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Hydration-controlled excited-state relaxation in protonated dopamine studied by cryogenic ion spectroscopy

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ABSTRACT

Ultraviolet (UV) and infrared (IR) spectra of protonated dopamine (DAH^+) and its hydrated clusters $\text{DAH}^+(\text{H}_2\text{O})_{1-3}$ are measured by cryogenic ion spectroscopy. DAH^+ monomer and hydrated clusters with up to two water molecules show a broad UV spectrum while it turns to a sharp, well-resolved one for $\text{DAH}^+(\text{H}_2\text{O})_3$. Excited state calculations of $\text{DAH}^+(\text{H}_2\text{O})_3$ reproduce these spectral features. The conformer-selected IR spectrum of $\text{DAH}^+(\text{H}_2\text{O})_3$ is measured by IR dip spectroscopy and its structure is assigned with the help of quantum chemical calculations. The excited state lifetime of DAH^+ is much shorter than 20 ps, the cross correlation of the ps lasers, revealing a fast relaxation dynamics. The minimal energy path along the $\text{NH} \rightarrow \pi$ proton transfer coordinate exhibits a low energy barrier in the monomer while this path is blocked by the high energy barrier in $\text{DAH}^+(\text{H}_2\text{O})_3$. It is concluded that the excited state proton transfer in DAH^+ is inhibited by water-

insertion.

Dopamine (DA), one of the catecholamines, plays an important role in homeostasis and addiction.¹ DA is a neurotransmitter involved in motor coordination, memory, reward processes and signal transmission from neurons. The lowering of the level of DA in the human brain is generally associated with the symptoms of Parkinson's disease.^{2,3} The generally low expression level of DA in vivo renders its detection difficult by optical methods such as fluorescence.⁴ Some indirect photodetection methods of DA have been reported but no photophysical properties including excited state dynamics have been reported. Interestingly, polydopamine (PDA) nanoparticles that are efficiently formed by oxidation under alkaline conditions show high fluorescence efficiency with possible application for cellular imaging.⁵ By their importance, the intrinsic conformational varieties of DA, which are strongly related to molecular recognition by the DA receptor, have been studied by infrared (IR) spectroscopy in the gas phase and theoretical calculations.^{6,7} On the other hand, its photophysical properties have not been understood sufficiently. Under physiological conditions, DA is protonated thus the excited state dynamics of protonated DA (DAH⁺) should be studied. In addition, hydration and dehydration effects on its photophysical properties are also important because DAH⁺ is hydrated in vivo but has to be dehydrated when it is recognized in the hydrophobic binding pocket of the DA receptor.⁸ In the last decade, cryogenic ion spectroscopy has emerged as a powerful method to reveal the structures and intrinsic photophysical properties of bare biomolecules. Studying mass-selected hydrated clusters in a cold ion trap allows revealing the solvation effects gradually through direct a comparison with quantum chemistry calculations. While excited state dynamics in small peptides and related systems have been investigated in the last decade as recently reviewed,⁹ the studies on hydrated species remain scarce and so to be explored.

Recently, excited state dynamics of protonated adrenaline, a closely related catecholamine, has been reported.¹⁰ It was found that the excited state proton transfer from the amine chain to the aromatic ring and H atom loss from the ammonium group compete with a branching ratio that depends on the excess energy. The energy barrier for both processes is relatively large, about 0.3 eV and 0.8 eV respectively, so the excited state dynamics is not ultrafast with lifetime in the nanosecond range. Nevertheless, because the most favored hydration site is the protonated ammonium group, both processes should be perturbed by hydration, which has however never

been reported so far. Drastic protonation and hydration effects on the excited state dynamics of biomolecules have only been reported in a very few cases, as for instance in the aromatic amino acid tryptophan. The ultraviolet (UV) spectrum of neutral tryptophan is well-structured, however, the spectrum becomes significantly broad by protonation due to a barrierless excited state proton transfer reaction.¹¹ Furthermore, the spectrum turns to a sharp, structured one when two water molecules are hydrogen-bonded to the protonated tryptophan.¹²

From this motivation, we apply cryogenic ion spectroscopy to DAH^+ and its hydrated clusters. The cold ion trap setup in Tokyo Tech^{13,14} allows us to hydrate DA in a stepwise manner, so the spectral changes due to hydration can be accurately measured for each cluster size. Conformer-selected IR spectroscopy is measured by IR-UV double resonance spectroscopy, which eases comparison with quantum chemical calculations to assign the structure. The excited state lifetime of DAH^+ has been recorded in Orsay by ps pump-probe photodissociation spectroscopy.¹⁵ Quantum chemical calculations were also performed to track the excited state dynamics changes with hydration at the molecular level. From these approaches, we have found that the excited state dynamics of DAH^+ is governed by a proton transfer process that is insensitive to hydration up to two water molecules, but drastically changed in a dominant conformer of the $\text{DAH}^+(\text{H}_2\text{O})_3$ cluster.

