

Solvent-mediated self-association of a Horning-crown macrocycle†

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A member of a new class of novel macrocycles possessing both polyether and phenolic functionalities, forms dimers in both the solid-state and in solution when exposed to chloroform, dichloromethane or toluene, but does not self-associate in the presence of dimethyl sulfoxide.

Self-associating supramolecular assemblies have been obtained by incorporation of complementary groups to form, amongst other motifs, capsules¹ or 'daisy chains'.² Although hydrogen-bonding is usually the primary driving force for such systems, macrocycles that self-associate by other means have also been reported. For example, Cram's 'velcrams' dimerise through shape-complementarity, van der Waals interactions and solvophobic effects.³ Macrocyclic arylene-ethynylene macrocycles aggregate via $\pi\cdots\pi$ stacking interactions.⁴ Two novel macrocycles that persist as non-covalent dimers in the solid, with the predominant interactions involving aromatic stacking, have also been reported.⁵

We now report a macrocycle with two 2,6-bis(benzyl)phenol units that exhibits remarkable self-complementarity both in the solid-state and in solution. Most interesting, however, and as shown herein, the self-complementarity is solvent-dependent.

3,4:9,10:18,19:24,25-Tetrabenzo-5,8,20,23-tetraoxa-tricyclo-[25.3.1^{12,16}]dotriaconta-1(30),3,9,12,14,16(32),18,24,27(31),28-decaene-31,32-diol **1** belongs to a new class of modularly constructed macrocycles that we have developed and termed Horning-crowns,⁶ family members of which have at least one phenolic unit, reminiscent of calixarenes and one polyether moiety, typical of crown ethers. Analyses of crystal structures of a number of solvate crystals of this macrocycle revealed interesting solvent-controlled conformational dependency.⁷

In the simplest case, solvent-free crystals isolated from DMSO, single crystal structure analysis[‡] revealed macrocycles in a stepped conformation with two unique phenol OH to ether –O– intramolecular hydrogen bonds: O1 \cdots O2: *d* O \cdots O 2.812(2) Å, *d* H \cdots O, 1.91(2) Å, \angle H–O \cdots H 165(2)°; O4 \cdots O5: *d* O \cdots O 2.680(2) Å, *d* H \cdots O, 1.77(2) Å, \angle H–O \cdots H 159(2)°. These packed so that CH \cdots π interactions with neighbouring molecules were maximised, Fig. 1 and Table 1.

Crystallisation from a variety of other solvents yielded dimeric macrocycle structures. For example, **1** crystallised as a 1 : 1 solvate by slow evaporation from dichloromethane solution. The low temperature crystal structure[§] exhibited clasped dimeric pairs of macrocycles associated by van der Waals interactions, with highly disordered dichloromethane molecules occupying channels. The crystals were highly susceptible to desolvation and the dichloromethane escaped readily.

The macrocycle adopted a twisted conformation (Fig. 2), creating a deep cleft, which accommodated a second macrocycle to form a dimer (> 10 Å measured across the π -stacked system and > 20 Å in the longest dimension). These dimers packed together, with only van der Waals interactions, in quite different arrays in the various solvate crystals isolated.

Self-association of **1** was readily detectable in solution. The ¹H NMR chemical shifts of protons H_{a,c-e} displayed remarkable

concentration dependence in CDCl₃. For example, the chemical shift of the etheral proton (H_c) moved upfield from δ 4.31 to 3.64 as the concentration increased from 4.36×10^{-5} to 3.78×10^{-2} M at 303 K. The upfield shift is typical of the anisotropic shielding effect resulting from the $\pi\cdots\pi$ stacking interactions.⁸ Assuming that monomer–dimer equilibrium is the predominant process of self association,⁹ the dimerisation constant can be determined from ¹H NMR measurements at different concentrations using a reported procedure.¹⁰ The self-association constant in CDCl₃ was determined to be 100(4) M⁻¹ at 303 K (triplicate determination) while no concentration dependent change in δ was detected in DMSO-*d*₆ solutions.

