

Charge and Temperature Dependence of Biomolecule Conformations: K^+ Tryptamine(H_2O) $_{n=0-1}Ar_{m=0-1}$ Cluster Ions

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In this report, we detail the role of charge and temperature on the conformation of tryptamine (Tryp)—an analogue of tryptophan and the neurotransmitter serotonin—and the Tryp–water complex. Seven of the nine tryptamine conformers have been experimentally observed.¹ The minimum-energy structure, Gpy(out), locates the NH_2 group gauche with respect to the pyrrole ring and its lone pair oriented away from the π cloud.¹ In the Tryp–water complex, *only* the Gpy(out) conformer is experimentally observed.^{2,3} As the natural environment for neurotransmitters and amino acids includes a relatively high potassium cation concentration (~ 150 mM intracellular⁴), a more accurate model for conformer selectivity should consider electrostatic influences. As Williams and co-workers have demonstrated,^{5–8} the presence of a cation can significantly alter the conformation of a biomolecule. However, the exact conformations cannot be predicted a priori, as many can be close in energy, and in the cases of lysine and glutamine, the M^+ (amino acid) structure was also alkali ion-dependent.^{5,6}

$K^+(\text{Tryp})(H_2O)_{0,1}Ar_{0,1}$ cluster ions are an appropriate model system for assessing the role of charge and temperature on the tryptamine conformation, as both can be experimentally controlled using mass-selective vibrational spectroscopy. Density functional theory (DFT) calculations aid the interpretation of the experimental spectra. The use of these methods has been described in detail recently.⁹ Briefly, neutral clusters are formed by a supersonic expansion of argon, water, and tryptamine (heated to ~ 115 °C). Potassium ions perpendicularly collide with the molecular beam, and the resulting cluster ions stabilize through evaporative cooling.¹⁰ Cluster ions formed primarily by evaporation of argon (achieved by increasing the Ar/H_2O ratio in the expansion) are “tagged” with an argon atom and have a lower effective temperature than those formed by evaporation of water.¹¹ The cluster ions are guided to the entrance of a triple quadrupole mass spectrometer where mass-selected clusters are photodissociated under single photon absorption using a tunable IR laser,⁹ and the resulting fragment ions are mass-detected. The infrared photodissociation (IRPD) spectrum is recorded as a function of laser frequency and linearly corrected for variations in the laser fluence.

Preliminary structures were generated using Spartan '02,¹² followed by geometry and frequency calculations using Gaussian¹³ (B3LYP/6-31+G*). Calculated frequencies were scaled by 0.976 (OH), 0.959 (NH), and 0.961 (CH) for the designated stretching modes. These scaling factors facilitate agreement between frequencies calculated at this level of theory and those reported experimentally for neutral H_2O and Tryp molecules.^{1,14} Theoretical spectra were generated using SWizard,¹⁴ and thermodynamic quantities were calculated using the THERMO.PL script.¹⁵

Vibrational spectra of $K^+(\text{Tryp})Ar$, $K^+(\text{Tryp})(H_2O)$, and $K^+(\text{Tryp})(H_2O)Ar$ are shown in Figure 1. Zwier and co-workers showed that analysis of the alkyl CH stretching region is essential to characterizing tryptamine configurations.¹ In Figure 1, the alkyl CH modes in the $2850\text{--}2980\text{ cm}^{-1}$ region are consistent, suggesting

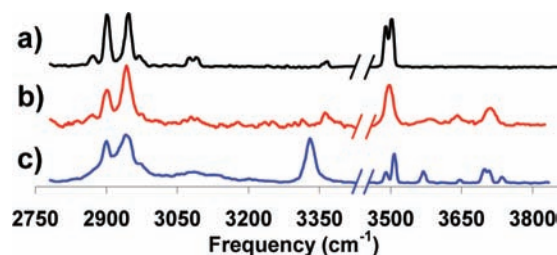


Figure 1. IRPD spectra of (a) $K^+\text{Tryp}Ar$, (b) $K^+\text{Tryp}(H_2O)$, and (c) $K^+\text{Tryp}(H_2O)Ar$. The $2800\text{--}3400\text{ cm}^{-1}$ region was magnified $\times 3$ for (a) and (b), while the $3450\text{--}3850\text{ cm}^{-1}$ region was magnified $\times 1.5$ for (c).

a common tryptamine conformer in all three species. This is particularly interesting for $K^+(\text{Tryp})Ar$ and $K^+(\text{Tryp})(H_2O)$, which differ in both composition and effective temperature. The broad underlying feature observed in the CH stretching region of the $K^+(\text{Tryp})(H_2O)Ar$ spectrum is indicative of strong OH hydrogen bonding (vide infra).

