Proton-Induced Chirality: Proton Complexation in the Chiral Cryptand 222-2H$^+$ Dication Isolated from a Liquid Clathrate Medium

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Received June 20, 1995

Extensive work by ourselves and others[1] has demonstrated the formation of two-phase liquid clathrate systems resulting from the interaction of a wide range of salts with aromatic solvents. In particular, we have recently reported the solid-state self-assembly *via* hydrogen bonding interactions of oxonium ion (*i.e.*, H_3O^+) crown ether complexes of inorganic anions isolated from such liquid clathrate media.[2] One- and two-dimensional solid-state networks have been observed with concomitant complexation of the oxonium ion or its less common higher hydrated species $H_3O^+(H_2O)_n$ (n = 1−4). In this paper, we report the extension of this work to the large, flexible macrobicyclic cryptands.[3] Cryptand 222, upon entrapment of positively charged guests, has been demonstrated to promote the formation of layered assemblies.[4,5] Within the proton-rich liquid clathrate we anticipated that internal protonation would lead to the formation of a discrete, spherical, cationic cryptand species possibly also inducing the assembly of a solid-state layered structure. To our surprise, the protonation led to the formation of a chiral dication. Herein we report the solution behavior and the first solid-state characterization of the 222-2H$^+$ dication.

Compound **1** was prepared in a toluene solution according to (1).[6] The formation of two liquid layers was

$$\text{cryptand 222} + HCl_g + H_2O \rightarrow (H_3O^+)_2[222\text{-}2H^+]Cl_4{\cdot}4H_2O \quad (1)$$

apparent over a period of approximately 10 min after the addition of HCl_g to the cryptand solution. Colorless crystals suitable for X-ray diffraction were obtained from the lower layer by allowing the reaction mixture to stand at −10 °C over a period of 1 week.

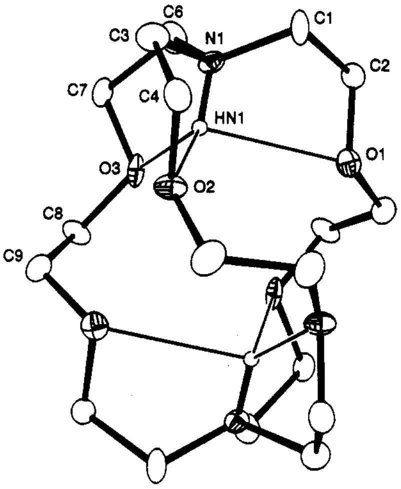

Figure 1. X-ray crystal structure of the 222-2H$^+$ dication. Selected interatomic distances (Å): N1···N1 = 5.71(2), N1−HN1 = 1.04(1), N1···O1 = 2.76(1), N1···O2 = 2.80(2), N1···O3 = 2.75(2), O1···HN1 = 2.539(6), O2···HN1 = 2.10(1), O3···HN1 = 2.26(1).

The X-ray crystal structure of one of the two independent 222-2H$^+$ dications is shown in Figure 1. Both are observed to lie on crystallographic 2-fold axes and adopt conformations with approximate D_3 symmetry. Endo protonation of the macrobicycle leads to the formation of two *intra*ionic trifurcated[7] N$^+$−H···O hydrogen bonds, and hence, an *in−in* conformation is adopted by each cryptate. As a result, the dications are chiral as a consequence of the twisting of the bridging chains. This result supports recent molecular dynamics simulations on the mono- and diprotonated cryptand 222 which favor *endo*- versus *exo*-protonation and internal hydrogen bonding.[8] The cavity of the ligand in **1** parallels the trigonal antiprism coordination polyhedra of the alkali metal cryptates.[9] All six oxygen atoms are directed inward toward the cavity as demonstrated by NCCO torsion angles which range from −53.7(7)° to −58.3(8)°. The nonbonding N···N distances (5.71 Å) are slightly shorter than those in the highly stable K$^+$ complex (5.75 Å),[10] while the average distance between the edges of the triangular faces[11] (3.74 Å) is similar to the $CaBr_2{\cdot}3H_2O$ complex (3.72 Å),[12] but smaller than in the K$^+$ cryptate (4.26 Å).[10] The corresponding N···N distances in the empty cryptand[13] and the *N,N'*-dimethylcryptand 222 diiodide salt[14] are 6.87 Å and 6.67 Å, respectively. The