Reduction in temperature led to broadening of most signals in the ¹H NMR spectrum. However, at 168 K, a resolved spectrum, ascribed to the macrocycle in its dimeric form, was observed. The methylene hydrogen atoms (H_c) of the etheral bridge were resolved into 8 signals ranging from δ = 1.5 to 4.3 ppm, Fig. 3. This indicated a large shielding effect on the hydrogen atoms contained in the centre of the dimer compared with limited shielding for those exposed on the outside, Fig. 4. Similarly one of the four aromatic protons of both H_d and H_e shifted upfield from δ = 6.61 to 4.75 and 6.93 to 5.57 (shifts of 1.86 and 1.36 ppm respectively). These signals were assigned to the protons of the macrocycle that lie deep in the cleft of the dimeric structure. Further, the two signals of the phenolic protons reflected the two differing hydrogen-bond environments noted in the crystal structure: O1–H1O \cdots O6: *d* H \cdots O 1.83(2) Å, *d* O \cdots O 2.759(2) Å, \angle OHO 168(2)°; O4–H4O \cdots O3: *d* H \cdots O 2.03(2) Å, *d* O \cdots O 2.871(2) Å, \angle OHO 169(2)°.

Thus, this phenol/ether macrocycle exhibited solvent dependent conformations, from clasped dimers stabilised by $\pi\pi$ interactions (occurring in most solvent systems tested) to an open, staggered conformation, which did not promote self-association, isolated

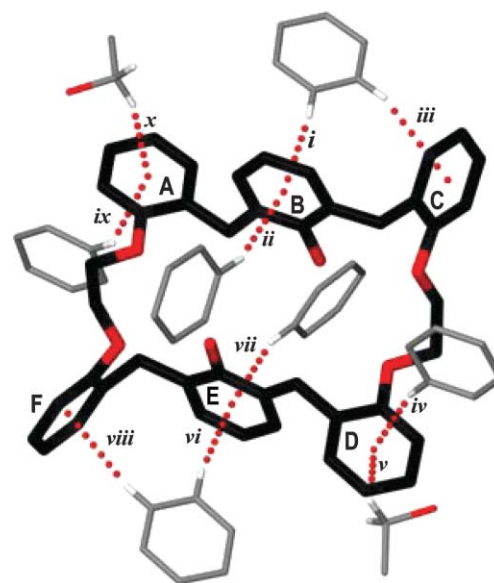


Fig. 1 **1** crystallised from dimethyl sulfoxide (DMSO). The asymmetric unit contains one molecule of **1**, depicted in bold, black 'stick' form. CH \cdots π interactions (numbered) form an infinite network.

† Electronic supplementary information (ESI) available: low temperature COSY spectra; ¹H NMR data, association data and tables of bond lengths and angles. See <http://www.rsc.org/suppdata/cc/b4/b408814j/>

Table 1 CH $\cdots\pi$ interactions in non-solvate crystals of **1**

Interaction		d H \cdots centroid/Å	d C \cdots centroid/Å	\angle CH \cdots centroid/ $^\circ$
<i>i</i>	C43–H43 ^{1-x,1-y,-z...B} ^a	2.701	3.641	170
<i>ii</i>	C28–H28 ^{x-1,y,z...B}	2.812	3.722	161
<i>iii</i>	C42–H42 ^{1-x,1-y,-z...C}	3.093	4.012	143
<i>iv</i>	C25–H25 ^{1-x,1-y,1-z...D}	2.611	3.539	166
<i>v</i>	C7–H7A ^{1-x,-y,1-z...D}	2.727	3.617	150
<i>vi</i>	C32–H32 ^{-x,-y,1-z...E}	2.506	3.444	169
<i>vii</i>	C39–H39 ^{1+x,y,z...E}	2.807	3.709	159
<i>viii</i>	C31–H31 ^{-x,-y,1-z...F}	2.776	3.710	168
<i>ix</i>	C36–H36 ^{-x,-y,-z...A}	2.998	3.844	149
<i>x</i>	C18–H18B ^{-x,1-y,-z...A}	2.942	3.851	153

^a All geometrical parameters are measured relative to the centroid of the acceptor aromatic ring.