The experimental setups in Tokyo¹⁶ and Orsay¹⁷ have already been described in detail. They are based on an ESI source, cold ion trap and time-of-flight mass spectrometer. In Tokyo, a clustering trap maintained at a low temperature by a liquid nitrogen cryostat is added to produce hydrates as developed in the group of E. Garand.¹⁸ UV photodissociation spectroscopy and double resonance IR/UV spectroscopy of bare and hydrated DAH^+ have been performed in Tokyo while ps excited state dynamics of bare DAH^+ have been recorded in Orsay. DFT and CC2 calculations have been performed by the two groups. Detailed experimental and computational procedures can be found in the supplementary material.

Fig. 1 shows the UV photodissociation spectra of DAH^+ and its hydrated clusters $\text{DAH}^+(\text{H}_2\text{O})_n$ ($n = 0 - 3$). All the spectra are obtained by monitoring the intensity of the fragment ion m/z 137, which corresponds to $\text{NH}_3 + n\text{H}_2\text{O}$ loss from $\text{DAH}^+(\text{H}_2\text{O})_n$. NH_3 loss is the main fragment of the bare molecule through collision induced dissociation¹⁹ and IRMPD,⁶ thus this channel is assigned to the dissociation in the ground state after internal conversion (IC). Interestingly, the second most intense photofragment is detected at m/z 30 (CH_2NH_2^+), emphasizing the $\text{C}_\alpha\text{-C}_\beta$ bond cleavage

with one hydrogen transferred to the neutral catechol ring moiety (Fig. S1). Such photo-specific bond cleavage has also been observed in related systems, such as protonated aromatic amino acids²⁰ and catecholamines^{10,21} and assigned to an excited state proton transfer reaction from the ammonium to the aromatic ring.⁹

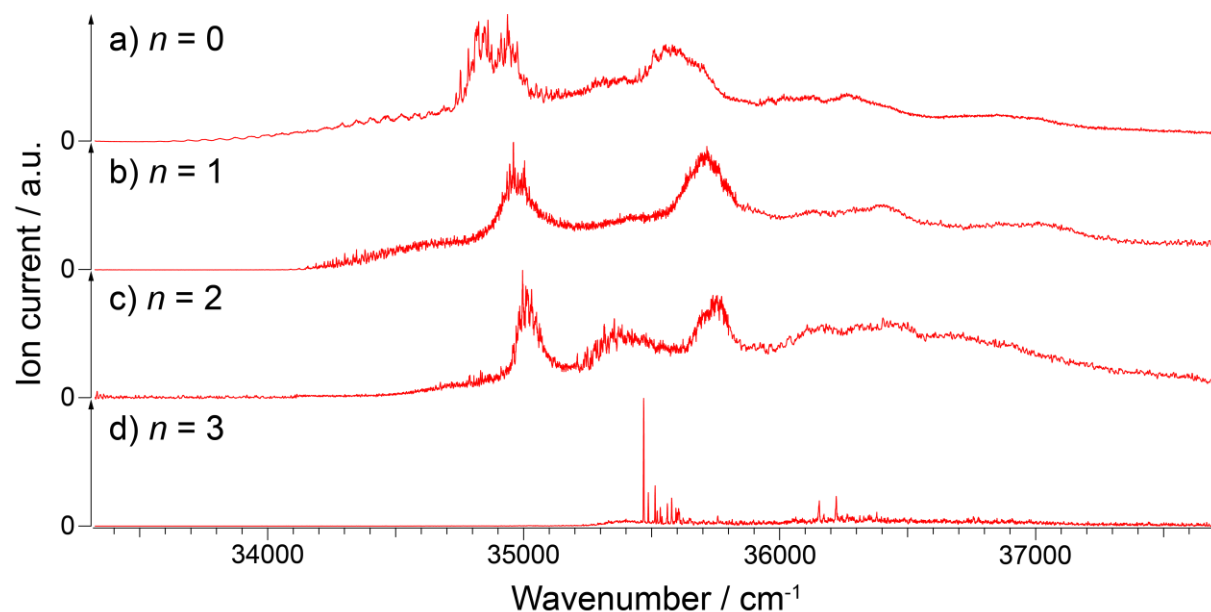


FIG. 1 UVPD spectra of $\text{DAH}^+(\text{H}_2\text{O})_n$ ($n = 0 - 3$).

