

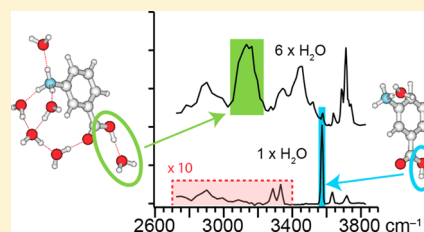
Hydration of Gaseous *m*-Aminobenzoic Acid: Ionic vs Neutral Hydrogen Bonding and Water Bridges

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S Supporting Information

ABSTRACT: Hydration of a protonated amine and a neutral carboxylic acid were investigated for protonated *m*-aminobenzoic acid (MABAH⁺) with up to 15 water molecules attached using infrared photodissociation spectroscopy, laser-induced dissociation kinetics, and computational chemistry. A free COO–H stretch in the spectra of MABAH⁺·(H₂O)_{1–5} indicates that water does not bind to the carboxylic acid H atom. This band is absent in the spectrum of MABAH⁺ with six or more water molecules attached, and there is a hydrogen-bonded (HB) COO–H stretch indicating that water hydrogen bonds to the carboxylic acid H atom for these larger clusters. Photodissociation kinetic data for MABAH⁺·(H₂O)₆ indicate that greater than 74 ± 13% of the ion population consists of the HB COO–H isomer, consistent with this isomer being ≥0.5 kJ mol^{–1} lower in energy than isomers where the carboxylic acid H atom does not donate a hydrogen bond. Calculations at the B3LYP/6-31+G** and MP2/6-31+G**//B3LYP/6-31+G** levels of theory indicate that this energy difference is 3–5 kJ mol^{–1}, in agreement with the experimental results. Lower effective ion heating rates, either by attenuation of the laser power or irradiation of the ions at a lower frequency, result in more time for interconversion between the free and HB COO–H isomers. These data suggest that the barrier to dissociation for the free COO–H isomer is less than that for the HB COO–H isomer but greater than the barrier for interconversion between the two isomers. These results show the competition between hydration of a primary protonated amine vs that of a neutral carboxylic acid and the effect of water bridging between the two functional groups, which provide valuable insight into the hydration of protonated amino acids and establish rigorous benchmarks for theoretical modeling of water–biomolecule interactions.



INTRODUCTION

Water plays an important role in many different physical properties of molecules in aqueous solution. In water, the basicities of methylamines follow the order NH₃ < Me₃N < MeNH₂ ≈ Me₂NH,^{1–3} whereas the gas-phase basicities of these molecules follow the order NH₃ < MeNH₂ < Me₂NH < Me₃N.^{4,5} The difference in the ordering between the gas- and solution-phase basicities of these molecules is due to the ability of water to effectively stabilize charge, which is hindered by the presence of multiple methyl groups. Such solvent–ion interactions can change the intrinsic structures and reactivities of ions.

Water can also influence the protonation^{6–9} or deprotonation^{10–12} sites of molecules. Protonation of isolated *p*-aminobenzoic acid occurs at the carbonyl O atom^{6,7} as a result of resonant stabilization of the positive charge,⁹ but protonation of the amine N atom occurs in water.⁸ This solution-phase structure is observed for gaseous ions with six or more water molecules attached.⁹ Water also affects the stabilities of the zwitterionic forms of amino acids. In the gas phase, amino acids are nonzwitterionic,^{13,14} whereas these molecules are zwitterionic in water over a wide range of pH. Results from spectroscopic studies of hydrated gaseous Trp indicate that it is nonzwitterionic with up to four water molecules attached, but there is a population of the zwitterionic form with five or six water molecules attached.¹⁵ The nonzwitterionic form of Gly is

calculated to be lowest in energy for Gly·(H₂O)_{1–6}, but the zwitterionic form is the lowest-energy structure for Gly·(H₂O)_{7,8}.¹⁶ Similarly, water can stabilize the zwitterionic forms of amino acid cation complexes. Results from IR photodissociation spectroscopy of Arg·Li⁺ indicate that Arg is nonzwitterionic,^{17,18} whereas the zwitterionic form of Arg, in which the side chain is protonated and the carboxylic acid is deprotonated, is more stable with the attachment of a single water molecule to this complex.¹⁹ These results demonstrate that interactions between an ion and even one water molecule can significantly affect the ion structure.

An advantage of studying the hydration of ions in the gas phase is that effects of each water molecule on the structure of hydrated ions can be probed. The sequential binding energies of individual water molecules to protonated^{20–23} and cationized^{24–31} amino acids have been measured using a variety of thermochemical methods. Structural information can be inferred from these data, but more detailed information is typically obtained by computations. Results from hydration equilibrium experiments for PheH⁺·(H₂O)_{*n*} (*n* = 1 – 5) show that the sequential water binding enthalpies decrease from 56 to 30 kJ mol^{–1} with increasing hydration, and calculations indicate that a single water molecule binds more strongly to the

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protonated amine by only 4 kJ mol⁻¹ in comparison to the binding at the neutral carboxylic acid H atom.²² Interactions between the phenyl ring and the carbonyl O atom with two of the H atoms of the protonated amine reduce the water binding affinities to these amine H atoms.

Detailed information about ion–water interactions can be directly obtained from ion spectroscopy,^{9,19,32–46} which can be used in combination with laser dissociation kinetics experiments to measure relative populations of noninterconverting isomers, from which accurate relative energies can be obtained.^{44,45} Spectroscopic and kinetic data for PheH⁺·(H₂O)₁ indicate that the attachment of a single water molecule to the neutral carboxylic acid H is only 1 kJ mol⁻¹ higher in Gibbs free energy than that to the fully exposed H atom of the protonated amine.⁴⁴ For ProH⁺·(H₂O)₁, hydration of the C-terminal H atom is enthalpically favored due to the ability for the water molecule to form a second, weak hydrogen bond (HB) to the carbonyl O atom of the carboxylic acid and is the preferred binding site at low temperature.⁴⁵

Here, the competitive solvation of a protonated amine and a neutral carboxylic acid is investigated for hydrated, protonated *m*-aminobenzoic acid (MABAH⁺) using infrared photodissociation (IRPD) spectroscopy, laser-induced dissociation kinetics, and computational chemistry. Unlike the case for *p*-aminobenzoic acid, protonation of the carbonyl O atom at the carboxylic acid is not resonantly stabilized, and the amine is calculated to be the favored gas-phase protonation site.⁴⁷ An intramolecular HB cannot be formed between these two functional groups, making MABAH⁺ an excellent model for investigating the intrinsic competition between the hydration of a protonated amine and neutral carboxylic acid. These results provide insight into how water interacts with both charged and neutral functional groups.