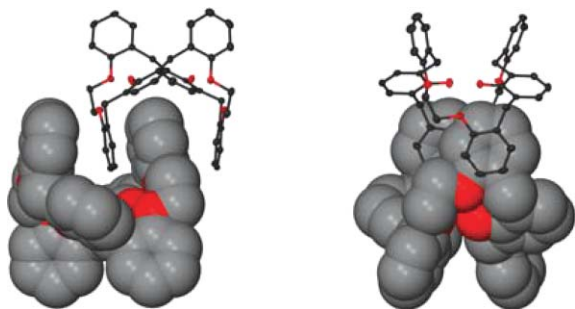


Fig. 2 1-dichloromethane in the solid-state. The macrocycles twist into a butterfly shape forming clapsed dimers (asymmetric unit depicted with ellipsoids at the 50% probability level and symmetry generated macrocycle with atoms at van der Waals radius). Left, side view showing cleft, and right, rotated through 90° showing registration of aromatic rings.

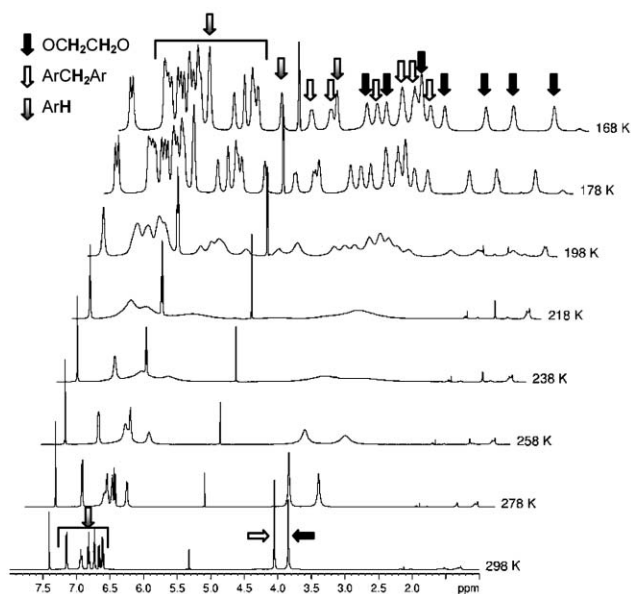


Fig. 3 ¹H-NMR data for **1** (12 mg in 0.8 mL CD₂Cl₂) in the temperature range 168 to 298 K. At low temperature the phenolic proton signal is resolved into two, while signals due to H_c and H_b resolve into 8 individual signals (assigned by reference to low T COSY spectra†).

from polar solvents such as DMSO. In an apparent reversal of the hydrophobic effect, the polar solvent DMSO serves to switch off aggregation to clapsed dimers and this phenomenon may serve as the basis for solvent dependent switching.

Notes and references

† *Crystal data for 1*: C₄₄H₄₀O₆, $M_r = 664.76$, triclinic, space group $P\bar{1}$, $a = 9.2575(2)$, $b = 12.7846(3)$, $c = 14.9507(5)$ Å, $\alpha = 97.761(1)$, $\beta = 95.264(1)$, $\gamma = 103.250(1)^\circ$, $V = 1692.72(8)$ Å³, $Z = 2$, $D_{\text{calc}} = 1.304$ g cm⁻³, $\mu(\text{MoK}\alpha) = 0.086$ mm⁻¹. Of 7937 unique reflections measured, 5091 $I > 2\sigma(I)$, R indices [$I > 2\sigma(I)$] $R_1 = 0.0498$, $wR_2 = 0.1008$, GoF on $F^2 = 1.024$ for 456 refined parameters and 0 restraints. CCDC 242571. See <http://www.rsc.org/suppdata/cc/b4/b408814j/> for crystallographic data in .cif or other electronic format.

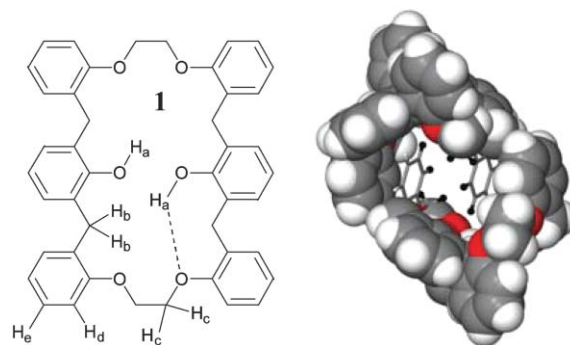


Fig. 4 The hydrogen atoms showing the greatest shift in signal on cooling or at high concentrations correspond to those located in the centre of the dimer.

www.rsc.org/suppdata/cc/b4/b408814j/ for crystallographic data in .cif or other electronic format.

