

Formation of an Amine-Water Cyclic Pentamer: A New Type of Water Cluster in a Polyazacryptand

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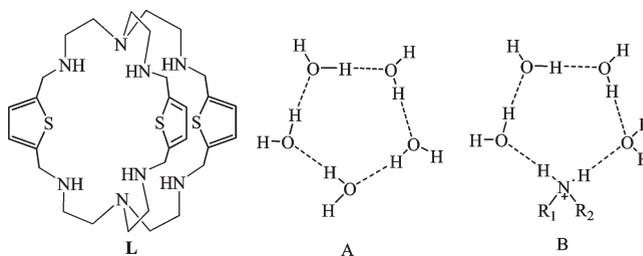
Received February 2, 2010; Revised Manuscript Received February 25, 2010

ABSTRACT: Structural analysis of an adduct of a thiophene-based cryptand with tosylic acid shows the formation of a hybrid amine-water cyclic pentamer composed of four water molecules and one protonated amine in the charged hydrophobic cavity. The bulky tosylate groups remain outside the cavity, making the ligand favorable for hosting water molecules. Ab initio calculations based on density functional theory (DFT) confirm that the hybrid amine-water pentamer is stabilized inside the hydrophobic cavity of the cryptand.

Despite significant progress in experimental and theoretical studies of discrete water clusters, a detailed understanding of molecular water within a confined hydrophobic cavity remains a challenge.¹ Within the peptide walls of a protein, molecular or clustered water can form in the hydrophobic cavity through hydrogen bonding and hydrophobic interactions,² playing a critical role in controlling the function, activity, and folding of the protein.³ Protein-bound water clusters have also been identified structurally, showing stable polygons composed of three to eight water molecules.⁴ At the molecular level, water clusters are thought to facilitate the transfer of a proton along the hydrogen-bonded chain,⁵ which is not only a fundamental biological process⁶ but also a key mechanism for the generation of electrical power in hydrogen fuel cells.⁷ Interests in this area continue to intrigue the scientific community both in terms of basic research and technological applications.⁸ In particular, the structural characterization of water clusters is critical in correlating and predicting the properties of bulk water at a molecular level. In the solid state, water clusters (H₂O)_n are known to exist as discrete rings, chains, tapes, and layers⁹ with different numbers of water molecules. Among these arrangements, cyclic water clusters¹⁰ have been shown to be stabilized as trimers,^{10a} tetramers,^{10b} pentamers,^{10c,d} hexamers,^{10e} octamers,^{10f} decamers,^{10g} undecamers,^{10h} and dodecamers¹⁰ⁱ in various organic environments. However, in contrast to their presence within crystal lattices or between hosts, cyclic water clusters inside the cavity are rare,¹¹ with the exception of tricyclic amide with hexamer,^{11a} *p*-xylyl cryptand for quasi-prismatic hexamer,^{11b} and self-assembled palladium-based cages for a decamer.^{11c} It is known that, in the solid state, most of the organic hosts (ca. 96%) forming water clusters are directly linked to water molecules via hydrogen bonding interactions.¹² However, to the best of our knowledge, the participation of a heteroatom in forming a ring has not been previously reported within a synthetic molecule. Herein, we present structural evidence and ab initio calculations based on a new type of hybrid pentamer [(H₂O)₄(NH₂)⁺] (Chart 1). This unique structure is stabilized within the charged cavity of a hexaprotonated cryptand **L**, bearing a similar structural topology to the cyclic pentamer, (H₂O)₅^{10c} or cyclopentane.

We recently reported that the bicyclic receptor **L** effectively binds chloride^{13a} and nitrate^{13b} ions in aqueous solution through the protonated bridgehead amines. While one chloride was found

Chart 1. Thiophene-Based Octaazacryptand (L), Cyclic Water Pentamer (A), and Hybrid Amine-Water Cyclic Pentamer (B)



to be encapsulated linearly within the cavity, three nitrates were bridged in **L** forming a [NH(NO₃)₃HN]⁺ motif in the solid state. The formation of trinitrate complex, however, was inconsistent with a 1:1 binding observed in aqueous solution, suggesting that water molecules occupied the cavity and prevented the competitive binding of more than one nitrate in solution. This observation inspired us to further explore the cryptand with bulky anions that are too large to enter the cavity, thus making an ideal environment in **L** for hosting water molecules.