The UVPD spectrum of the monomer (Fig. 1a) is broad and consists of two band systems: a low intensity progression starting from $\sim 33700 \text{ cm}^{-1}$ and an intense broad band at $\sim 34800 \text{ cm}^{-1}$ of 300 cm^{-1} width. DAH^+ has two low energy conformers G1 syn and G1 anti (Fig. S2), which differ by the orientation of the $\text{C}_6\text{H}_2\text{NH}_3^+$ group above the catechol ring. Their adiabatic excitation energies are quite similar (Table 1) and predicted within 800 cm^{-1} to the red of the onset of the experimental excitation spectrum, in line with the expected error of the SCS-CC2 method (see ESI). In addition, the simulated vibronic spectra of both conformers are broad with a long progression of low frequency modes (Fig. S2), revealing a significant geometry change in S_1 . Both calculated band origins and simulated Franck-Condon spectra are thus consistent with the observed unstructured vibronic spectra. The excited state lifetime of DAH^+ excited at the maximum of the intense broad band has been measured by pump-probe photodissociation spectroscopy (Fig. S3). The transient is characterized by a Gaussian function reflecting the cross correlation of the lasers,

evidencing that the lifetime is much shorter than 20 ps. It is noteworthy that the lifetime of DAH^+ is significantly shorter than those of neutral catecholamines that display well-structured vibronic spectra consistent with nanosecond excited state lifetimes.²²⁻²⁴ The short lifetime of the locally excited state of DAH^+ suggests that a fast relaxation channel accounts for the deactivation process.

TABLE 1 Adiabatic excitation energies corrected by the difference of the zero-point-energy between the S_0 and S_1 state of DAH^+ and $\text{DAH}^+(\text{H}_2\text{O})_3$

System	Structure	$E_{S_1}^{\text{adia}}$ (calc)		0_0^0 (exp)	
		cm^{-1}	eV	cm^{-1}	eV
DAH^+	G1- syn	32 973	4.08	33 715 ^{a)}	4.18 ^{a)}
	G1- anti	33 427	4.14		
$\text{DAH}^+(\text{H}_2\text{O})_3$	G1-1	34 747	4.31	35 485	4.40
	G1-2	34 446	4.27	35 240 ^{a)}	4.37 ^{a)}

a) Tentative origin. Onsets are difficult to identify because of poor Franck-Condon factors around the origin.

The hydrated clusters $\text{DAH}^+(\text{H}_2\text{O})_{1, 2}$ show similar spectral features, which consist of low intensity background and intense broadened bands. The onsets of the background and position of the broad bands are systematically blue-shifted by stepwise hydration. This suggests that the π -ring system of DAH^+ is perturbed by hydration with a destabilization of the π^* orbital. The spectral feature changes drastically when DAH^+ is hydrated by three water molecules. The background signal is weakened significantly and the broad bands become very sharp. Clearly it shows the drastic change in the dynamics in the excited state by addition of the third water molecule. For this cluster size, vibronic bands are now well resolved. The lowest frequency band, *i. e.* S_1 origin, is the most intense, which indicates that the structure of $\text{DAH}^+(\text{H}_2\text{O})_3$ is similar in both S_1 and S_0 . Thus, the structural assignment in S_0 gives a good clue to understand such a change in dynamics by hydration.

