The Fortuitous Discovery of a Synthetic Cationic Molecular Receptor System for Methanol

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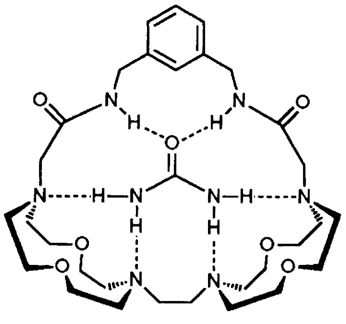
A single crystal X-ray structural study of a diprotonated bis(1,7-diaza-12-crown-4), crystallised from a methanolic solution, reveals that a methanol molecule is bound to each protonated crown *via* both [O–H···N] and [N$^+$–H···O] hydrogen bonds.

A few years ago, we synthesised[1] a range of potential receptors for urea **1**. One of the design concepts (Fig. 1) was the 1 : 1 complex **1·2** involving compound **2** as a potential receptor. We have now determined the crystal structure‡ of the MeOH solvate of **2** and found that the principal interactions are (Fig. 2) intramolecular hydrogen bonds between the amide protons and the oxygen and nitrogen atoms of their adjacent 12-membered rings: it showed no propensity to bind§ urea **1**. Subsequently, we also screened some of the synthetic intermediates (Scheme 1) for their ability to complex with uronium hexafluorophosphate **1**·HPF$_6$. One of these intermediates — 7,7′-bis-benzyl-1,1′-ethylenebis(1,7-diaza-4,10-dioxacyclododecane) **5** — was treated with **1**·HPF$_6$ and the product was recrystallised by diffusion of light petroleum into an EtOAc–MeOH solution. Here, we report (*a*) the synthesis of the bisamide **2** *via* the intermediate **5**, (*b*) their X-ray crystal structures and (*c*) provide evidence in the solid state for the ability of **5**·2HPF$_6$ to bind *two* MeOH molecules.

Compound **5** was obtained (Scheme 1) in 72% yield from the reaction of *N*-benzyl-1,7-diaza-4,10-dioxacyclododecane[2] **3** and ethylene glycol bistosylate **4** with Na$_2$CO$_3$ in MeCN under reflux for 48 h. It was isolated, characterised¶ and crystallised from CHCl$_3$–C$_5$H$_{12}$. Compound **2** was obtained (Scheme 1) by the hydrogenolysis (H$_2$, Pd/C) of **5** in MeOH and subsequent condensation (Na$_2$CO$_3$, MeCN) of the product with 2,2′-dichloro-*N*,*N*′-*meta*-phenylenedimethylene



1·2

Fig. 1 The proposed 6-point binding model for the complexation of urea **1** by the bisamide **2**

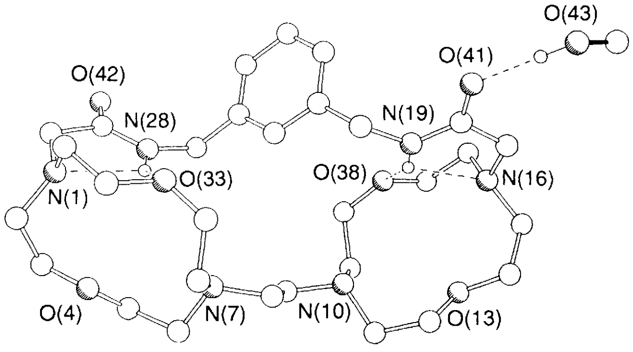


Fig. 2 The structure of **2**·MeOH in the crystal. Transannular [N···N] and [O···O] distances (Å): [N(1)···N(7)], 4.61; [N(10)···N(16)], 4.48; [O(4)···O(33)], 3.53; [O(13)···O(38)], 3.60. Hydrogen bonding geometries [X–H···Y] expressed as [X···Y], [H···Y] distances (Å), [X–H···Y] angle (°): [O(43)–H···O(41)], 2.73, 1.78, 171; [N(19)–H···N(16)], 2.71, 2.21, 111; [N(19)–H···O(38)], 3.02, 2.16, 149; [N(28)–H···N(1)], 2.73, 2.24, 111; [N(28)–H···O(33)], 3.16, 2.31, 148.

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‡ *Crystal data* for **2**·MeOH: $C_{31}H_{54}N_6O_7$, $M = 622.8$, triclinic, space group $P\bar{1}$, $a = 8.609(1)$, $b = 11.804(2)$, $c = 17.811(2)$ Å, $\alpha = 72.93(1)$, $\beta = 87.60(1)$, $\gamma = 76.91(1)°$, $U = 1685$ Å^3, $Z = 2$, $D_c = 1.23$ g cm^{-3}, $\mu = 7$ cm^{-1}.