EXPERIMENTAL SECTION

IRPD Spectroscopy. The IRPD spectra of hydrated, protonated MABA and *m*-aminobenzoic acid methyl ester (MABAOMe) were measured using a 7.0 T Fourier-transform ion cyclotron resonance (FT/ICR) mass spectrometer. The compounds (Sigma-Aldrich, St. Louis, MO, USA) were dissolved in water purified by a Milli-Q purification system (Millipore, Billerica, MA, USA) to a concentration of ~4 mM. Sample solutions were transferred into borosilicate capillaries that were pulled to an inner tip diameter of ~2 μm. Electrospray was induced by applying a ~700 V difference between a platinum filament that is in contact with the solution and the heated metal capillary entrance of the mass spectrometer. Electrostatic lenses guide the hydrated ions through five stages of differential pumping into the ion cell. A copper jacket surrounding the cell is maintained at a temperature of ~133 K by a regulated flow of liquid nitrogen. Dry nitrogen gas is pulsed into the vacuum chamber to enhance thermalization and trapping of the ions. Between 6 and 11 s after ions are trapped, the cell pressure is <10⁻⁸ Torr. Ions of interest are isolated by a stored waveform inverse Fourier transform. Photodissociation was induced by irradiating the precursor ions using an OPO/OPA (LaserVision, Bellevue, WA, USA) pumped by the fundamental of a Nd:YAG laser (Continuum Surelight I-10, Santa Clara, CA, USA) at a repetition rate of 10 Hz. Irradiation times of 5–60 s were used for spectroscopy and up to 120 s to measure more accurate laser-induced dissociation kinetic data at a fixed laser frequency. Dissociation of all hydrated ions occurs by sequential loss of water molecules. First-order dissociation rate constants, obtained from the precursor and product ion abundances after irradiation and corrected for laser power and absorption of ~133 K blackbody photons, are plotted as a function of laser frequency to generate IRPD spectra.⁴⁸ The kinetic data were fit with Igor Pro v6 (WaveMetrics, Inc., Lake Oswego, OR, USA). For fitting biexponential data, the

uncertainties in the relative isomer abundances correspond to ±1 standard deviation of the associated pre-exponential values.

Computational Chemistry. Macromodel 9.1 (Schrodinger, Inc., Portland, OR) was used for Monte Carlo conformational searches for MABAH⁺ with up to six water molecules attached to generate at least 2000 initial geometries for each hydration state. A selection of the low-energy conformers as well as structures obtained from chemical intuition that represent different hydrogen-bonding patterns were used as starting geometries for density functional calculations. Q-Chem 4.0⁴⁹ (Q-Chem, Inc., Pittsburgh, PA) was used to perform a geometry optimization as well as vibrational frequency and intensity calculations at the B3LYP/6-31+G** level of theory. Calculated vibrational frequencies were scaled by 0.955 and convolved with 30 and 15 cm⁻¹ fwhm Gaussians for the 2600–3550 and 3550–3900 cm⁻¹ regions, respectively. MP2/6-31+G** single-point energies were computed using B3LYP/6-31+G** optimized geometries. All zero-point energy, enthalpy, and entropy corrections at 133 K were calculated for these structures using unscaled B3LYP/6-31+G** harmonic oscillator vibrational frequencies.

RESULTS AND DISCUSSION

Protonation Site for MABAH⁺. Hydration of MABAH⁺ with up to 15 water molecules attached was investigated by IRPD spectroscopy in the region from 2700 to 3900 cm⁻¹ and by computational chemistry. Protonation of the N atom of the amine for isolated MABAH⁺ is favored over protonation at the carbonyl O atom of the carboxylic acid by 8 and 36 kJ mol⁻¹ at the B3LYP/6-31+G** and MP2/6-31+G**//B3LYP/6-31+G** levels of theory, respectively. Although these relative energies differ significantly, results from both levels of theory indicate that the preferred gas-phase protonation site is the amine, consistent with earlier PM3 calculations.⁴⁷

The IRPD spectrum of MABAH⁺·(H₂O)₁ (Figure 1a) has bands at 3287 and 3332 cm⁻¹ corresponding to the free N–H symmetric and asymmetric stretches (s.s. and a.s., respectively) of a protonated amine that donates a HB to a single water molecule. The HB N–H stretch of the protonated amine appears at 2901 cm⁻¹. There are also free O–H bands from the s.s. and a.s. of water molecules that accept a single HB (single acceptor, SA) at 3634 and 3718 cm⁻¹, respectively. These frequencies are within 50 cm⁻¹ for the HB N–H stretch and within 10 cm⁻¹ for the free N–H and O–H stretches of the corresponding peaks in the IRPD spectrum of protonated aniline (C₆H₅NH₃⁺) with one water molecule attached.⁹ These results indicate that the amine group is protonated and that the water molecule attaches at this site.

There is an intense and relatively sharp band in the IRPD spectrum of MABAH⁺·(H₂O)₁ at 3573 cm⁻¹. This feature corresponds to the carboxylic acid free COO–H stretch, which occurs near 3560 cm⁻¹ in the spectra of hydrated, protonated amino acids.^{19,44–46} The IRPD spectrum of *p*-aminobenzoic acid, for which hydration and protonation occur at the carboxylic acid group, has free N–H s.s. and a.s. at 3443 and 3553 cm⁻¹,^{6,9} respectively. There is no significant dissociation in the spectrum of MABAH⁺·(H₂O)₁ from 3360 to 3550 cm⁻¹, the region where the free N–H s.s. for a neutral amine should appear. Thus, there is no significant population of ions that are protonated and hydrated at the carboxyl group. These data support our conclusion that both the proton and the water molecule are located at the amine group.

The lowest-energy structures for N-protonated MABAH⁺·(H₂O)₁ with water attached to either the protonation site or the carboxylic acid are shown in Figure 1b. Calculations indicate that the structure where the water molecule forms an ionic HB to the protonated amine (MABAH1a) is 25–27 kJ

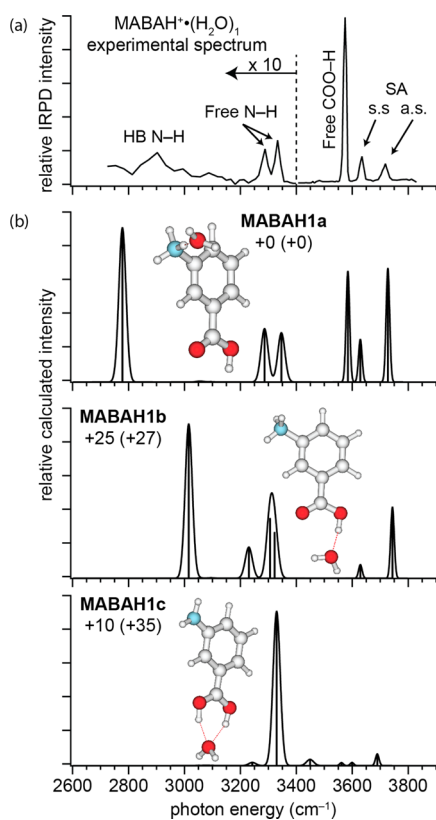


Figure 1. (a) IRPD spectrum of $\text{MABAH}^+\cdot(\text{H}_2\text{O})_1$ measured at 133 K and (b) calculated spectra of three isomers. Relative Gibbs free energies (at 133 K in kJ mol^{-1}) calculated at the B3LYP/6-31+G** (MP2/6-31+G**//B3LYP/6-31+G**) level of theory are also given.

mol^{-1} lower in energy than that in which the water molecule accepts a neutral HB from the carboxylic acid hydroxyl group (**MABAH1b**). As was the case for isolated MABAH^+ , the structure where protonation and hydration occur at the carboxylic acid group (**MABAH1c**, Figure 1) is calculated to be 10 and 35 kJ mol^{-1} higher in energy in comparison to **MABAH1a** at the B3LYP/6-31+G** and MP2/6-31+G**//B3LYP/6-31+G** levels of theory, respectively. These results indicate that attachment of a water molecule does not change the relative affinities of these protonation sites at either level of theory.