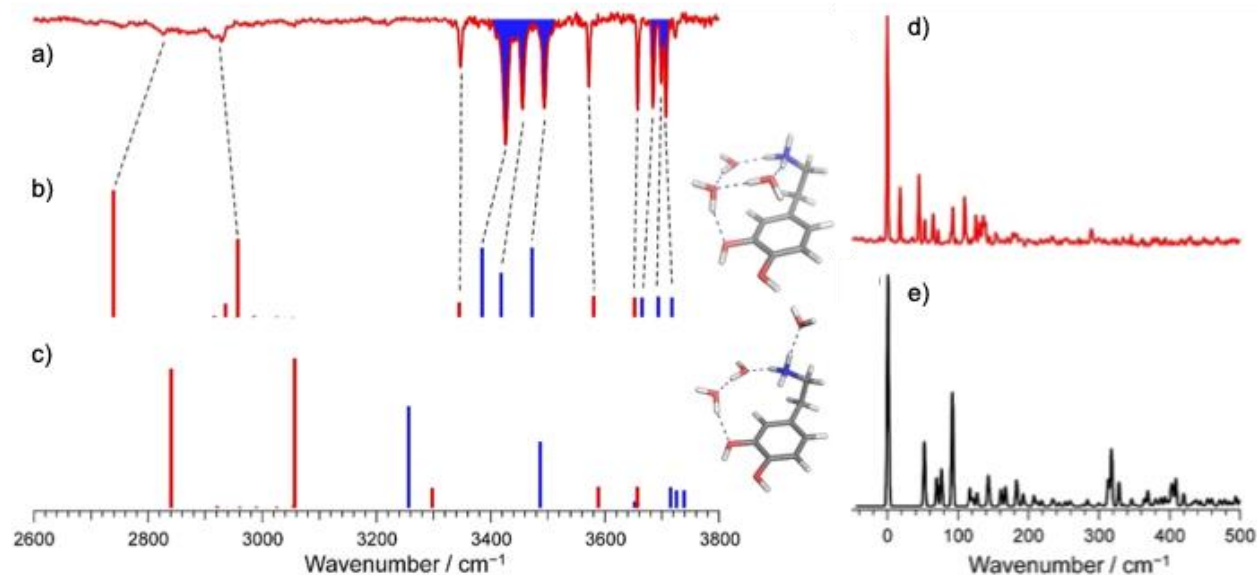


FIG. 2 Observed (a) and calculated (b and c) IR spectra of $\text{DAH}^+(\text{H}_2\text{O})_3$. Observed (d) and calculated (e) UV spectra around the S_1 origin.

To assign the structure of $\text{DAH}^+(\text{H}_2\text{O})_3$, its infrared (IR) spectrum is measured by IR dip spectroscopy (Fig. 2a). The IR dip spectroscopy is a double resonance spectroscopy, which detects the IR transition by depletion of the UVPD signal. The IR spectrum shown in Fig. 2a is measured by labeling the S_1 origin by the UV laser. Blue shaded bands are assigned to OH stretching of water molecules because these bands disappear in the IR dip spectrum of $\text{DAH}^+(\text{D}_2\text{O})_3$ (Fig. S4). To assign the structure of the cluster, quantum chemical calculations are performed and the 10 lowest energy conformers of $\text{DAH}^+(\text{H}_2\text{O})_3$ (Table S1) are shown in Fig. S5 along with the theoretical spectra in the $3\ \mu\text{m}$ range in Fig. S6. The structures and theoretical IR spectra of the two most stable conformer G1-1 and G1-2 are shown in Fig. 2b and 2c, respectively. The OH stretching of water molecules in the clusters are shown with blue bars, while other vibrations of DAH^+ are indicated with red bars. As can be seen in Fig. 2, the theoretical IR spectrum of the most stable conformer G1-1 provides a fair agreement with the observed IR dip spectrum. It should be noted that the set of the three water stretches observed between 3400 and $3500\ \text{cm}^{-1}$ is predicted only for the G1-1 conformer, none of the other nine conformers display such a pattern. The adiabatic excitation energy, corrected by the difference in zero-point-energy between the excited and ground state, is calculated at $34\ 747\ \text{cm}^{-1}$, only $750\ \text{cm}^{-1}$ to the red of the experimental 0_0^0 transition. In addition, the simulated Franck-Condon spectrum shown in Fig. 2e (see the supplementary material

for details) also reproduces the main spectral features of the UV spectrum (Fig. 2d). The S_1 origin is the strongest and low frequency bands appear within 400 cm^{-1} from the origin. The active low frequency modes in S_1 are identified as out-of-plane bending of OH catechol and vibrational motions of hydrated amine chain (Fig. S7). Thus G1-1 can be confidently assigned to the structure of the $\text{DAH}^+(\text{H}_2\text{O})_3$.

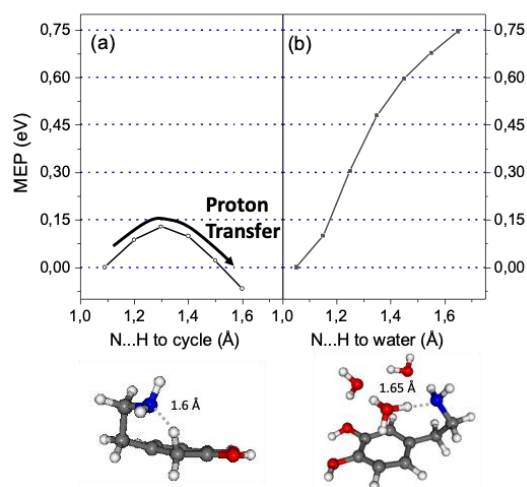


FIG. 3 Minimum Energy Path (MEP) along the N-H coordinate for (a) DAH (b) $\text{DAH}^+(\text{H}_2\text{O})_3$. Energy above the adiabatic $\pi\pi^*$ excitation transition in eV.