Crystal data for **5**: $C_{32}H_{50}N_4O_4$, $M = 554.8$, triclinic, space group $P\bar{1}$, $a = 6.250(1)$, $b = 10.715(2)$, $c = 12.405(2)$ Å, $\alpha = 94.43(1)$, $\beta = 99.18(1)$, $\gamma = 104.66(1)°$, $U = 787.6$ Å^3, $Z = 1$ (the molecule is positioned about a centre of symmetry), $D_c = 1.17$ g cm^{-3}, $\mu = 6$ cm^{-1}.

Crystal data for **5**·2HPF$_6$·2MeOH: $C_{34}H_{60}F_{12}N_4O_6P_2$, $M = 910.8$, triclinic, space group $P\bar{1}$, $a = 10.328(2)$, $b = 13.323(3)$, $c = 17.004(4)$ Å, $\alpha = 108.19(2)$, $\beta = 98.70(2)$, $\gamma = 95.72(2)°$, $U = 2170$ Å^3, $Z = 2$, $D_c = 1.39$ g cm^{-3}, $\mu = 18$ cm^{-1}.

Data for the three structures were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. The structures were solved by direct methods and refined anisotropically to give for **2**·MeOH, $R = 0.058$, $R_w = 0.063$ for 2783 independent observed reflections $[|F_o| > 3\sigma(|F_o|), 2\theta \leq 100°]$; for **5**, $R = 0.039$, $R_w = 0.056$ for 1907 independent observed reflections $[2\theta \leq 110°]$; for **5**·2HPF$_6$·2MeOH, $R = 0.060$, $R_w = 0.066$ for 4366 independent observed reflections $[2\theta \leq 100°]$. All computations were carried out using the SHELXTL program system. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ The quest for a synthetic molecular receptor for urea has been responsible for some highly innovative and inspired research in the area of supramolecular chemistry. A variety of approaches has been pursued involving (*a*) crown ethers (*e.g.* J. W. H. M. Uiterwijk, S. Harkema, D. N. Reinhoudt, K. Daasvatn, H. J. den Hertog, Jnr., and J. Geevers, *Angew. Chem. Suppl.*, 1982, 1100; C. J. Staveren, V. M. L. J. Aarts, P. D. J. Grootenhuis, W. J. H. Droppers, J. van Eerden, S. Harkema and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1988, **110**, 8134); (*b*) transition metal–crown ether co-complexes (C. J. van Staveren, J. van Eerden, F. C. J. M. van Veggel, S. Harkema and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1988, **110**, 4994; W. F. Nijenhuis, A. R. van Doorn, A. M. Reichwein, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1991, **113**, 3607); (*c*) acyclic polyethers (F. Vögtle, H. Sieger and W. M. Müller, *Top. Curr. Chem.*, 1981, **98**, 107), and molecular clefts (T. W. Bell and J. Liu, *J. Am. Chem. Soc.*, 1988, **110**, 3673; V. Hedge, P. Madhukar, J. D. Madura and R. P. Thummel, *J. Am. Chem. Soc.*, 1990, **112**, 4549; M. Crego, J. J. Marugán, C. Raposo, M. J. Sanz, V. Alcázar, M. C. Caballero and J. R. Morán, *Tetrahedron Lett.*, 1991, **32**, 4185).

¶ *Spectroscopic data* for **2**: colourless crystals, m.p. 150–152 °C, (Found: *M* (EIMS), 590. Calc. for $C_{30}H_{54}N_6O_6$: *M*, 590). ^{1}H NMR (CD$_2$Cl$_2$, 250 MHz), δ 2.17–2.90 (20H, br m), 3.15–3.62 (20H, br m), 4.44 (4H, d), 7.12–7.28 (4H, m), 8.68–8.90 (2H, br t).

Spectroscopic data for **5**: colourless crystals, m.p. 73–74 °C, (Found: *M* (EIMS), 554. Calc. for $C_{32}H_{50}N_4O_4$: *M*, 554). ^{1}H NMR (CDCl$_3$, 220 MHz), δ 2.68 (4H, s), 2.70–2.80 (16H, m), 3.54–3.72 (16H, m), 4.65 (4H, s), 7.17–7.42 (10H, m).