The calculated frequencies for the free N–H and COO–H stretches for **MABAH1a** are within 15 cm^{-1} of the corresponding bands in the measured spectrum. The computed frequencies for the SA water s.s. and a.s. are within 10 cm^{-1} of the bands in the measured spectrum at 3634 and 3718 cm^{-1} , respectively. The frequency of the HB N–H stretch for **MABAH1a** is 125 cm^{-1} lower than the measured band at 2901 cm^{-1} . The greater difference in the calculated and measured frequencies for this feature can be attributed to the anharmonic potential of vibrational modes that participate in HBs, which is not accounted for by the harmonic frequency calculations.

The calculated spectrum for **MABAH1a** is a good frequency match to the measured spectrum, whereas the calculated spectra for **MABAH1b** and **MABAH1c** are not. There is no free COO–H band for either **MABAH1b** or **MABAH1c**, which eliminates the possibility of significant contributions from either structure. *p*-Aminobenzoic acid with one water molecule attached has a hydrogen-bonding motif similar to that of **MABAH1c**, but the HB O–H stretches are noticeably absent

from this region of the spectrum.⁹ In summary, the results indicate that the water molecule forms an ionic HB to the protonated amine group (**MABAH1a**).

Water–Ammonium vs Water–Water Hydrogen Bonding. MABAH^+ has four H atoms that can donate HBs to water molecules: the three H atoms of the ammonium group and the hydroxyl H atom of the carboxylic acid. The IRPD spectrum for $\text{MABAH}^+\cdot(\text{H}_2\text{O})_2$ (Figure 2a) has an intense carboxylic acid

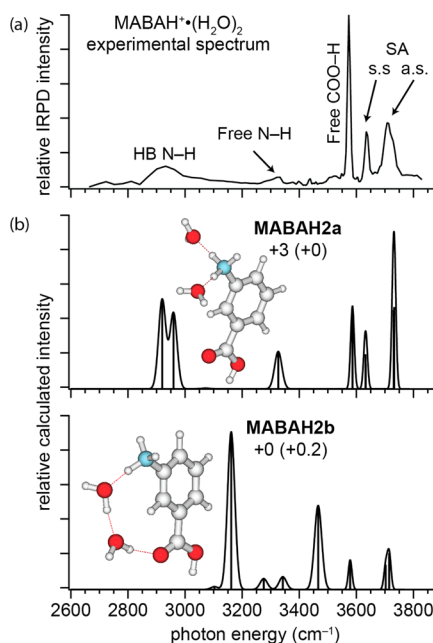


Figure 2. (a) IRPD spectrum of $\text{MABAH}^+\cdot(\text{H}_2\text{O})_2$ measured at 133 K and (b) calculated spectra of two isomers. Relative Gibbs free energies (at 133 K in kJ mol^{-1}) calculated at the B3LYP/6-31+G** (MP2/6-31+G**//B3LYP/6-31+G**) level of theory are also given.

free COO–H stretch, indicating that water does not bind to this hydration site. There is only one distinguishable free N–H stretch at $\sim 3325 \text{ cm}^{-1}$, indicating that two H atoms of the ammonium group each donate a HB. The SA water s.s. and a.s. that appear in the measured spectrum of $\text{MABAH}^+\cdot(\text{H}_2\text{O})_1$ are also present for $\text{MABAH}^+\cdot(\text{H}_2\text{O})_2$. These results are consistent with each of the two water molecules accepting a HB from the protonated amine group for $\text{MABAH}^+\cdot(\text{H}_2\text{O})_2$.

Two low-energy structures computed for $\text{MABAH}^+\cdot(\text{H}_2\text{O})_2$ are shown in Figure 2b. In **MABAH2a**, both water molecules bind to the protonated amine, whereas in **MABAH2b**, the water molecules form a bridge between the amine and the carbonyl O atom of the carboxylic acid. The Gibbs free energies of these two structures calculated at both levels of theory differ by $\leq 3 \text{ kJ mol}^{-1}$ and indicate that these structures are energetically competitive. The calculated spectrum for **MABAH2a** matches the IRPD spectrum well, with the vibrational frequencies near the measured frequencies (to within 10 cm^{-1} for the free N–H and O–H stretches and to within 30 cm^{-1} for the HB N–H stretch). The close frequency match results indicate that the ion population for MABAH^+ with two water molecules attached predominantly consists of **MABAH2a**, but the bands computed for this structure do not fully account for the IRPD spectrum.

The free N–H and O–H features at ~ 3330 and $\sim 3720 \text{ cm}^{-1}$, respectively, have shoulders, indicating the presence of more than one band. The calculated spectrum for **MABAH2b**

has two free N–H stretches at 3276 and 3342 cm^{-1} and a free O–H stretch of water molecules that accept and donate a HB (acceptor–donor, AD water molecules) near 3710 cm^{-1} . It is possible that the shoulders in the measured spectrum are a result of a minor population of isomers similar to **MABA2b**. There is also some dissociation measured from 3000 to 3200 cm^{-1} and a minor band near 3440 cm^{-1} that can be explained by the HB O–H stretches computed for this structure near 3160 and 3470 cm^{-1} . These results suggest that there may be a small population of structures similar to **MABA2b** for $\text{MABA}^+(\text{H}_2\text{O})_2$. There is a small, broad peak at ~ 3530 cm^{-1} , and the width of this feature suggests that is due to HB O–H stretches. The appearance of this band indicates that a small population of an unidentified isomer may also be present, or it may be an overtone or combination band. This feature also overlaps with a peak in the measured spectrum of $\text{MABA}^+(\text{H}_2\text{O})_3$ (Figure 3a) at ~ 3520 cm^{-1} , but the former is wider than the latter. It is unclear whether these two bands originate from similar vibrational modes.

