagging the carboxylic group. This geometry is not stable experimentally (in fact the OHr peak appears only when 3 or more H2 molecules are involved) but it can be investigated theoretically. The system is reported in panel (a) of Fig.(6), and we focus on the OH stretch.
Figure 5: The same as in Fig.(4) but for (GlyH + 3H$_2$)$_+$ . Numerical values of the frequencies are reported in the SI.
Figure 6: (GlyH + H$_2$)$^+$ spectra, with the H$_2$ molecule coordinated to the carboxylic group. The labels (a)-(d) are as in Fig. (4).
Still in panel a) the harmonic stick spectrum (at DFT-B3LYP level of theory with aVDZ basis set) for the OH stretch is presented after scaling by a factor of 0.96, which is the same coefficient employed in the previous simulations. This estimate is definitely off the mark. On the contrary, both the classical (panel c) and the semiclassical (panel d) peaks are quite accurate for the OH stretch, confirming that the OHr band is indeed due to the interaction between a H$_2$ molecule and the carboxylic group. The presence of the H$_2$ molecule weakens the OH bond leading to the observed red shift.

**Amino group deuteration**

To further prove that the differences between the classical and the semiclassical spectra reported respectively in panel c) and d) of Fig.(5) are due to quantum mechanical effects only, we quenched them by deuterating all the three hydrogen atoms, pictorially represented by the gray atoms of the molecule in Fig.(7).

Then, we calculated the spectra for the deuterated GlyH$^+$ molecule tagged by the three H$_2$ molecules. We focus on the amide modes and selectively plot the NDa (previously NHa) band, both using the classical Eq.(2) and the quantum formulation of Eqs.(1) and (3) spectrum formulation. The results are reported in Fig.(7). The NDa band is centered around 2350 cm$^{-1}$, which is significantly red-shifted with respect to the previous NHa band, because of the heavier deuterium mass. However, we note that the classical and semiclassical peaks are almost identical in this case. This proves that the previous discrepancy of about 150 cm$^{-1}$ between the classical and the semiclassical NHa band location of Fig.(5) was exquisitely due to a quantum mechanical effect of the light hydrogen atom. It is quite surprising that this quantum anharmonic effect is so huge. However, when considering the strong anharmonicity of the NHa potential well and the consequent huge delocalization of the quantum mechanical vibrational eigenfunction (as pictorially represented in the Supplemental Material),
the prominent quantum mechanical nature of this hydrogen bond interaction appears fully justified.

Conclusions

We conclude by remarking the importance to employ a quantum dynamical approach in calculating vibrational frequencies and to go beyond the scaled-harmonic level. This has been demonstrated by means of divide-and-conquer semiclassical dynamics, which has permitted to reproduce experimental anharmonicities quite well and to explain some open issues involving the protonated glycine dimer and the tagging of protonated glycine with molecular hydrogen. In particular, for the former, the CS01 conformer has been assigned consistently in the whole frequency range, while, for the latter, some peculiar spectral quantum features due to hydrogen bonding and intermolecular interactions have been rigorously explained, a task that neither scaled-harmonic nor classical approaches were able to accomplish. On this point, we notice that the reference experiments were performed at very low temperatures, so we did not run standard thermalized classical simulations (which would have provided just harmonic estimates), but we estimated a classical analog of the quantum mechanical vibrational spectral density. Nevertheless, these classically-inspired calculations were not as satisfactory as semiclassical ones. Interestingly, due to the interaction, vibrational frequency calculations of the tagging H$_2$ molecules display a red shift ($\sim 50$ cm$^{-1}$) comparable to that of the OH stretch of glycine. Remarkably, the DFT-B3LYP level of electronic theory adopted is not only suitable for a realistic description of the entire supramolecular system but also able to provide frequency estimates in quantitative agreement with the experiments. Finally, we are able to answer the questions with which we introduced the paper by stating that quantum effects play certainly a very important role in these protonated systems, the intramolecular hydrogen bond interaction has a strong impact on the NH stretch revealing an elevated degree of delocalization of the proton shared with the carboxylic group, and the very same interaction is influenced by the dynamics with the hydrogen bond being less and less directional as the number of tagging molecules increases. All these findings point out very clearly the crucial role that quantum dynamics may have, suggesting that it should not be neglected even when dealing with larger systems.

Conflicts of Interest

There are no conflicts to declare.

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