Notably, the CH signatures observed in these spectra are different than those observed in the neutral tryptamine study.¹ A computational study of the $K^+(\text{Tryp})$ conformational landscape identifies AGpy(in) and AGph(in) (shown in Figure 2 with their calculated

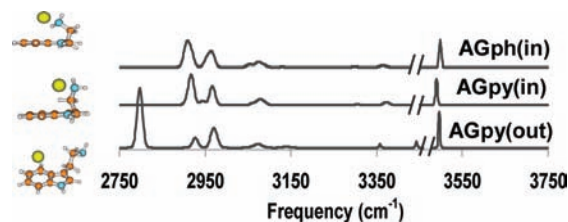


Figure 2. Calculated geometries and spectra for low-lying $K^+(\text{Tryp})$ conformers. The $2700\text{--}3450\text{ cm}^{-1}$ region was magnified $\times 5$.

spectra) as the two lowest-energy isomers, with all other calculated structures $40\text{--}50$ kJ/mol higher in energy. In contrast, the neutral Gpy(in) and Gph(in) conformers were the highest-energy conformers theoretically located and were not experimentally observed in the neutral tryptamine study.¹ The potassium cation significantly impacts the tryptamine conformation, favoring structures previously unobserved. Figure 2 also includes a calculated spectrum for the AGpy(out) conformer of $K^+(\text{Tryp})$ to emphasize the differences in the CH stretching region that result from different conformers.

The gas-phase tryptamine monomer exhibits the indole NH stretch as a strong feature near 3525 cm^{-1} , while the significantly weaker symmetric/asymmetric amino NH_2 stretches appear between 3300 and 3400 cm^{-1} .¹⁶ The indole NH stretch in $K^+(\text{Tryp})Ar$ is observed near $3490/3503\text{ cm}^{-1}$ (the doublet arises from the two low-lying AGpy(in) and AGph(in) conformers), while the NH_2 asymmetric stretch is near 3364 cm^{-1} . The symmetric NH_2 stretch is too weak to be observed.

The $K^+(\text{Tryp})(\text{H}_2\text{O})$ spectrum preserves these NH stretching features near 3500 and 3360 cm^{-1} . While a single water molecule should give rise to only two OH stretching features, this spectrum has three distinct OH features between 3550 and 3750 cm^{-1} , indicating more than one structural isomer in the molecular beam. The OH asymmetric/symmetric stretches of the water monomer at 3756 and 3657 cm^{-1} ¹⁷ shift to slightly lower frequencies when bound to a cation, as observed in $K^+(\text{H}_2\text{O})\text{Ar}$ with corresponding frequencies at 3710 and 3636 cm^{-1} , respectively.¹¹ The features centered at 3711 and 3640 cm^{-1} in the $K^+(\text{Tryp})(\text{H}_2\text{O})$ spectrum indicate an ion–water interaction consistent with structure **1D**, as depicted in Figure 3. Hydrogen bonding generally shifts OH

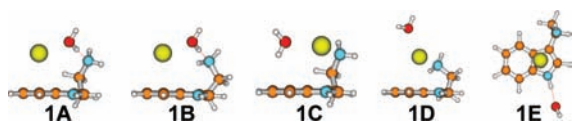


Figure 3. Five lowest-energy isomers identified for $K^+(\text{Tryp})(\text{H}_2\text{O})$.

stretches below 3600 cm^{-1} , as observed for the feature centered at 3582 cm^{-1} . This shift is attributed to a π -hydrogen bond between one OH group and the indole ring, based on the assignment of a similar band observed near 3560 cm^{-1} in $K^+(\text{Indole})(\text{H}_2\text{O})_2$.¹⁸ In this hydrogen-bonded configuration (**1C** in Figure 3), the other OH oscillator remains free with a vibrational frequency near 3710 cm^{-1} .¹⁸ The OH free and asymmetric features are not always fully resolved in our experiments, and the observed band near 3711 cm^{-1} is likely a convolution of these vibrations, arising from a combination of isomers **1C** and **1D**.