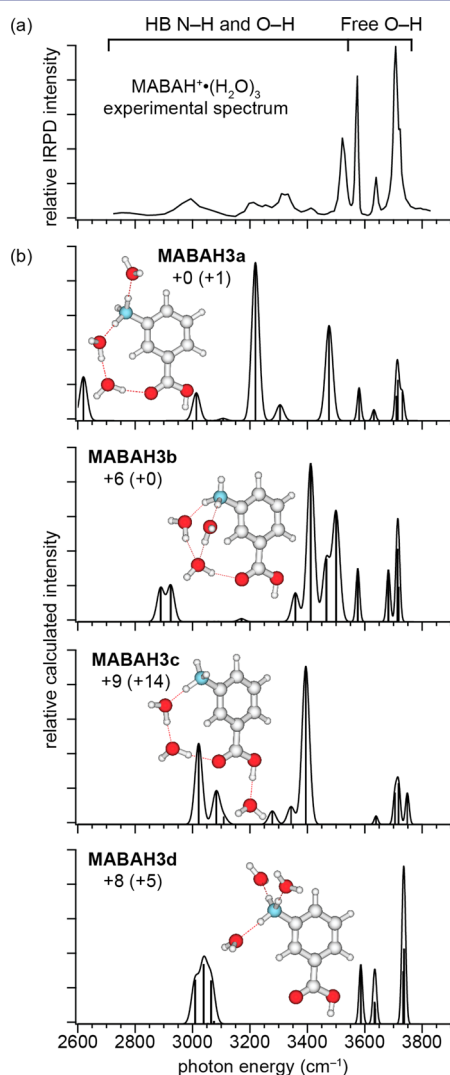


Figure 3. (a) IRPD spectrum of $\text{MABA}^+(\text{H}_2\text{O})_3$ measured at 133 K and (b) calculated spectra of four isomers. Relative Gibbs free energies (at 133 K in kJ mol^{-1}) calculated at the B3LYP/6-31+G** (MP2/6-31+G**//B3LYP/6-31+G**) level of theory are also given.

The IRPD spectrum of $\text{MABA}^+(\text{H}_2\text{O})_3$ (Figure 3a) has a relatively sharp and intense band at 3708 cm^{-1} that corresponds to the free O–H stretch of an AD water molecule. There are also features in the region from 3150 to 3550 cm^{-1} that correspond to HB O–H stretches, although there may be contributions from free N–H stretches in this region as well. The AD free O–H and HB O–H bands occur from 3700 to 3730 cm^{-1} and from 3250 to 3450 cm^{-1} , respectively, for hydrated $\text{C}_6\text{H}_5\text{NH}_3^+$ and NH_4^+ ,^{9,50} consistent with the assignment of these features in the spectrum of $\text{MABA}^+(\text{H}_2\text{O})_3$. These bands indicate the presence of water–water HBs. The ion population for $\text{MABA}^+(\text{H}_2\text{O})_{1,2}$ predominantly consists of structures where the water molecules coordinate directly to the protonated amine. For $\text{MABA}^+(\text{H}_2\text{O})_3$, the formation of water–water HBs is more favorable than the formation of an additional HB to the H atom of either the ammonium or the carboxylic acid group. In contrast, the major isomer for $\text{C}_6\text{H}_5\text{NH}_3^+(\text{H}_2\text{O})_3$ has all three water molecules hydrogen bonded to the ammonium group, although there is a minor population of isomers where one water molecule forms a second solvation shell, and the ammonium group for protonated *p*-aminobenzoic acid methyl ester with three water molecules attached is also fully hydrogen-bonded.⁹ The stability of structures with water–water HBs for $\text{MABA}^+(\text{H}_2\text{O})_3$ is enhanced owing to the ability to form a hydrogen-bonding bridge to the carboxylic acid group.

The IRPD spectrum for $\text{MABA}^+(\text{H}_2\text{O})_4$ (Figure 4a, bottom) is similar to that for MABA^+ with three water molecules attached (Figure 5). Both spectra have the same features in the HB and free O–H regions (3200–3900 cm^{-1}). The similarities between the two spectra indicate that $\text{MABA}^+(\text{H}_2\text{O})_4$ also adopts structures where there are water–water HBs. The carboxylic acid free COO–H stretch remains a major feature, indicating that water does not coordinate to the carboxylic acid H atom.

The HB N–H stretch for $\text{MABA}^+(\text{H}_2\text{O})_3$ is relatively weak and appears at ~ 3000 cm^{-1} , whereas this feature is much more intense and is centered at ~ 3050 cm^{-1} for $\text{MABA}^+(\text{H}_2\text{O})_4$. The greater relative intensity and the frequency of the HB N–H stretch for $\text{MABA}^+(\text{H}_2\text{O})_4$ is indicative of the HB N–H stretches of a fully hydrogen bonded ammonium group. The IRPD spectrum of $\text{C}_6\text{H}_5\text{NH}_3^+$ with three water molecules attached, for which the ammonium group is fully hydrogen bonded, has HB N–H stretches from 2950 to 3150 cm^{-1} (Figure 4a, top),⁹ consistent with the results for $\text{MABA}^+(\text{H}_2\text{O})_4$. These data indicate that the fourth water molecule hydrates the third and remaining H atom of the ammonium group.

The lowest-energy structures identified for $\text{MABA}^+(\text{H}_2\text{O})_{3,4}$ (Figures 3b and 4b, respectively) all have water bridges. For $\text{MABA}^+(\text{H}_2\text{O})_3$, the two lowest-energy structures, **MABA3a** and **MABA3b**, have two water molecules coordinated to the protonated amine, and the third water molecule forms the water bridge. **MABA3a** has a SA water molecule, whereas all three water molecules participate in the water bridge in **MABA3b**. For **MABA3c**, there is a water molecule that forms a HB to the carboxylic acid H atom. In contrast to **MABA3a–c**, all three water molecules attach to an H atom at the protonated amine in **MABA3d** (+5–8 kJ mol^{-1}), and there are no water–water HBs. For $\text{MABA}^+(\text{H}_2\text{O})_4$, the structures with either two or three water molecules interacting directly with the protonated amine are similar in

