5596 *J. Am. Chem. Soc.* **2001,** *123,* 5596−5597

The Role of Water Bridges in Directing the Conformational Preferences of 3-Indole-propionic Acid and Tryptamine

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Received March 22, 2001
Revised Manuscript Received May 1, 2001

One of the foundations of modern biochemistry is that the aqueous environment plays a crucial role in directing the conformational preferences of proteins.[1] Current research is focusing increasing attention on the crucial role played by water molecules in the first solvation shell, particularly when they can form bridges between H-bonding sites in the protein.[2] Gas-phase biomolecule−(water)$_n$ molecular clusters offer a unique venue for directly probing how water molecules bound at specific sites dictate the conformational preferences of flexible biomolecules. In this communication, mass-selected, resonant two-photon ionization (R2PI) and resonant ion-dip IR (RIDIR) spectroscopies[3] are used to record the IR and UV spectra of single conformations of water-containing clusters of 3-indole-propionic acid (IPA) and tryptamine (TRA). The H-bonding topologies of these clusters are determined, and the effect that water binding has on the conformational preferences is assessed. In both IPA and TRA, the water molecules form bridges between H-bonding sites that reorient the flexible side-chain into conformations without population in the absence of the water bridges.

IPA and TRA each have two primary sites of flexibility along the propionic acid or ethylamine side chains. Previous studies[4−8] have determined that the isolated TRA monomer population is spread over seven low-energy conformational minima representing the seven most stable structures of the nine that are formed by rotating the *position* (about the C(α)−C(β) bond) and *orientation* of the amino group. In IPA, by contrast, only two conformers are observed, with the carboxylic acid position either gauche on the pyrrole side (Gpy, conformer A) or anti (conformer B) relative to the indole ring.[9] The gauche-phenyl side-chain conformation is destabilized by about 5 kJ/mol due to steric hindrance with the indole ring, and is not observed in the expansion.

Molecular clusters were formed in a supersonic expansion from heated IPA and TRA samples (410 K) entrained in a 3 bar, 70% neon/30% helium/0.1% water gas mixture. UV spectra of the clusters were taken using R2PI spectroscopy. Figure 1 shows two-color R2PI spectra of the IPA−$(H_2O)_n^+$ mass channels with n = 1 and 2. The transitions assigned to the various sized neutral clusters are indicated in the spectra, based on mass selection, water concentration studies, rotational coherence measurements,[10] and the IR spectra. There are two conformers of IPA−$(H_2O)_1$, but four of IPA−$(H_2O)_2$. The small frequency shifts from the IPA-(A,B) monomers, and similar relative intensities of the bands marked $W_{1,2}$(A,B) suggest that the first two water molecules in the IPA(A,B)−$(H_2O)_n$ clusters retain the conformational preferences of the IPA monomer (Gpy and anti), consistent with the deductions of rotational coherence measurements on these bands by Connell, et al.[10]

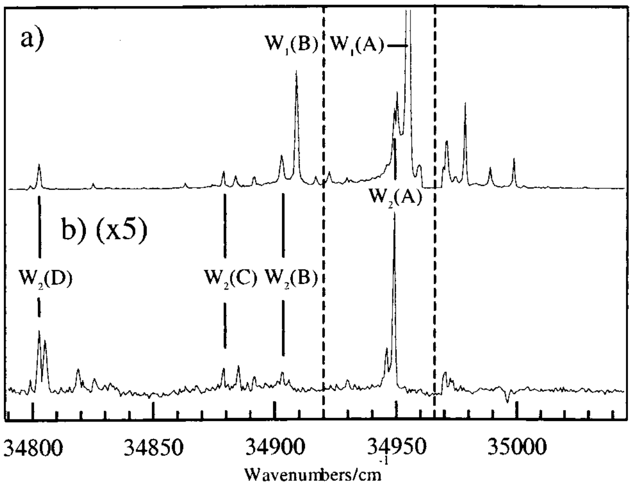

Figure 1. R2PI spectra of IPA−$(H_2O)_n^+$ mass channels with (a) n = 1and (b) n = 2. The label W_n(A) = IPA(A)−$(H_2O)_n$. The transitions due to IPA−W_2 appear in both mass channels due to fragmentation following photoionization. Dashed lines represent the IPA monomer A and B origins at 34966 and 34920 cm^{-1}, respectively.