Crystallographic analysis of the tosylate salt of **L** revealed that the ligand in its hexaprotonated form crystallizes in the monoclinic space group *P*2₁/*n* with 6 tosylate anions and 12 water molecules.¹⁴ As shown in Figure 1, a cyclic pentamer is formed with four water molecules (O3W, O1W, O2W, and O6W) and one protonated amine (N6) group inside the cavity. The hydrogen-bonding interactions facilitate the formation of a pentamer which adopts a puckered conformation, with one water (OW1) lying at 1.410 Å above the mean plane formed by the three oxygens and the linking nitrogen (Figure 1b). The protonated amine involved in the ring acts as two hydrogen bond donors for two waters with 2.894(2) and 2.754(2) Å for N6⋯O3W and N6⋯O6W, respectively.

The large anions are located outside the cavity without interacting with the macrocycle. The secondary amines are protonated in the macrocycle exhibiting a C₃ symmetry along the bridgehead nitrogens, N1 and N4. The absence of an anion inside the cavity makes **L** favorable for hosting the water molecules. The distance between the bridgehead nitrogen sites is longer (7.891 Å) than the corresponding distance in the chloride (6.096(4) Å)^{13a} or nitrate (5.528(6) Å)^{13b} complex, where the internally bound anion brings the two bridgehead amines closer through electrostatic interactions. The geometry of the hybrid pentamer is similar to the

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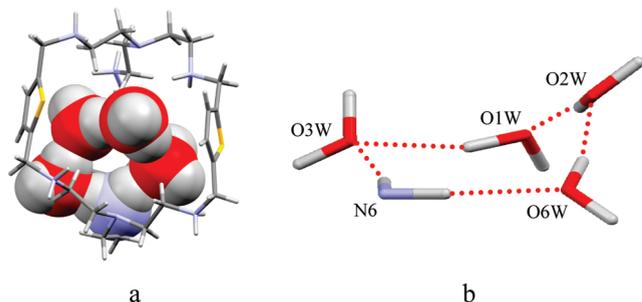


Figure 1. (a) Crystal structure of $[\text{H}_6\text{L}(4\text{H}_2\text{O})]^{6+}$ showing the hybrid amine-water pentamer $[(\text{H}_2\text{O})_4(\text{NH}_2)]^+$ in a space-filling model. (b) Representation of the hybrid amine-water pentamer $[(\text{H}_2\text{O})_4(\text{NH}_2)]^+$ in puckered conformation in $[\text{H}_6\text{L}]^{6+}$.

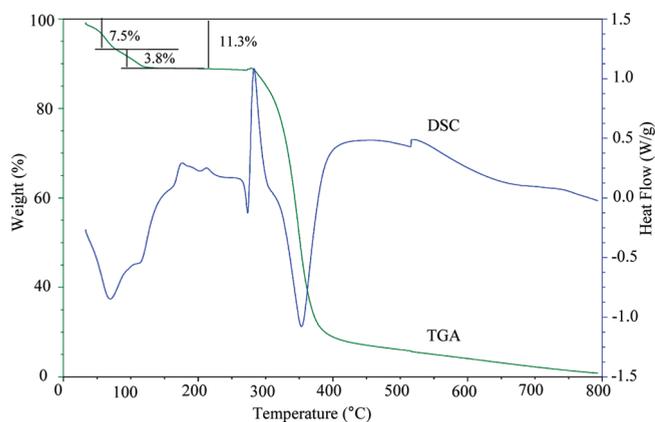


Figure 2. Thermograms of $[\text{H}_6\text{L}(4\text{H}_2\text{O})](\text{TsO})_6 \cdot 8\text{H}_2\text{O}$ showing TGA (green) and DSC (blue) at the heating rate of $10\text{ }^\circ\text{C}/\text{min}$.

cyclic pentamer observed in a lattice of hydrated *trans*-bis(4-pyridyl)ethylene dioxide.²¹ The $\text{O} \cdots \text{O}$ ($\text{O1W} \cdots \text{O3W} = 2.885(2)\text{ \AA}$, $\text{O2W} \cdots \text{O1W} = 2.868(3)\text{ \AA}$, and $\text{O6W} \cdots \text{O2W} = 2.750(16)\text{ \AA}$) distances in the hybrid pentamer are comparable to the reported pentamer ($2.706(3)$ – $2.918(3)\text{ \AA}$),^{10c} liquid water (2.85 \AA),¹⁵ and ab initio calculations (2.813 – 2.831 \AA by Hartree–Fock and 2.689 – 2.700 \AA by DFT).¹⁶ Additional water molecules remain outside the cavity and are involved in various hydrogen-bonding interactions, forming an acyclic trimer with OW9, OW10, and OW11, and a dimer with OW8 and OW12. The trimer is associated to N2 through OW11 with a $\text{N} \cdots \text{O}$ bond distance of $2.715(3)\text{ \AA}$. The water with OW4 and OW5 forms two acceptor hydrogen bonds with N7, giving a bond distance of $2.764(2)$ and $2.682(2)\text{ \AA}$, respectively. Clearly, the absence of interactions between anionic groups with the macrocycle makes the cavity versatile not only for water in this case but also for other anions.¹³