It is clear that the binding of three water molecules to DAH^+ changes the excited state dynamics significantly. Based on the assigned structures of DAH^+ and its tri-hydrated cluster, the possible relaxation pathways are investigated by excited state calculations. In the bare molecule, the lowest excited state S_1 corresponds to a $\pi-\pi^*$ transition, the S_2 $\pi\sigma^*$ state lying more than 1 eV above at the optimized geometry of the $\pi\pi^*$ state. In the S_1 $\pi\pi^*$ state, the N-H bond pointing toward the catechol ring elongates by 0.031 \AA as compared to the ground state structure. The inter atomic distance between H and C is reduced to 1.96 \AA . The Minimum Energy Path (MEP) along the N-H coordinate exhibits a small barrier of less than 0.15 eV, leading ultimately to a proton transfer reaction as shown in Fig. 3a. Full optimization of this structure leads to internal conversion (IC) with the ground state providing an efficient nonradiative deactivation mechanism (Fig. S8). Such a process has already been proposed in related systems, such as protonated aromatic amine,²⁵ amino acids²⁰ and catecholamine.¹⁰ At the conical intersection with the ground state, there is a

competition between IC and direct dissociation from the excited state proton transfer structure. The molecule can return to the ground state with a back proton transfer reaction and dissociates by ammonia loss through a statistical type of fragmentation. The second path implies dissociation along the C α -C β bond, which is destabilized in the proton transferred structure.⁹ The low energy barrier for the proton transfer reaction is thought to be responsible for the short excited state lifetime (less than 20 ps, the cross correlation of the ps lasers) measured at 286 nm, *i. e.* with about 0.15 eV of excess energy in S₁.

For the 1-3 complex, the adiabatic excitation energy is calculated within less than 800 cm⁻¹ compared to the experimental band origin. In addition, the simulated Franck-Condon spectrum compares quite well with the experimental vibronic spectrum, with a strong band origin and few vibronic transitions up to 400 cm⁻¹ of excess energy. Interestingly, the ammonium group is now involved in two H-bond with two water molecules, preventing direct interaction of the NH₃⁺ moiety with the catechol ring. The N-H bond interacting with the water molecule is slightly elongated by 0.015 Å as compared to the ground state structure. MEP for the proton transfer from the ammonium to the water sitting above the catechol ring has been evaluated. As reported in Fig. 3b, the excited state energy continuously increases up to 0.75 eV above the adiabatic $\pi\pi^*$ energy as the N-H bond stretches until 1.65 Å. Full optimization starting from this structure without geometrical constraints leads to the initial $\pi\pi^*$ optimized structure. The proton transfer reaction is impeded in the hydrated complex by the inclusion of three water molecules. Therefore, it can be concluded that the water molecules block the non-radiative mechanism invoked for the bare DAH⁺.

In conclusion, we have evidenced the drastic hydration effect on the photophysics of DAH⁺ embedded in small water clusters. Hydration by three water molecules blocks the excited state proton transfer occurring in DAH⁺ and the 1-1 and 1-2 complexes. The complete survey including the structural assignment of the 1-1 and 1-2 and the small background signal of the 1-3 complexes will be published in a forthcoming paper. The combination of cryogenic ion spectroscopy with mass-selected hydrated species allows us to precisely investigate the subtle hydration effects on the photophysical processes of such neurotransmitters. Studying mass-selected hydrated biomolecules paves the way to disentangle the complex photochemistry occurring in solution, while it provides stringent tests for developing theoretical methods applied to the molecular excited state.

SUPPLEMENTARY MATERIAL

See the supplementary material for the experimental and computational methods, the UV-PID mass spectrum, ps pump-probe photodissociation spectrum, Franck-Condon simulated spectra of DAH^+ , the structures, Gibbs energies and calculated IR spectra of the ten lowest energy conformers of $\text{DAH}^+(\text{H}_2\text{O})_3$ and the IR spectrum of $\text{DAH}^+(\text{D}_2\text{O})_3$.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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