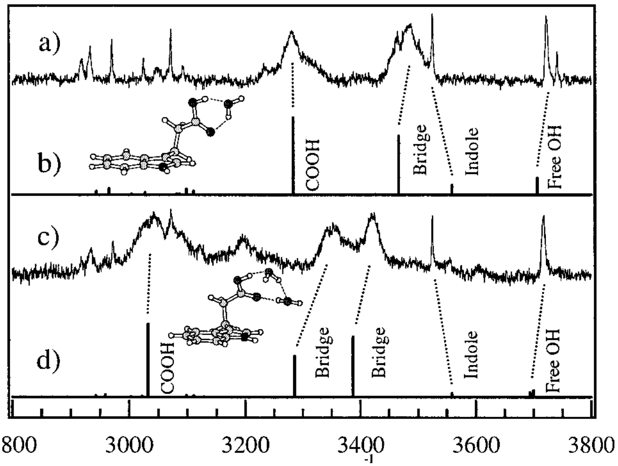

Figure 2. Experimental RIDIR (a,c) and calculated (b,d) IR spectra of IPA(A)−H_2O (a,b) and IPA(A)−$(H_2O)_2$ (c,d). The absorption at 3200 cm^{-1} in (c) is attributed to the water bend overtone

The R2PI transitions were used as the basis for RIDIR spectra of the clusters in the hydride stretch region of the IR (2800−3800 cm^{-1}), which is sensitive to the hydrogen-bonding and conformations of the XH groups in the cluster.[3] Figure 2, a and c, shows the RIDIR spectra of IPA(A)−$(H_2O)_1$ and IPA(A)−$(H_2O)_2$.[10] As an aid in assigning these spectra, density functional theory (DFT) calculations employing the Becke3LYP functional[11,12] with a 6-31+G* basis set[13] were used to calculate the minimum-energy structures, harmonic vibrational frequencies and IR intensities of the clusters. The calculated minimum-energy structures and IR spectra for IPA(Gpy)−$(H_2O)_1$ and IPA(Gpy)−

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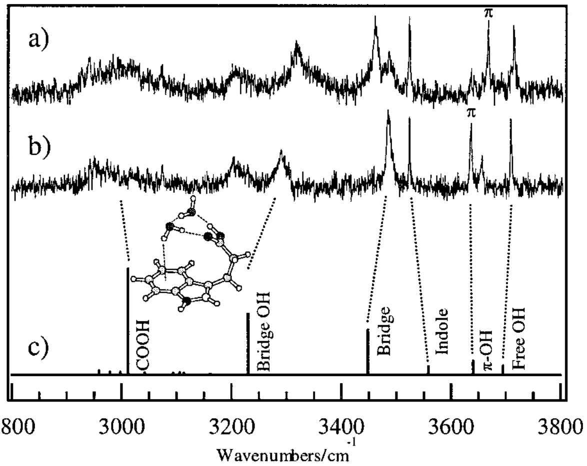

Figure 3. Experimental RIDIR spectra of (a) IPA(C)−$(H_2O)_2$ and (b) IPA(D)−$(H_2O)_2$. (c) Calculated IR spectrum of one of the gauche-phenyl IPA−$(H_2O)_2$ minima (shown as an inset). The absorption at 3200 cm^{-1} in (a,b) is attributed to the water bend overtone.

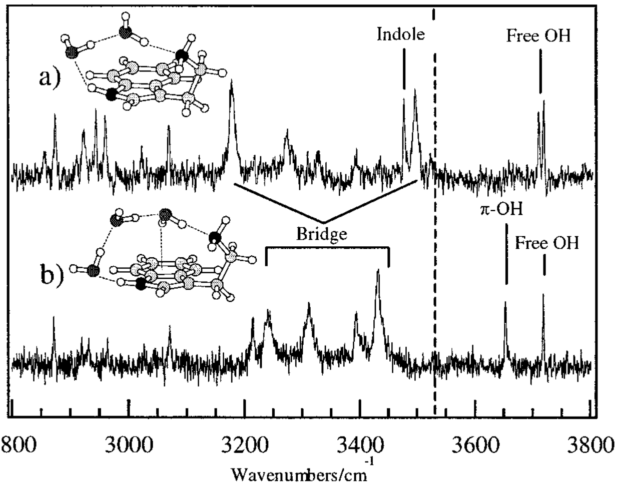

Figure 4. Experimental RIDIR spectra of (a) TRA−$(H_2O)_2$ and (b) TRA−$(H_2O)_3$. (Calculated structures TRA−$(H_2O)_2$ and TRA−$(H_2O)_3$ shown as an inset respectively.) The position of the free indole-NH is marked with a dashed line at 3525 cm^{-1}.