In order to characterize the bound and unbound water molecules in the complex, we performed thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) of $[\text{H}_6\text{L}(4\text{H}_2\text{O})](\text{TsO})_6 \cdot 8\text{H}_2\text{O}$ (Figure 2). As shown on the TGA curve, the complex exhibits a first weight loss of 7.5% before reaching a temperature of $100\text{ }^\circ\text{C}$, displaying a large endothermic peak on the DSC at around $70\text{ }^\circ\text{C}$. The first weight loss, which corresponds to eight water molecules, could be due to the removal of unbound water molecules outside the cavity. The weight loss in the second phase on TGA is about 3.8%, corresponding to four water molecules that are assigned to the internally bound water cluster in the hybrid pentamer observed in the crystal structure. The removal of water clusters results in the appearance of another endothermic peak at $112\text{ }^\circ\text{C}$. Thus, the 11.3% decrease in the original weight below $120\text{ }^\circ\text{C}$ corresponds to the 12 water molecules as per the chemical composition of $[\text{H}_6\text{L}(4\text{H}_2\text{O})](\text{TsO})_6 \cdot 8\text{H}_2\text{O}$ observed in the solid state. After losing the crystalline

water, the complex appears to be stable up to $275\text{ }^\circ\text{C}$. The exothermic and endothermic peaks at $\sim 275\text{ }^\circ\text{C}$ and $\sim 350\text{ }^\circ\text{C}$ on the DSC curve could be due to the melting and decomposition of the complex, respectively. Furthermore, the presence of water in the complex was identified by FT-IR spectra (Supporting Information). The complex showed a broad band at around 3420 cm^{-1} that can be assigned to the $\text{O} \cdots \text{H}$ stretching vibration of water present in the sample, similar to the calculated frequency, 3443 cm^{-1} obtained for the pentamer¹⁷ or to the experimental value, 3400 cm^{-1} observed for other water clusters.¹⁰ⁱ This band almost disappeared after heating the sample at $120\text{ }^\circ\text{C}$ for 12 h, confirming the exclusion of water molecules from the complex, an observation that is consistent with the TGA observations and theoretical calculations discussed below.

In order to quantitatively understand the unique bonding involved in the hybrid amine-water pentamer, ab initio calculations based on density functional theory (DFT) were carried out. All quantum chemical calculations were carried out with Truhlar's M06-2X meta-GGA hybrid functional¹⁸ which has been shown to accurately predict the relative energies of water hexamers and other noncovalent bonding interactions in large molecular systems.^{19,20} Ground-state geometries were optimized at the M06-2X/6-31G(d,p) level of theory, and harmonic frequencies were computed to verify that all structures were true minima. The initial geometry was modeled from the crystallographic coordinates of the protonated cluster-cryptand. At the optimized geometries, single-point energies with a larger 6-311G(d,p) basis set were carried out (a diffuse 6-311+G(d,p) basis set was used for the H, O, and N atoms involved in the amine-water pentamer within the complex). Figure 3a,b shows the optimized geometry and electrostatic potential of the cluster-cryptand, respectively. From the DFT-optimized geometry, we find that the bond distances compare excellently with the experimental crystal structure, confirming the puckered conformation of the amine-water pentamer (Supporting Information). The electrostatic potential also shows a localization of positive charge on the protonated amine groups within the cryptand structure. From the optimized geometry, the stabilization energy of complexation was calculated as $E_s = E(\text{cluster-cryptand}) - E(\text{cryptand}) - 4 * E(\text{water})$ and was found to be -68.5 kcal/mol , resulting from strong electrostatic interactions between the hydrogen-bonded water molecules and the highly charged macrocycle, in addition to strong hydrogen bonds which stabilize the entire complex. In order to compare this binding energy with other complexes, we also calculated stabilization energies for an isolated water pentamer (Chart 1A) and an isolated $\text{NH}_4^+ \cdots \text{water}$ pentamer (Chart 1B). At the M06-2X/6-311+G(d,p) level of theory, we find that the $\text{NH}_4^+ \cdots \text{water}$ complex has a binding energy of -71.2 kcal/mol , while the isolated water pentamer complex has a smaller binding energy of -40.4 kcal/mol . The cluster-cryptand stabilization energy is slightly less (more positive) than the $\text{NH}_4^+ \cdots \text{water}$ complex due to additional steric interactions (cf. Figure 3b) within the cryptand.

