Structural consequences of competing noncovalent forces: the out–out conformation of the doubly protonated [2.2.2]cryptand

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The reaction of [2.2.2]cryptand 1 with 2,6-dihydroxybenzoic acid (dhbH) in toluene affords the complex [1-2H]-[(2,6-dhb)₂]; its crystal structure exhibits the first solid state evidence of the out–out form of the doubly protonated macrobicycle and illustrates the role of C–H···O hydrogen bonds in providing additional stability to the cavity of the ligand.

Although it is now generally accepted that noncovalent interactions (*e.g.* hydrogen bonds, π–π interactions, ion pairs) play an important role in determining the conformation and corresponding ionophoric properties of macro(poly)cyclic receptors (*e.g.* crown ethers, cryptands)[1] in solution,[2a] the gas phase,[2b] and the solid state,[2c] less is known about their structure determining roles in the presence of competing forces.[3] This is, perhaps, not surprising considering the difficulty in generating and analysing discrete, multi-component supramolecular assemblies and delineating the contributions of each interaction to the resulting structure.[4] Indeed, understanding the cooperativity[5] exhibited by noncovalent interactions, especially in the context of molecular recognition processes, promises to yield insight into areas of both chemical and biological relevance including the nucleation and crystallization of molecules[6] and the mechanisms by which the secondary structures of proteins (*e.g.* α-helices) are formed.[3]

Extensive work has demonstrated the self-assembly of proton cryptate complexes of the flexible macrobicyclic ionophore [2.2.2]cryptand 1 with inorganic anions isolated from liquid clathrate media.[7] In particular, we have illustrated the ability of two trifurcated intraionic N⁺–H···O hydrogen bonds to slow down its rapid in–in, in–out, and out–out equilibrium[8] in solution and reorganize its structure to a chiral, in–in conformation with approximate D_3 symmetry in the solid state.[7a] In such a context, recent molecular dynamics simulations have shown the doubly protonated in–in form of 1 to be more stable than its corresponding out–out conformer by 21 kcal mol⁻¹.[9] This additional stability has been attributed, in part, to the intraionic N⁺–H···O hydrogen bonds within the cavity.

As part of our ongoing studies of proton cryptates, we now report the synthesis and X-ray crystal structure of a complex, [1-2H][(2,6-dhb)₂] 2 (dhb = dihydroxybenzoate, dhbH = dihydroxybenzoic acid), which provides the first solid state evidence of the out–out form of the doubly protonated 1. The complex exhibits two 2,6-dhb ions which interact with the outer surface of the cryptate *via* two interionic N⁺–H···O⁻ hydrogen bonds. As a consequence of these interactions, the ligand has undergone a structural reorganization from the in–in form, by breakage of its internal N⁺–H···O hydrogen bonds, to the out–out conformation. Furthermore, in response to this reorganization, the ligand has formed four intraionic C–H···O interactions[10] inside its cavity. Such observations provide insight into molecular recognition processes involving hydrogen bond cooperativity where understanding the structural consequences of competing noncovalent forces is of much current interest.[5a,b]

Addition of 1 (0.040 g) to a hot toluene solution (40 ml) containing 2,6-dhbH (0.033 g) according to eqn. (1) imme-

$$1 + 2(2,6\text{-dhbH}) \rightarrow [1\text{-}2H][(2,6\text{-dhb})_2] \ 2 \qquad (1)$$

diately yielded a white precipitate 2. Colourless crystals of 2 suitable for X-ray analysis were obtained by dissolving a portion of the precipitate in MeCN and allowing the solution to evaporate to dryness. The formulation of 2 was confirmed by single-crystal X-ray diffraction‡ and analytical data.§

An ORTEP perspective of 2 is shown in Fig. 1. *Exo* protonation leads to the formation of two interionic N⁺–H···O⁻ hydrogen bonds between constituent ions, and hence, an out–out conformation is adopted by the cryptate. As a result, the cavity of the ligand is substantially distorted from approximate D_3 symmetry. This is illustrated by N(1)–CCO and N(2)–CCO torsion angles, which range from −65.6 to 171.1° and −60.0 to 174.4°, and the distances for the edges of each triangular face, which range from 4.228 to 4.931 Å and 4.070 to 4.867 Å, for atoms O(1), O(3), O(5) and O(2), O(4), O(6), respectively.¶ These values compare favourably to those of the *N,N′*-dimethyl-1 diiodide salt[13] and the bisborohydride of 1[14] which adopt similar *exo* conformations owing to the bulk of the substituents which precludes their entrance in the cavity. The corresponding torsion angles and O···O separations in [H₃O]₂[1-2H][4Cl]·4 H₂O 5 range from −53.7(7) to −58.3(8)° and 3.69(2) to 3.79(2) Å, respectively.[7a] Furthermore, the nonbonding N···N separation (6.33 Å), which is shorter than that of the empty cryptand (6.87 Å),[14] is longer than in 5 (5.71 Å) but comparable to that of 3 (6.67 Å) and 4 (6.77 Å).