$(H_2O)_2$ are shown in Figure 2, b and d, respectively. In these clusters, the water molecule(s) form H-bonded bridges between the carbonyl and OH groups of the carboxylic acid. The corresponding spectrum of W_1(B) confirms that it is also a water bridge structure that retains the anti conformation for the COOH group.[10] Thus, the water molecules in IPA(A,B)−$(H_2O)_{1,2}$ bind to IPA in such a way that the conformational preferences of the IPA monomer are retained.

However, the W_2(C) and W_2(D) R2PI transitions (Figure 1) are without analogues in the IPA monomer and have not been observed in previous work. These R2PI transitions are shifted further to the red than W_2(A) and W_2(B), indicating a stronger interaction with indole's π cloud. Their RIDIR spectra are shown in Figure 3, a and b. A striking feature of these spectra is the π H-bonded OH stretch band that appears in both spectra in the 3650−3670 cm^{-1} region characteristic of the weak H-bond formed between a water OH and the indole π cloud.[14] Apart from this, the spectra are reminiscent of the W_2(A) bridge structure (Figure 2c). The π H-bonded OH stretch can only occur if the COOH group is in the gauche-phenyl position, as shown in the inset of Figure 3c. Low-lying minima of this type have been identified via the DFT calculations. The calculated hydride stretch IR spectra of these structures (e.g., Figure 3c) correctly predict the presence of a π H-bond, confirming the structural identification. Thus, in the IPA−$(H_2O)_2$ clusters, the formation of water dimer bridges across the carboxylic acid group forms and stabilizes population in the gauche-phenyl conformation that is not significantly populated in the monomer due to its higher energy.

In TRA, the water bridges stretch between the amino acceptor and the indole NH donor sites. The first water molecule attaches preferentially at the amino group, but cannot reach to the indole NH. Nevertheless, the seven conformations with population in the TRA monomer are collapsed into a single dominant conformation upon this binding (Gpy(out)).[9,15] The RIDIR spectrum of the TRA−$(H_2O)_2$ (Figure 4a) shows two bridge OH stretch fundamentals of a water dimer attached to the amino group, and an indole NH stretch that is shifted down in frequency from its value in the monomer by 48 cm^{-1}, indicating that one of the water molecules is interacting with the indole NH. Similarly, in TRA−$(H_2O)_3$, the RIDIR spectrum (Figure 4b) shows a set of bridge hydride stretch fundamentals in the 3200−3450 cm^{-1} region assignable to the indole NH and three water OH groups making up the bridge. One of the free OH groups is now involved in a π H-bond with the indole ring. Extensive searches for cluster structures consistent with these features have been carried out. Calculated TRA−$(H_2O)_2$ and TRA−$(H_2O)_3$ structures consistent with the RIDIR spectra are shown as insets in Figure 4 a,b. Notably, in both TRA−$(H_2O)_2$ and TRA−$(H_2O)_3$, formation of the water bridge can only be accomplished at an amino orientation that points the lone pair in toward the indole π cloud in a conformation that is not populated in the monomer.

In summary, the IPA−$(H_2O)_n$ and TRA−$(H_2O)_n$ clusters provide clear examples of the ways in which strongly bound water molecules can change the conformational preferences of flexible biomolecules. In the clusters, water bridges are formed between H-bond donor and acceptor sites whenever possible. In both TRA and IPA, the ethylamine or propionic acid conformations in the clusters are ones having no monomer population in the expansion. Single-point calculations indicate that the new conformations taken up by TRA and IPA in the presence of water possess 12−15 kJ/mol of conformational strain relative to the monomer global minima. These conformations must be populated and stabilized in the process of forming the H-bond(s) with water. The energy released by H-bond formation gives energy to the flexible sites nearby to overcome the barriers separating minima, effectively annealing the molecule into new conformations not accessible to the bare molecule at the preexpansion temperature ($T \approx 410$ K). It remains an open question whether water molecules play a similar role in inducing conformational change via H-bond formation in room-temperature aqueous solution.

Acknowledgment. We acknowledge the support of the National Science Foundation (9728636-CHE) for this work.

JA015863M

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