In conclusion, we have structurally identified a novel hybrid amine-water cyclic pentamer formed inside the cavity of a cryptand. Ab initio calculations not only support the stabilization of the hybrid pentamer inside the hydrophobic cavity but also reveal that the hybrid amine water pentamer is energetically more stable than the conventional water pentamer. The tosylate group used as a counteranion is not complementary in size to the cryptand, allowing neutral water molecules to reside inside the cavity. This observation clearly indicates that an appropriate selection of counteranions makes the ligand useful for caging water in the charged hydrophobic environment. The hybrid pentamer, in which a protonated amine is an important component in the ring, adopts a puckered conformation similar to cyclopentane or cyclic water pentamer. In vivo water clusters formed within a protein cavity or cleft are known to be stabilized

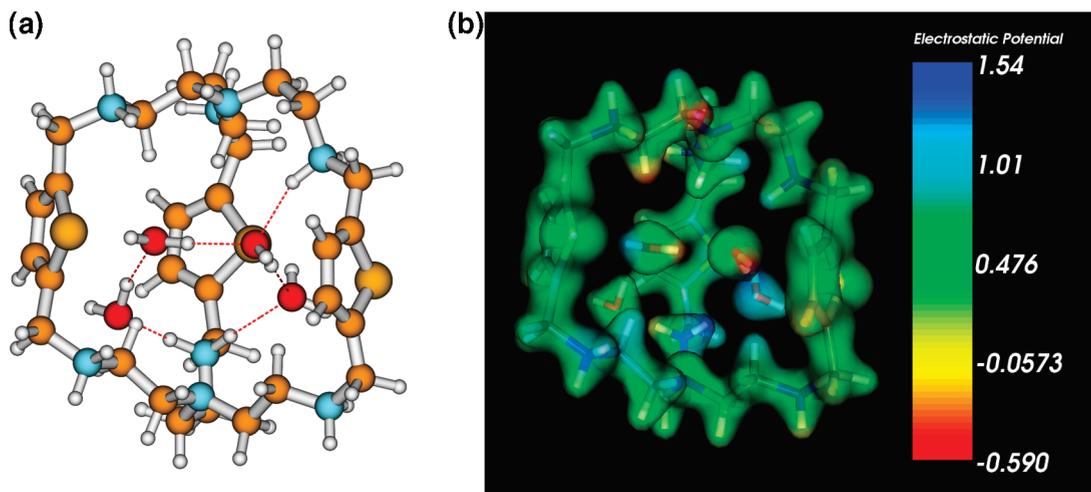


Figure 3. (a) Optimized geometry of the amine-water cluster, $[\text{H}_6\text{L}(4\text{H}_2\text{O})]^{6+}$ at the M06-2X/6-31G(d,p) level of theory. (b) Electrostatic potential of $[\text{H}_6\text{L}(4\text{H}_2\text{O})]^{6+}$.

predominantly through hydrogen-bonding interactions with CO groups at the C termini and NH groups at the N termini²¹ as well as with the charged amino acid side chains.²² While there is an abundance of discrete water clusters reported in the literature, the formation of the hybrid pentamer described in this work has not been observed before in a synthetic host. Given the novel role of water clusters in chemical and biological systems, the present findings provide insight and serve as a prototype for stabilizing other pure and hybrid water clusters.

Acknowledgment. The project described was supported by Grant Number G12RR013459 from the National Center for Research Resources. This material is based upon work supported by the National Science Foundation under CHE-0821357. Purchase of the diffractometer was made possible by Grant No. LEQSF (1999-2000)-ENH-TR-13, administered by the Louisiana Board of Regents.

Supporting Information Available: One crystallographic file in CIF format, synthetic procedures, hydrogen bonding interactions, ORTEP diagram with numbering scheme, FTIR spectra, and experimental and computed bond distances within the amine-water complex in PDF format. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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