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(6) In a typical experiment cryptand 222 (0.20 g, 0.53 mmol) was moistened with distilled water (0.01 mL, 0.53 mmol) and subsequently layered with toluene (30 mL). Anhydrous HCl_g was then bubbled through the mixture, resulting in the formation of two liquid layers over a period of ca. 10 min. Colorless crystals of **1** were obtained from the lower layer by allowing the reaction mixture to stand at −10 °C over a period of 1 week. Data collection was conducted on an Enraf-Nonius CAD-4 diffractometer under a liquid nitrogen-cooled gas stream at −100 °C. The space group is the monoclinic $C2$ with a = 14.614(9) Å, b = 8.425(2) Å, c = 25.10(2) Å, β = 100.96(3)°, and D_c = 1.37 g mL for Z = 4. Least-squares refinement based on 2131 observed reflections with $I_{net} > 2.5\sigma(I_{net})$ led to final values of R = 0.084 and R_w = 0.105.

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(11) The triangular faces are defined by the planar arrangement of oxygen atoms O1−O2−O3 and O4−O5−O6.

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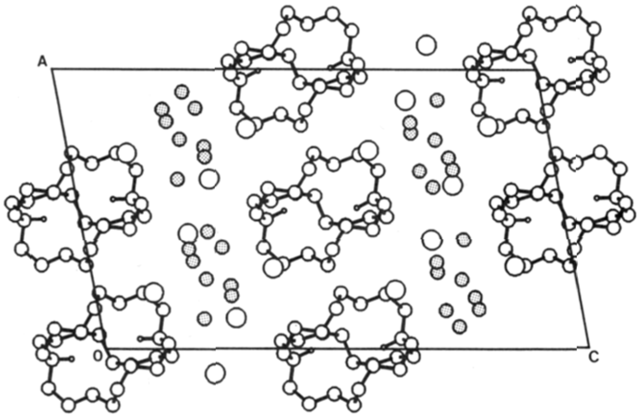

Figure 2. Crystal packing of **1** viewed along the crystallographic *b* axis. Oxonium oxygen atoms are dotted.

reduction of the N···N distance in the 222-2H$^+$ dication compared to the free ligand contrasts to the cryptand 111-2H$^+$ dication in which the N···N separation increases to accommodate the two protons in the cavity.[15]

A view along the crystallographic *b* axis depicting the assembly of **1** is shown in Figure 2. Internal protonation results in an outer hydrophobic surface around the protons. As a result, the guests are shielded from the surrounding ionic medium, and an alternating assembly of hydrophobic and hydrophilic layers is observed. The hydrophobic layer consists of 222-2H$^+$ dications aligned in two dimensions, while the hydrophilic layer is composed of oxonium and chloride ions bound together *via* hydrogen bonding interactions. Similar layered architectures have been reported in the structures of Rb$^+$, Cs$^+$, and Tl$^+$ cryptates.[5] In all cases, the anions possess the ability to form a hydrogen-bonded array and hence assist the assembly process.

Variable temperature ^{1}H NMR and ^{13}C NMR spectra of **1** provide *definitive* evidence for interconverting *in−in*, *in−out*, and *out−out* cryptate conformations.[16] At 253 K, the ^{1}H NMR spectrum[17] in CD_3CN shows a doubling of the number of resonances expected for a single conformer,[18] including two widely separated NH singlets (δ 12.57 and 6.47 ppm) as well as a pair of pseudo quartets assigned to the methylene protons adjacent to each nitrogen atom. The pairing of these signals suggests that protonation has slowed down the rapid *in−in*/*out−out* equilibrium, and discrete conformers are observable on the NMR timescale. Additional signals of less intensity are also observed and are assigned to the asymmetrical *in−out* conformer. Selective irradiation of the broad singlets at 12.57 and 6.47 ppm causes the pseudoquartets at 3.26 and 3.42 ppm, respectively, to broaden indicating that these resonances are coupled to the ammonium protons. The N−H signal at 6.47 ppm is assigned to the *in−in* conformation in accordance with related systems.[19,20] Upon heating the NMR probe to 298 K, the pairing of the spectrum remains while the signals of the *in−out* conformer, two triplets (δ 3.95 and 3.89 ppm), two multiplets (δ 3.64 and 3.58 ppm), and two pseudoquartets (δ 3.46 and 3.35 ppm) become better resolved. The ^{13}C NMR spectrum[21] of **1** at this temperature exhibits resonances corresponding to six inequivalent carbon atoms consistent with slowly interconverting *in* and *out* conformers rather than the previously suggested restricted N−C bond rotation of D_3 structures.[16a,22] As with the ^{1}H NMR data, peaks of less intensity attributed to the *in−out* conformer are also present. At 350 K resonances assigned to the NH protons in the ^{1}H NMR spectrum broaden into the base line, and the *in−out* methylene signals coalesce with those of the major conformations. At 405 K in DMSO-d_6 the methylene peaks coalesce into three broad singlets (relative intensities 1:1:1) suggesting that interconversion between the three conformational isomers is rapid at this temperature.