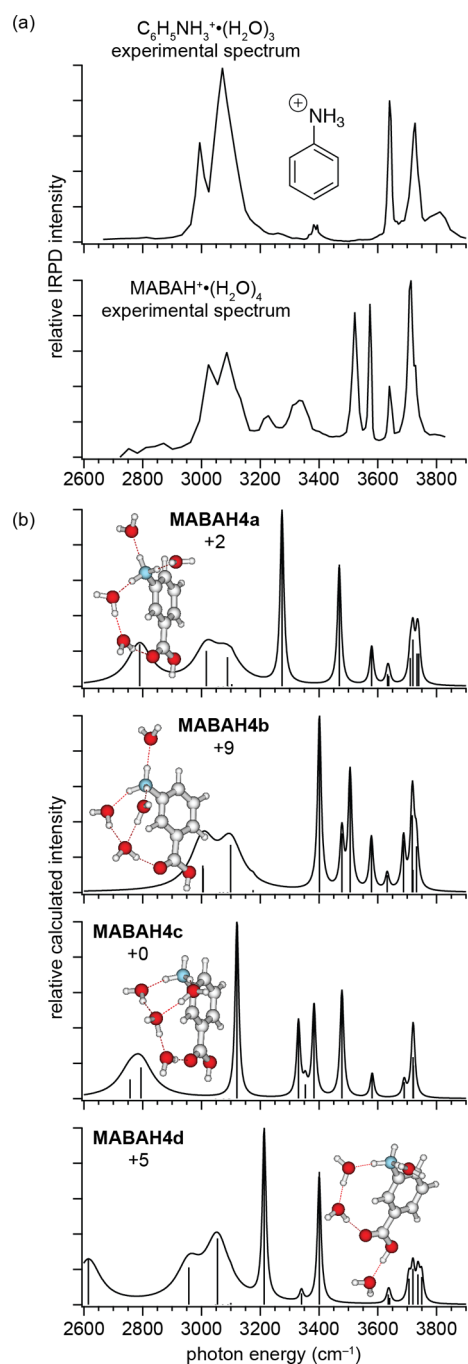


Figure 4. (a) IRPD spectra of $C_6H_5NH_3^+(H_2O)_3$ reproduced from ref 9 and $MABAH^+(H_2O)_4$ (top and bottom, respectively) measured at 133 K. (b) Calculated spectra of four isomers. Relative Gibbs free energies (at 133 K in kJ mol^{-1}) calculated at the B3LYP/6-31+G** (MP2/6-31+G**//B3LYP/6-31+G**) level of theory are also given.

energy, indicating that formation of an additional neutral HB is similar in energy to the formation of a single ionic HB.

The calculated spectrum for **MABAH3a** (Figure 3b) is a good frequency match to the measured spectrum. Calculated intensities can differ significantly from measured IRPD intensities for reasons described elsewhere.¹⁷ The bands below 3500 cm^{-1} are broad, indicative of HB features, which may exacerbate the difference between measured and calculated intensities. The spectral frequencies for **MABAH3b–d** poorly match the IRPD bands. **MABAH3b** does not have any SA

water s.s. or a.s. features, which are in the measured spectrum at ~ 3640 and $\sim 3725\text{ cm}^{-1}$. In addition, the HB O–H stretches occur between 3400 and 3500 cm^{-1} for **MABAH3b**, whereas they appear in a broader range, from 3200 to 3550 cm^{-1} , in the measured spectrum. The spectrum for **MABAH3c** has a HB COO–H stretch at $\sim 3020\text{ cm}^{-1}$, which overlaps with the measured HB N–H stretch at $\sim 3000\text{ cm}^{-1}$, but the HB COO–H stretch is typically an intense feature in IRPD spectra.^{44–46} Water–water HBs are absent from **MABAH3d**. Despite the differences between the measured spectrum and those calculated for **MABAH3b–d**, minor contributions from these three structures cannot be ruled out. Similarly, the calculated spectrum for **MABAH4a** is most consistent with the measured spectrum for $MABAH^+(H_2O)_4$, but contributions from minor populations of **MABAH4b–d** may be possible. The comparisons between the measured and simulated spectra indicate that the ion populations for $MABAH^+$ with three and four water molecules attached consist of isomers that have a water bridge between the ammonium and carboxylic acid functional groups.

Hydration of the Carboxylic Acid H Atom. The carboxylic acid free COO–H stretch, which appears in the IRPD spectra for $MABAH^+(H_2O)_{1–4}$, is also a major feature in the measured spectrum for $MABAH^+(H_2O)_5$ (Figure 5). These data indicate that a substantial population of ions, where water does not form a HB to the carboxylic acid H atom, remains for $n = 5$. In contrast, the carboxylic acid free COO–H stretch is a relatively weak band in the spectrum of $MABAH^+(H_2O)_6$, and there are two broad bands below 3200 cm^{-1} . The band at $\sim 3150\text{ cm}^{-1}$ is blue-shifted from the HB N–H stretches for $MABAH^+(H_2O)_{4,5}$ (~ 3050 and $\sim 3120\text{ cm}^{-1}$, respectively), but it is also significantly more intense. The higher intensity is attributed to the presence of a HB COO–H stretch, which occurs between 2800 and 3200 cm^{-1} for hydrated, protonated phenylalanine.⁴⁴ These results indicate that there is a significant population of ions for $MABAH^+(H_2O)_6$ where each of the H atoms of both the ammonium and the carboxylic acid group donate a HB to a water molecule: i.e., the ion is fully hydrogen bonded.

The band at $\sim 2900\text{ cm}^{-1}$ in the IRPD spectrum of $MABAH^+(H_2O)_6$ is too low in energy for a HB O–H stretch. Thus, this feature is attributed to HB N–H stretches. It is likely that this band is due to the stretching motion of N–H bonds that donate HBs to AD water molecules involved in the water bridge. The frequency of this vibrational mode is calculated to be between 2350 and 3100 cm^{-1} in the low-energy structures for $MABAH^+(H_2O)_{2–4}$ where the water bridge is present, and this absorption may be below the range of the measured spectra for $MABAH^+(H_2O)_{2–5}$ or may be too weak to induce measurable dissociation in these experiments.

The HB COO–H stretch is also present in the IRPD spectra for $MABAH^+(H_2O)_{8–15}$, and the free COO–H stretch is nearly or entirely eliminated. These results indicate that the vast majority of the ion populations for these hydration states consists of isomers where the $MABAH^+$ ion is fully hydrogen bonded. There is a HB COO–H stretch in the measured spectrum for $MABAH^+$ with 10 water molecules attached, but there are also two sharp bands near 3575 cm^{-1} that are within 5 cm^{-1} of the free COO–H stretch that appears for $MABAH^+(H_2O)_{1–6}$. These bands are also present in the spectrum of the methyl ester form of this ion ($MABAOMeH^+$) with 10 water molecules attached (Figure S1, Supporting Information). The appearance of these bands for both $MABAH^+(H_2O)_{10}$ and $MABAOMeH^+(H_2O)_{10}$ indicates that these features do not

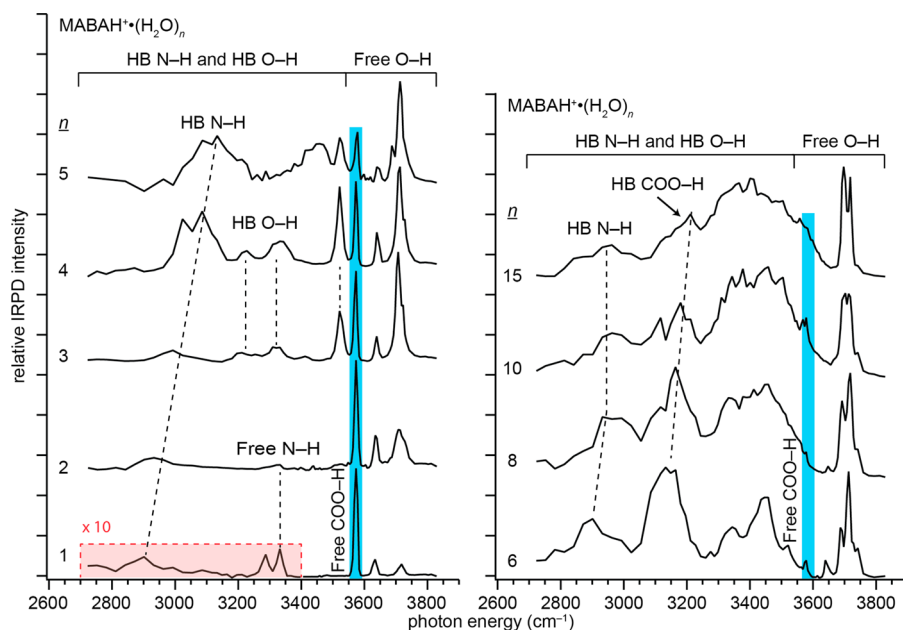


Figure 5. IRPD spectra of $\text{MABAH}^+(\text{H}_2\text{O})_n$ with up to 15 water molecules attached measured at 133 K. Regions corresponding to free O–H, HB N–H, and HB O–H stretches are labeled. The free N–H and free COO–H stretches are also indicated.

correspond to a free COO–H stretch. They may be due to overtones or HB O–H stretches, although these features are much narrower than typical HB O–H bands.