§ *Crystal data for 1-dichloromethane*: C₄₅H₄₂Cl₂O₆, $M_r = 749.69$, triclinic, space group $P\bar{1}$, $a = 10.7695(2)$, $b = 12.4730(2)$, $c = 14.8399(4)$ Å, $\alpha = 82.229(1)$, $\beta = 71.597(1)$, $\gamma = 81.080(1)^\circ$, $V = 1860.66(7)$ Å³, $Z = 2$, $D_{\text{calc}} = 1.248$ g cm⁻³, $\mu(\text{MoK}\alpha) = 0.225$ mm⁻¹. Of 8882 unique reflections 5024 had $I > 2\sigma(I)$, R indices [$I > 2\sigma(I)$] $R_1 = 0.0505$, $wR_2 = 0.1148$, GoF on $F^2 = 0.978$ for 512 refined parameters and 0 restraints. CCDC 242572. See <http://www.rsc.org/suppdata/cc/b4/b408814j/> for crystallographic data in .cif or other electronic format.

- 1 F. Hof, S. L. Craig, C. Nuckolls and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 2002, **41**, 1488.
- 2 (a) P. R. Ashton, I. Baxter, S. J. Cantrill, M. C. T. Fyfe, P. T. Glink, J. F. Stoddart, A. J. P. White and D. J. Williams, *Angew. Chem., Int. Ed.*, 1998, **37**, 1294; (b) P. J. Ashton, I. W. Parsons, F. M. Raymo, J. F. Stoddart, A. J. P. White, D. J. Williams and R. Wolf, *Angew. Chem., Int. Ed.*, 1998, **37**, 1913; (c) S. J. Cantrill, G. J. Youn, J. F. Stoddart and D. J. Williams, *J. Org. Chem.*, 2001, **66**, 6857; (d) S. J. Coles, M. B. Hursthouse, A. Kilic and G. Y. Ciftci, *Acta Crystallogr., Sect. E*, 2002, **58**, o83; (e) O. P. Kryatova, S. V. Kryatov, R. J. Staples and E. V. Rybak-Akimova, *Chem. Commun.*, 2002, 3014; (f) O. P. Kryatova, I. V. Korendovych and E. V. Rybak-Akimova, *Tetrahedron Lett.*, 2003, **44**, 4251
- 3 (a) D. J. Cram, H. J. Choi, J. A. Bryant and C. B. Knobler, *J. Am. Chem. Soc.*, 1992, **114**, 7748; (b) J. A. Bryant, C. B. Knobler and D. J. Cram, *J. Am. Chem. Soc.*, 1990, **112**, 1254; (c) J. A. Bryant, J. L. Ericson and D. J. Cram, *J. Am. Chem. Soc.*, 1990, **112**, 1255.
- 4 (a) J. Zhang and J. S. Moore, *J. Am. Chem. Soc.*, 1992, **114**, 9701; (b) Y. Tobe, N. Utsumi, K. Kawabata and K. Naemura, *Tetrahedron Lett.*, 1996, **37**, 9325; (c) Y. Tobe, N. Utsumi, K. Kawabata, A. Nagano, K. Adachi, S. Araki, M. Sonoda, K. Hirose and K. Naemura, *J. Am. Chem. Soc.*, 2002, **124**, 5350; (d) D. Zhao and J. S. Moore, *Chem. Commun.*, 2003, 807.
- 5 (a) H. M. Colquhoun, F. Arico and D. J. Williams, *New J. Chem.*, 2002, **26**, 1703; (b) I. Baxter, D. J. Williams, A. Ben-Haida, P. Hodge, F. H. Kohnke and H. M. Colquhoun, *Chem. Commun.*, 1998, 2213.
- 6 L. T. Higham, U. P. Kreher, C. L. Raston, J. L. Scott and C. R. Strauss, *Org. Lett.*, 2004, in press.
- 7 The dimeric nanoballs crystallise from numerous other solvents including: chloroform, toluene, pyridine, and aniline.
- 8 H. Friebolin, *Basic One- and Two-Dimensional NMR Spectroscopy*, 2nd Edition, VCH, Weinheim, 1993, pp. 45–48.
- 9 M. Saunders and J. B. Hyne, *J. Chem. Phys.*, 1958, **29**, 1319.
- 10 I. Horman and B. Dreux, *Helv. Chim. Acta*, 1984, **67**, 754.