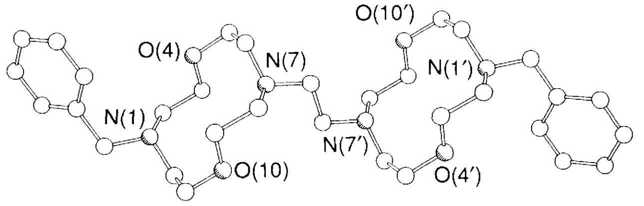


Fig. 3 The structure of **5** in the crystal. The transannular [N···N] and [O···O] distances are 4.30 and 4.32 Å, respectively.

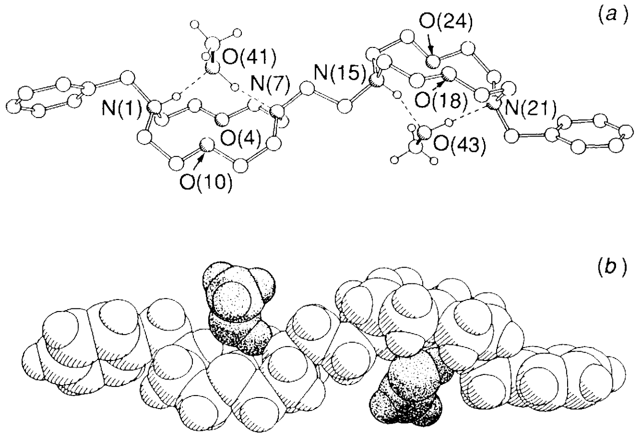
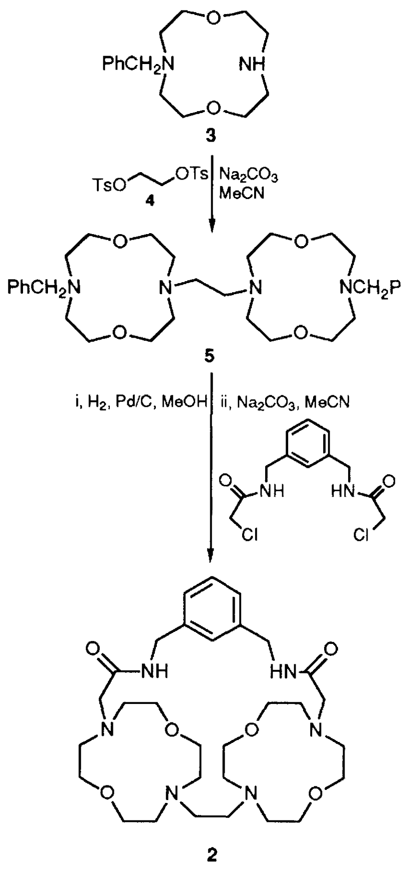


Fig. 4 (*a*) Framework and (*b*) space-filling representations of the structure of $5 \cdot 2HPF_6 \cdot 2MeOH$ in the solid state. In the space-filling representation, the two MeOH molecules are shaded. Transannular [N···N] and [O···O] distances (Å): [N(1)···N(7)], 4.60; [N(15)···N(21)], 4.49; [O(4)···O(10)], 3.02; [O(18)···O(24)], 3.08. Hydrogen-bonding geometries [X–H···Y] expressed as [X···Y], [H···Y] distances (Å), [X–H···Y] angle (°): [N(1)–H···O(41)], 2.78, 1.83, 169; [O(41)–H···N(7)], 2.91, 1.82, 168; [N(15)–H···O(43)], 2.73, 1.81, 162; [O(43)–H···N(21)], 2.82, 1.82, 178.



Scheme 1

bisacetamide.[1] It was isolated, characterised¶ and crystallised from an EtOAc–MeOH solution layered with light petroleum in an overall yield of 21%.

The solid-state structure‡ (Fig. 3) of **5** has crystallographic C_i symmetry and shows that both 12-membered rings adopt a [66] conformation.[3,4] In addition to the fact that the oxygen atoms are pointing in opposite directions, the nonbonding electron pairs on the nitrogen atoms are also directed over opposite faces of the macrocycles.