Confirmation of Band Assignments. To confirm the band assignments for hydrated MABAH^+ , the IRPD spectra for hydrated MABAOMeH^+ with up to 10 water molecules attached were measured. The basicity of the carbonyl O atom is higher for MABAOME than for MABA due to the methyl group's greater polarizability in comparison to the carboxylic H atom.^{4,5} The differences in Gibbs free energies between protonation of the N and O atoms for MABAOME are +5 and -21 kJ mol^{-1} at the B3LYP/6-31+G** and MP2/6-31+G**//B3LYP/6-31+G** levels of theory, respectively. With one water molecule attached, the N-protonated form is more stable by 6 and 28 kJ mol^{-1} at these respective levels of theory. The energy differences between the N- and O-protonated forms consistently differ by $22\text{--}28 \text{ kJ mol}^{-1}$ between B3LYP/6-31+G** and MP2/6-31+G**//B3LYP/6-31+G** calculations for MABAH^+ and MABAOMeH^+ with and without a water molecule attached.

The IRPD spectrum for $\text{MABAOMeH}^+(\text{H}_2\text{O})_1$ (Figure 6) is nearly identical with that of MABAH^+ with one water molecule attached, but the carboxylic acid free COO–H stretch is notably absent from the former. These results indicate that protonation and hydration for $\text{MABAOMeH}^+(\text{H}_2\text{O})_1$ occurs exclusively at the amine and confirm the assignment of the free COO–H stretch in the spectra of $\text{MABAH}^+(\text{H}_2\text{O})_{1-6}$. The spectra of $\text{MABAOMeH}^+(\text{H}_2\text{O})_{4,5}$ are identical with those for $\text{MABAH}^+(\text{H}_2\text{O})_{4,5}$ except for the absence of a free COO–H stretch. These results indicate that the hydration structures of both ions are the same with up to five water molecules attached and that the carboxylic acid H atom does not participate in hydrogen bonding. The spectra of MABAH^+ and MABAOMeH^+ with six water molecules attached are also similar, except both the HB and the free COO–H stretching bands at 3133 and 3578 cm^{-1} , respectively, are absent from the latter. These results confirm the band assignments and the conclusion that the majority of the ion population for $\text{MABAH}^+(\text{H}_2\text{O})_6$

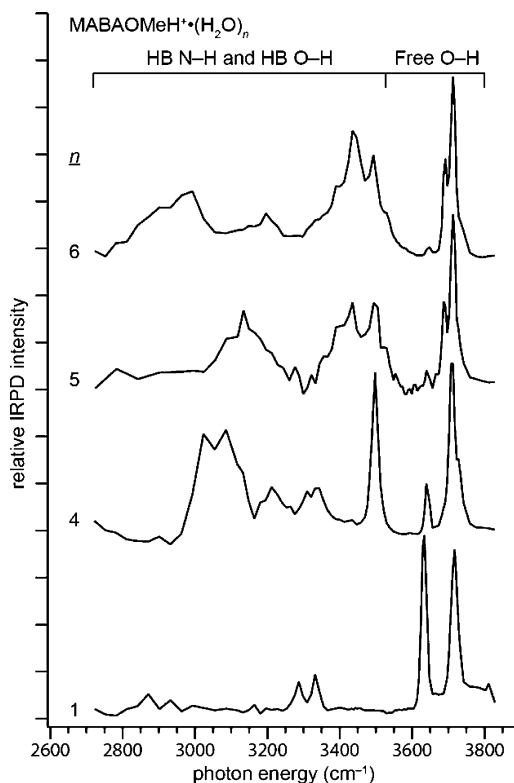


Figure 6. IRPD spectra of $\text{MABAOMeH}^+(\text{H}_2\text{O})_n$ with up to six water molecules attached, measured at 133 K. Regions corresponding to the HB N–H and O–H stretches as well as the free O–H stretches are indicated.

consists of structures where the ion is fully hydrogen bonded. In sum, the confirmation of the band assignments in the spectra of hydrated MABAH^+ suggest that the ion is fully hydrogen bonded upon solvation by six or more water molecules.

Identifying Multiple Isomers. When more than one isomer is present in an ion population, the relative contribution

of each isomer to an IRPD spectrum can be challenging to determine. Calculated band intensities can differ significantly from those measured in IRPD spectra,⁵¹ and isomers may have significantly different fragmentation efficiencies, which can affect the contribution of each isomer to an IRPD spectrum unless the entire ion population is dissociated.^{6,51,52} Dissociation kinetics have been used to determine the relative contributions of different isomers to ion populations,⁵³ and the method has been recently applied to IRPD spectroscopy.^{6,44,45,51,52}

On the basis of the calculated relative Gibbs free energies, only a single structure for $\text{MABAH}^+(\text{H}_2\text{O})_1$, **MABAH1a** (Figure 1b), is expected under these experimental conditions. Irradiation of the ion packet at the free COO–H stretch at 3573 cm^{-1} should lead to selective dissociation of **MABAH1a** but not **MABAH1b** (Figure 1b), which does not have a free COO–H stretch. Dissociation kinetics obtained by irradiating these ions at 3573 cm^{-1} are first order up to 98% depletion of the precursor population (Figure 7a). This is consistent with

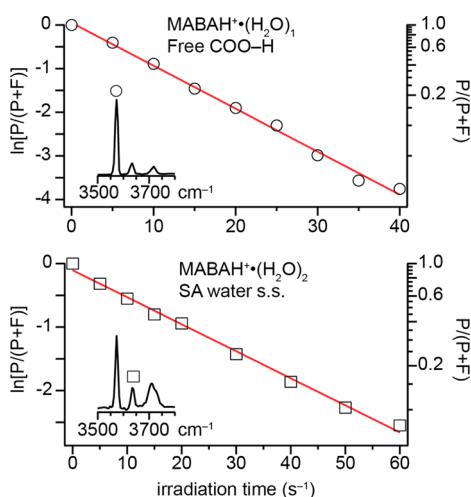


Figure 7. Laser photodissociation kinetic data for (a) $\text{MABAH}^+(\text{H}_2\text{O})_1$ at 3573 cm^{-1} (open circles) and (b) $\text{MABAH}^+(\text{H}_2\text{O})_2$ at 3622 cm^{-1} (open squares) measured at 133 K. Insets give partial IRPD spectra (see Figures 1 and 2) showing the corresponding bands for resonant excitation. Lines are least-squares fits to the first-order kinetic data. P and F correspond to the precursor and fragment abundances, respectively.

the exclusive presence of isomer **MABAH1a** or the presence of rapidly interconverting structures. These results also demonstrate that there is excellent overlap between the laser beam and the ion cloud.