The geometry of the cavity of the cryptate in 2 may be attributed to the contributions of four C–H···O hydrogen bonds involving four α-hydrogen atoms, from two different methylene groups, and the four ethereal oxygen atoms which are directed inward toward the cavity. Indeed, Fig. 1 illustrates that *exo* protonation facilitates inversion at each bridgehead nitrogen
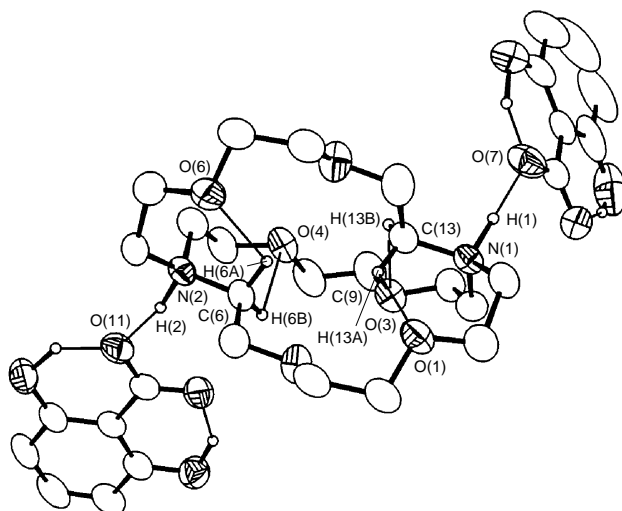
Fig. 1 X-Ray crystal structure of 2. Selected interatomic distances (Å) and angles (°): N(1)···O(7) 2.687(4), N(1)–H(1)–O(7) 177(2), N(2)···O(11) 2.689(4), N(2)–H(2)–O(11) 166(2), C(6)···O(4) 3.010(4), C(6)–H(6B)–O(4) 111, C(6)···O(6) 2.919(4), C(6)–H(6A)–O(6) 110, C(13)···O(3) 3.042(4), C(13)–H(13B)–O(3) 117, C(13)···O(1) 2.964(4), C(13)–H(13A)–O(1) 117.
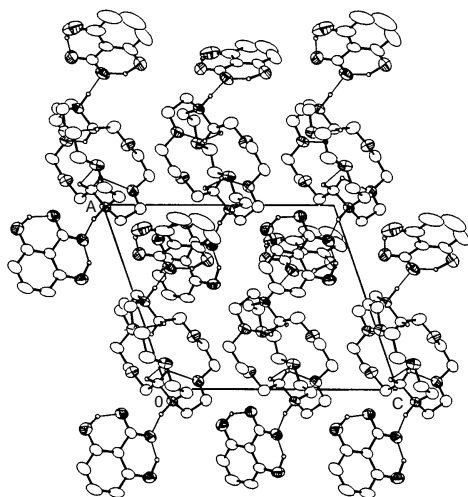
Fig. 2 Crystal packing of **2** viewed along the crystallographic *b* axis

atom which subsequently enables one methylene group at each end of the cryptate to extend its hydrogen atoms inside the cavity and form the C–H···O interactions.‖ The ability of C–H···O hydrogen bonds to provide structural stability to macrocyclic polyether components (*e.g.* cyclophanes) is known[15] and there is growing evidence that such interactions play a role in stabilizing the tertiary structures of bio-molecules.[16] To our knowledge, this is the first case in which C–H···O hydrogen bonds have been recognized to impart conformational stability to the out–out topology of **1**.

A view along the crystallographic *b* axis depicting the crystal structure of **2** is shown in Fig. 2. The assembly process results in an alternating assembly of aliphatic and aromatic layers, involving cations and anions, respectively, within the *ac* plane. Interestingly, **5** exhibits a similar layered architecture despite the fact that its proton cryptate adopts the in–in topology.[7a]

The results reported herein lie at the heart of molecular recognition. By simply introducing an appropriate hydrogen bond acceptor along its outer surface, the [**1**-2H]²⁺ ion has undergone a structural reorganization, *via* breakage of its internal N⁺–H···O hydrogen bonds, to the out–out form which recognizes the anion *via* interionic N⁺–H···O⁻ interactions. In response, the cryptate has formed four C–H···O interactions inside its cavity. Such observations may provide insight into understanding those factors which influence the secondary structures of proteins since similar competing noncovalent forces are thought to play a role in contributing to their stability.[3a]

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Footnotes

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‡ *Crystal data* for [**1**-2H][(2,6-dhb)₂]; monoclinic, space group *P*2₁/*c*, *a* = 12.346(1), *b* = 20.519(1), *c* = 14.626(1) Å, β = 109.27(4)°,

U = 3497(1) Å³, *D*_c = 1.30 g cm⁻¹, Cu-Kα radiation (λ = 1.54060 Å) for *Z* = 4. Least-squares refinement based on 3206 reflections with $I_{net} > 2.0\sigma(I_{net})$ (out of 5176 unique reflections) collected on an Enraf Nonius CAD-4 diffractometer equipped on a rotating anode generator and 449 parameters on convergence gave a final value of *R* = 0.063. Methylene, aromatic and hydroxy hydrogen atoms were placed by modelling the moieties as rigid groups with idealised geometry, maximising the sum of the electron density at the calculated hydrogen positions. Quaternary ammonium hydrogen atoms were loacted *via* inspection of a difference Fourier map and refined at a restrained distance of 1.10 Å from the N atoms to which they are bonded. Structure solution was accomplished with the aid of SHELXS-86[11] and refinement was conducted using SHELX93[12] locally implemented on a pentium-based IBM compatible computer. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/361.

§ Anal. Calcd: C, 56.13; H, 7.07; N, 4.09. Found: C, 56.30; H, 7.00; N, 4.06.

¶ Two oxygen atoms from each triangular face [O(1), O(3) and O(4), O(6)] are directed inward toward the cavity.

‖ We have recently demonstrated the ability of the α-hydrogen atoms of the [**1**-2H]²⁺ ion to contribute to the structural stability of the cavity of the ligand by participating in a cation–π interaction.[7c]

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