The results reported herein address the importance of molecular recognition. Simple protonation of cryptand 222 has induced a convergence of etheral binding sites, thereby "switching" the ligand to a solid-state chiral conformation reminiscent of spherical cation cryptates. In solution, direct evidence supporting the interconversion of *in* and *out* conformers has also been established. These observations may bear relevance to separations problems since metal cryptates have been shown to decomplex under acidic conditions,[23] while the cryptand ligand may act as a cation carrier from aqueous to organic phases[24] in a way similar to that for macrocycle-based liquid clathrate systems.

Acknowledgment. We are grateful for funding from the National Science Foundation, the Natural Sciences and Engineering Research Council of Canada (NSERC) for a research fellowship (L.R.M.), and the International Centre For Diffraction Data for a research scholarship (L.R.M.).

Supporting Information Available: Crystallographic report and tables of positional and thermal parameters, bond lengths and angles (5 pages).

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(17) ^{1}H NMR data (CD_3CN, 500 MHz, −20 °C, δ/ppm, J/Hz): for **1**, *out−out* δ 12.57 (bs, 2H, NH), 3.83 (t, 2H, $^3J = 5.4$, $-CH_2O$), 3.53 (s, 2H, OCH_2CH_2O), 3.26 (pseudo q, 2H, $J_{obs} = 4.9$, $^+N\text{-}CH_2$); *in−in* δ 6.47 (bs, 2H, NH), 3.73 (t, 2H, $^3J = 4.9$, $-CH_2O$), 3.61 (s, 2H, OCH_2CH_2O), 3.42 (pseudo q, 2H, $J_{obs} = 5.0$, $^+NCH_2$); *in−out* δ 3.92 (t, 2H, $^3J = 5.3$, $-CH_2O$), 3.60 (m, 2H, OCH_2CH_2O), 3.32 (pseudo q, 2H, $J_{obs} = 5.0$, $^+$-NCH_2); (25 °C) *out−out* δ 12.80 (bs, 2H, NH), 3.89 (t, 2H, $^3J = 5.6$, $-CH_2O$), 3.58 (s, 2H, OCH_2CH_2O), 3.32 (pseudo q, 2H, $J_{obs} = 5.0$, $^+$-NCH_2); *in−in* δ 6.74 (bs, 2H, NH), 3.77 (t, 2H, $^3J = 5.40$, $-CH^2O$), 3.67 (s, 2H, OCH_2CH_2O), 3.45 (pseudo q, 2H, $J_{obs} = 5.0$, $^+NCH_2$); *in−out* δ 3.95 (t, 2H, $^3J = 5.5$, $-CH_2O$), 3.89 (t, 2H, ^3J (masked), $-CH_20$), 3.64 (m, 2H, OCH_2CH_2O), 3.58 (m, 2H, OCH_2CH_2O), 3.46 (pseudo q, 2H, $J_{obs} = 5.6$, $^+NCH_2$), 3.35 (pseudo q, 2H, $J_{obs} = 5.1$, $^+NCH_2$).

(18) ^{1}H NMR data (CD_3CN, 250 MHz, 25 °C, δ/ppm, J/Hz): for cryptand 222 δ 3.59 (s, 2H, OCH_2CH_2O), 3.53 (t, 2H, $^3J = 5.7$, $-CH_2O$), 2.57 (t, 2H, $^3J = 5.7$, $-CH_2N$).

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(21) ^{13}C NMR data (CD_3CN, 126 MHz, 25 °C, δ/ppm): for **1**, *in−in*/*out−out* δ 71.53 ($-CH_2O$), 71.09 ($-CH_2O$), 66.07 ($-CH_2O$), 64.29 ($-CH_2O$), 54.31 ($^+NCH_2$), 53.03 ($^+NCH_2$); *in−out* 71.23 ($-CH_2O$), 70.42 ($-CH_2O$), 65.87 ($-CH_2O$), 54.66 ($^+NCH_2$), 52.51 ($^+NCH_2$).

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