The two isomers for $\text{MABAH}^+(\text{H}_2\text{O})_2$, **MABAH2a** and **MABAH2b** (Figure 2b), are within 3 kJ mol^{-1} of each other. To distinguish between these two nearly isoenergetic isomers, dissociation kinetics were measured at 3622 cm^{-1} , corresponding to the SA water OH s.s. band for the **MABAH2a** isomer. **MABAH2b**, which lacks SA water molecules, does not absorb at this frequency. The data (Figure 7b) fit first-order kinetics up to 92% depletion. This indicates the presence of a single dominant conformer corresponding to **MABAH2a**. Therefore, attachment of a water molecule to the protonated amine group is preferred over formation of the HB bridge to the carboxylic group.

Partially vs Fully Hydrogen Bonded Isomers of $\text{MABAH}^+(\text{H}_2\text{O})_6$. Calculations indicate that structures of

$\text{MABAH}^+(\text{H}_2\text{O})_{1-4}$, with a water molecule attached to the carboxylic acid H atom, are $\geq 5\text{ kJ mol}^{-1}$ higher in energy than partially hydrogen bonded structures with a free COO–H. However, the lowest-energy structure for $\text{MABAH}^+(\text{H}_2\text{O})_6$ is fully hydrogen bonded with a water molecule at the carboxylic acid H atom. The lowest-energy structure with a free COO–H is less than $\sim 5\text{ kJ mol}^{-1}$ higher in Gibbs free energy at 133 K (Figure S2, Supporting Information). These results indicate that the fully and partially hydrogen bonded isomers are energetically competitive with each other at both levels of theory. Dissociation kinetics were measured to determine the relative contributions of these isomers to the ion population.

Irradiation of the free COO–H stretch at 3578 cm^{-1} results in biexponential kinetics (Figure 8a). This can be attributed to

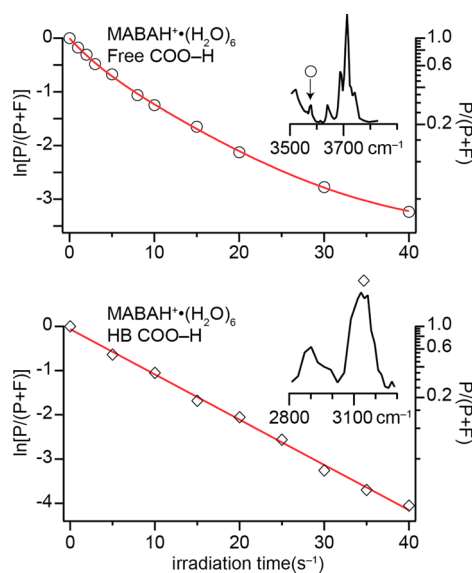


Figure 8. Laser photodissociation kinetic for $\text{MABAH}^+(\text{H}_2\text{O})_6$ at (a) 3578 cm^{-1} and at (b) 3133 cm^{-1} (open circles and diamonds, respectively) measured at 133 K. Insets give partial IRPD spectra (see Figure 5) showing the corresponding bands for resonant excitation. A least-squares biexponential fit to the kinetic data measured at 3578 cm^{-1} indicates the presence of two isomers that interconvert on a slower time scale than dissociation. A least-squares fit to first-order kinetic data measured at 3133 cm^{-1} indicates the presence of a single isomer or two rapidly interconverting isomers. P and F correspond to the precursor and fragment abundances, respectively.

the presence of two isomers: one that dissociates quickly owing to resonance absorption at this frequency and another that does not absorb strongly at this frequency. The relative populations of the resonant partially hydrogen bonded (free COO–H) and off-resonant fully hydrogen bonded isomers are $26 \pm 14\%$ and $74 \pm 13\%$, respectively.

Photodissociation kinetics for $\text{MABAH}^+(\text{H}_2\text{O})_6$ were also measured at 3133 cm^{-1} , corresponding to the stretching frequency of HB COO–H in isomers where MABAH^+ is fully hydrogen bonded. The fit is first order to $\sim 98\%$ precursor depletion (Figure 8b), suggesting the exclusive presence of ions that are solvated at the carboxylic group or two rapidly interconverting isomers. However, the kinetic data from the free COO–H stretch excitation at 3578 cm^{-1} indicates two coexisting isomers that do not interconvert rapidly when excited at this higher energy.

The different kinetic behaviors at these two frequencies are likely due to a difference in the dissociation rates. The rate

constant at 3578 cm^{-1} (the free COO–H stretch) is 0.393 s^{-1} but only 0.101 s^{-1} at 3133 cm^{-1} (the HB COO–H stretch). The difference in dissociation rate constants is not accurately reflected by the peak intensities of the absorption bands in the IRPD spectrum. The OPO/OPA system has a higher power output at 3578 cm^{-1} than at 3133 cm^{-1} , but the IRPD spectral intensities are corrected to account for the frequency-dependent variation in laser power. Therefore, further kinetic studies were carried out with attenuated power at 3578 cm^{-1} to investigate the influence of lower energy deposition on the relative rates of dissociation and interconversion between the isomers. The apparent relative abundance of the free COO–H isomer determined from these power-dependent kinetic measurements increases from $26 \pm 14\%$ at 1.6 mJ pulse^{-1} to $95 \pm 1\%$ at $0.12\text{ mJ pulse}^{-1}$ (Figure S3 (Supporting Information) and Table 1).