In total, five low-energy $K^+(\text{Tryp})(\text{H}_2\text{O})$ isomers, found in computations, are shown in Figure 3, with their calculated spectra in the Supporting Information. Each of these low-energy isomers contains either a Gpy(in) or Gph(in) tryptamine conformer. Other conformers were 30 – 40 kJ/mol higher in energy and thus unlikely to be present in this study. A free energy analysis (Supporting Information) indicates that while structure **1A** is preferred at 0 K , it becomes entropically unfavorable as the cluster temperature increases. Structure **1D** has the lowest free energy at temperatures above 170 K and is likely the major contributor under the warmer ($\sim 300\text{ K}$) experimental conditions. Structures **1A**, **1B**, and **1C** are almost isoenergetic near 300 K (and about 8 kJ/mol higher in free energy than **1D**), but only **1C** is in agreement with the remaining spectral features and is assigned as a second, minor contributor to the $K^+(\text{Tryp})(\text{H}_2\text{O})$ spectrum; **1A** and **1B** are, at best, very minor contributors.

The spectrum of $K^+(\text{Tryp})(\text{H}_2\text{O})\text{Ar}$ shows several new features compared to the warmer $K^+(\text{Tryp})(\text{H}_2\text{O})$ spectrum. While the intensity of the indole NH feature around 3500 cm^{-1} decreased, a new strong feature at 3330 cm^{-1} is observed. Also, a broad feature convoluted with the CH stretching modes in the 2850 – 2950 cm^{-1} region is now present. The intensity and breadth of these new features are hallmarks of hydrogen-bonded XH stretching modes. The reduction in temperature has allowed new hydrogen-bonded isomers to form.

Under the conditions for the $K^+(\text{Tryp})(\text{H}_2\text{O})\text{Ar}$ experiment (~ 50 – 150 K), conformers with more hydrogen bonds are enthalpically favored.^{9,19} The broad band underlying the CH stretching region is presumably due to a hydrogen-bonded OH mode that is strongly red-shifted. Isomers **1A** and **1B**, which have the lowest free energies in this temperature range, contain a hydrogen bond

between the water molecule and the amino nitrogen, calculated to have an OH stretch centered around 2950 cm^{-1} . The new feature present at 3330 cm^{-1} is consistent with isomer **1E**, with the indole NH group acting as a proton donor to the water molecule. Isomer **1E** is $\sim 20\text{ kJ/mol}$ higher in free energy than **1A** and not expected to contribute to the observed spectrum, yet the presence of this feature indicates otherwise. As the ion approaches the neutral complex embedded in argon, the rapid evaporation process must allow this higher-energy conformer to form. This was noted previously for $\text{Li}^+(\text{H}_2\text{O})_4\text{Ar}$, where a significant barrier to isomerization prevented rearrangement to a lower-energy conformer.¹⁹ A second example of trapping a high energy conformer by rapid argon evaporation has been recently observed in $K^+(\text{18-crown-6})\text{H}_2\text{O}\cdot\text{Ar}$.²⁰ For the other $K^+(\text{Tryp})(\text{H}_2\text{O})\text{Ar}$ features, the band near 3570 cm^{-1} is again assigned to the conformer with the π -hydrogen bond (isomer **1C**), and the OH modes at higher frequency arise from a combination of isomers **1A**, **1B**, **1C**, and **1E**.

The role of both charge and temperature has a dramatic impact on the favored conformers of tryptamine and the nature of tryptamine–water hydrogen bonding. Two previously unobserved, high-energy conformers of neutral tryptamine become the lowest-energy and *only* conformers observed in the K^+ -bearing cluster ions reported here. In addition, the presence of a high-energy conformer trapped by the argon evaporative cooling process was identified. Exploration of the conformational landscape of hydrated cluster ions bearing flexible biomolecules is now possible.

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Supporting Information Available: Calculated geometries of low-energy isomers; calculated spectra and relative free energies of conformers **1A**–**1E**; complete refs 12 and 13. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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