The X-ray crystal structure‡ (Fig. 4) of the product of the treatment of **5** with $\mathbf{1} \cdot HPF_6$ in MeOH revealed that, though no $\mathbf{1} \cdot HPF_6$ was present in the crystal lattice, *two* molecules of MeOH were intimately bound, one to each diaza-12-crown-4 macrocycle in $\mathbf{5} \cdot 2HPF_6$. Furthermore, selective protonation was observed to have occurred in a constitutionally unsymmetrical manner within **5**. The transfer of a proton from a uronium salt to the diaza-crown nitrogen atoms is not unexpected, taking into account the difference in pK_a values[5] between urea (*ca.* 0.1) and tertiary alkyl amines (*ca.* 10–11). The binding of each MeOH molecule is *via* both [O–H···N] (2.82, 2.91 Å) and [N^+–H···O] (2.73, 2.78 Å) hydrogen bonds. An important feature of this association between neutral MeOH molecules and the monoprotonated diaza-12-crown-4 units is an appealing logical variation of the two-point binding model observed[6] previously for primary alkyl and secondary dialkyl ammonium ions with neutral diaza-12-crown-4 systems. Whereas in the latter situation, positively charged guests are complexed by *neutral hosts*, in the former, the positive charge is located within the host which thence binds *neutral guests*.[7] In this manner, strong association of a pole–dipole type is preserved, *i.e.* it is immaterial whether the charge resides in the host or in the guest. As a result of alcohol consumption the diaza-12-crown-4 macrocycles both adopt a [48] conformation[3] wherein both nitrogen atoms within each macrocycle are directed over one face of their parent 12-membered ring. The oxygen atoms, on the other hand, are still essentially positioned 'one up and one down', though one CH_2OCH_2 group within each macrocycle lies close to the mean planes of their associated macrocycles. This results in transannular [O···O] distances of *ca.* 3 Å.

The fortuitous discovery of a synthetic cationic molecular receptor system for alcohols|| is a salutary reminder of

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|| Different approaches have been employed for the demanding task of recognising alcohols selectively. These include the involvement of (*a*) clathrates (*e.g.* see F. Toda, K. Okada and T. C. W. Mak, *Chem. Lett.*, 1988, 1829; D. Worsch and F. Vögtle, *J. Incl. Phenom.*, 1986, 163; S. A. Bourne, L. R. Nassimbeni, K. Skobridis and E. Weber, *J. Chem. Soc., Chem. Commun.*, 1991, 282; M. Czugler and E. Weber, *J. Incl. Phenom.*, 1991, **10**, 355); (*b*) cyclodextrins (Y. Matsui, K. Mochida, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 2808; A'. B. A'ri, J. Szejtli and L. Barcza, *J. Incl. Phenom.*, 1983, **1**, 151); (*c*) cyclophanes (K. Kobiro, M. Takahashi, N. Nishikawa, K. Kakiuchi, Y. Tobe and Y. Odaira, *Tetrahedron Lett.*, 1987, **28**, 3825; Y. Kikuchi, Y. Kato, Y. Tanaka, H. Toi and Y. Aoyama, *J. Am. Chem. Soc.*, 1991, **113**, 1349); (*d*) crown ethers (E. Weber, H.-P. Josel, H. Puff and S. Franken, *J. Org. Chem.*, 1985, **50**, 3125); (*e*) vanadium bilayers (J. W. Johnson, A. J. Jacobson, W. M. Butler, S. E. Rosenthal, J. F. Brody and J. T. Lewandowski, *J. Am. Chem. Soc.*, 1989, **111**, 381); and (*f*) other miscellaneous receptors (B. Dung and F. Vögtle, *J. Incl. Phenom.*, 1988, **6**, 429; W. Moneta, P. Baret and J.-L. Pierre, *J. Chem. Soc., Chem. Commun.*, 1985, 899; T. I. Richards, K. Layden, E. E. Warminski, P. J. Milburn and E. Haslam, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2765).

Note added in proof: Since this communication was submitted for publication, novel boron-containing crown ethers (M. T. Reetz, C. M. Niemeyer and K. Harms, *Angew. Chem.*, 1991, **103**, 1515; *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1472) have been shown (M. T. Reetz, C. M. Niemeyer and K. Harms, *Angew. Chem.*, 1991, **103**, 1517; *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1474, to bind alcohols, such as MeOH, EtOH, Pr^iOH, and $PhCH_2OH$, with good selectivities in the presence of amines like $PhCH_2NH_2$ or $PhCHMeNH_2$.

the serendipitous element which pervades supramolecular chemistry.

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7 For another example of the use of cationic receptors for the complexation of neutral guests, see B. Odell, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1547; P. R. Ashton, B. Odell, M. V. Reddington, A. M. Z. Slawin, J. F. Stoddart and D. J. Williams, *Angew. Chem. Int. Ed. Engl.*, 1988, **27**, 1550; T. T. Goodnow, M. V. Reddington, J. F. Stoddart and A. E. Kaifer, *J. Am. Chem. Soc.*, 1991, **113**, 4335; M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, C. Vicent and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1991, 630; D. Philp, A. M. Z. Slawin, N. Spencer, J. F. Stoddart and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1991, 1584.