Table 1. Relative Populations for Resonant and Off-Resonant Isomers (Irradiation at 3578 cm^{-1}) for MABAH⁺·(H₂O)₆ Measured at Different Laser Powers

laser power (mJ pulse^{-1})	rel population (%)	
	resonant	off-resonant
1.6	26 ± 14	74 ± 13
0.7	57 ± 30	43 ± 24
0.12	95 ± 1	5 ± 1

Slower dissociation at lower laser powers result in different measured isomer abundances owing to the increased extent of interconversion between isomers because of the longer ion lifetimes. Figure 9 is a qualitative illustration of relative stabilities of the isomers and their fragmentation thresholds

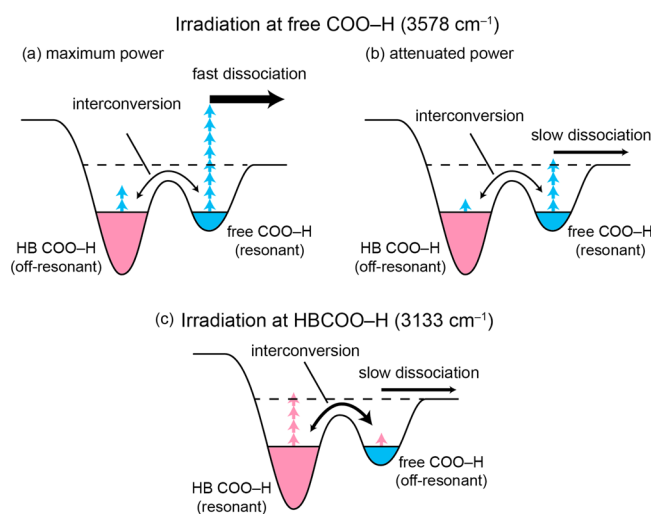


Figure 9. Illustration of the potential energy surface for the dissociation of MABAH⁺(H₂O)₆ at two laser powers and at two different photon energies. (a) Irradiation of the free COO–H stretch at 3578 cm^{-1} at maximum power results in biexponential kinetics owing to the rapid depletion of the resonant isomer in comparison to the slow replenishment via off-resonant excitation and interconversion. (b) Irradiation at lower laser fluence results in slower depletion of the resonant isomer so that replenishment via excitation and interconversion of the off-resonant isomer occurs more rapidly in comparison. (c) Irradiation at the HB COO–H stretch (3133 cm^{-1}) results in relatively slow heating followed by interconversion and subsequent slow dissociation.

deduced from these kinetic data. Clusters in which MABAH⁺ is fully hydrogen bonded are the most stable and constitute the majority of the ion population, as indicated by kinetic data at 3578 cm^{-1} . Photon absorption at 3578 cm^{-1} drives dissociation of the isomer with the free COO–H at a rate faster than interconversion, as a result of both higher laser power and higher photon energy (Figure 9a). When the laser power at 3578 cm^{-1} is reduced, the measured relative abundance of the isomer with a free COO–H is greater owing to replenishment of the population by isomerization of the isomer with the HB COO–H due to off-resonant excitation (Figure 9b). These results indicate that the isomerization barrier between the isomers is lower than either of their dissociation thresholds.

Resonant excitation of the HB COO–H stretching frequency at 3133 cm^{-1} deposits energy in the HB COO–H isomer, but this occurs slowly, owing to the lower laser fluence and photon energy in comparison to excitation of the isomer with the free O–H stretch at full laser power. The dissociation barrier of the HB COO–H isomer is likely higher than that of the free COO–H isomer, so that fragmentation proceeds through the latter isomer. The result is the appearance of a single isomer from the kinetic data (Figure 9c) at 3133 cm^{-1} . A more accurate estimate of the relative population of these isomers could be obtained by increasing laser power sufficiently to induce prompt dissociation of the resonant structure before its population can be replenished by interconversion between isomers. Under these conditions, apparent populations deduced from these experiments should no longer depend on laser power.

Although the uncertainties associated with fitting biexponential data can be high,^{45,53} the range in Gibbs free energy deduced from the HB and free COO–H isomer abundances ($74 \pm 13\%$ and $26 \pm 14\%$, respectively) is quite small ($0.5\text{--}2.2\text{ kJ mol}^{-1}$). However, the apparent relative abundance derived for the HB COO–H isomer measured at 3578 cm^{-1} with the greatest laser power is a lower limit: i.e., $\geq 74 \pm 13\%$ of the ion population for MABAH⁺·(H₂O)₆ consists of this isomer. Assuming a Boltzmann distribution (at 133 K) for the ion population, the HB COO–H isomer is lower in energy than the free COO–H isomer by more than 0.5 kJ mol^{-1} , consistent with the computed $3\text{--}5\text{ kJ mol}^{-1}$ energy difference.

CONCLUSION

Hydration of the protonated amine and neutral carboxylic acid functional groups of MABAH⁺ was investigated using IRPD spectroscopy, laser-induced dissociation kinetics, and computational chemistry. These two functional groups are oriented so that they cannot form a HB to each other. For MABAH⁺ with six or more water molecules attached, the vast majority of the ion population consists of isomers where the carboxylic acid H atom donates a HB to a water molecule, whereas results for MABAH⁺·(H₂O)_{1–5} indicate that there is no water molecule attached to this hydration site for these ions. In contrast, results for ProH⁺ and PheH⁺, where N and C termini interact with each other, indicate that isomers where a water molecule is hydrogen bonded to the carboxylic acid H atom are present even with one water molecule attached.^{44,45} These results indicate that the interaction of the N terminus with the C termini or a side chain can significantly influence the propensity for a water molecule to bind to the N or C terminus of an amino acid.

The formation of a water bridge between the protonated amine and the carbonyl O atom for MABAH⁺·(H₂O)₃ is more

favorable than the attachment of a water molecule at each of the H atoms of the protonated amine. In contrast, the dominant isomers for protonated aniline or *p*-aminobenzoic acid methyl ester with three water molecules attached have an ammonium group that is fully hydrogen bonded.⁹ These results show that a water bridge to a nearby carboxylic acid can be more favorable than solvation of each H atom of a protonated amine.

Photodissociation kinetics data for $\text{MABAH}^+(\text{H}_2\text{O})_{1,2}$ are first order to >90% precursor depletion, indicating that the vast majority of the ion population for these two ions consists of a single isomer or rapidly interconverting structures. Dissociation induced by irradiating $\text{MABAH}^+(\text{H}_2\text{O})_6$ at the HB COO–H stretch is also first order, whereas data measured at the free COO–H stretch of the same ion are biexponential and indicate that the fully solvated isomer is predominant. Irradiation at the free COO–H stretch with lower laser power results in slower dissociation, which allows more time for interconversion between isomers. These data are consistent with the results obtained at the HB COO–H stretching frequency, where the laser has lower power in comparison to that at the free COO–H stretch, and indicate that the first-order kinetics observed for the HB COO–H stretching excitation are due to interconversion over the time scale of the experiment.

These results show that, although laser-induced kinetics data can provide information about the relative populations of the isomers in an ion population, it is possible for resonant and off-resonant isomers to interconvert when the dissociation rate is small. By an increase in laser power, dissociation can occur more rapidly than interconversion, leading to more accurate information about the relative abundances of isomers. The results from this study illustrate the competition between water binding to a protonated primary amine vs that to a neutral carboxylic acid and the formation of water bridges between the two functional groups. These results provide new insights into hydration of protonated amino acids and provide stringent benchmarks for modeling biomolecule–water interactions.

■ ASSOCIATED CONTENT

Supporting Information

The full citation for ref 49; text, figures, and tables giving B3LYP/6-31+G** optimized geometries and single point energies calculated at both the B3LYP/6-31+G** and MP2/6-31+G**//B3LYP/6-31+G** levels of theory, and calculated structures and additional laser-induced kinetics data obtained at the free COO–H stretching frequency for $\text{MABAH}^+(\text{H}_2\text{O})_6$. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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