Water-soluble macrocyclic receptors for small neutral guests

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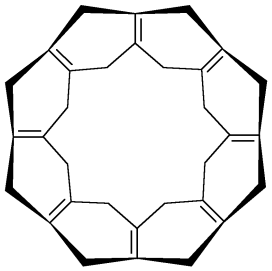
Two new water-soluble dicationic spiro-cyclophanes, **1** and **2**, with CH_2 and $(CH_2)_2$ links between phenolic oxygens, have been prepared and characterised crystallographically. The binding properties of these cyclophanes have been compared with those of seven other water-soluble macrocycles: Diederich-type cyclophanes with $(CH_2)_3$ and $(CH_2)_4$ links, (**3** and **4**), Stoddart's cyclophane (**5**), α-cyclodextrin (**6a**), 2,6-dimethyl-α-cyclodextrin (**6b**), 2,3,6-trimethyl-α-cyclodextrin (**6c**) and β-cyclodextrin (**7**). The affinities of all nine macrocycles for 1,6-hexanediol (**8**) and hexa-2,4-diyne-1,6-diol (**9**) in D_2O were investigated by ^1H NMR. The strongest binding was observed between **9** and 2,6-dimethyl-α-cyclodextrin (**6b**) ($K = 1.2 \times 10^3$ M^{-1}). The alkyne diol **9** also forms a 1 : 2 complex with β-cyclodextrin (**7**) ($K_1 = 18$ M^{-1}, $K_2 = 4$ M^{-1}). The small cyclophanes **1** and **2** exhibit very little affinity for these hydrophobic guests. This unexpected finding was explained by an analysis of their crystal structures: **1** has an open cavity with an internal van der Waals radius of *ca.* 1.2–1.7 Å; it binds nitromethane and ethyl acetate in the solid state by C–H···π interactions, but is slightly too narrow to accommodate an alkyne, and **2** has a collapsed cavity.

Introduction

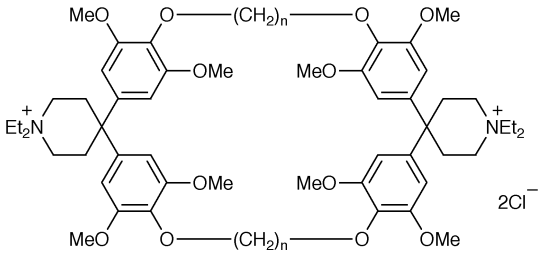
Spectacular macrocyclic receptors have been synthesised to bind large hydrophobic molecules, such as steroids, in aqueous solution.[1] Less progress has been made towards receptors for very simple hydrophobic guests, such as *n*-alkanes, alkenes and alkynes. Solid state clathrate complexes of small hydrocarbons are well known,[2] but few receptors have been designed to bind such species in water.[3] The smaller surface area of these simple guests means that the potential binding energy is much less. For example ethyne has a solvent-accessible surface area of 160 Å^2, compared to about 700 Å^2 for cholesterol (calculated using a 1.4 Å probe radius). The magnitude of the hydrophobic binding free energy[4] is about 0.2 kJ mol^{-1} Å^{-2}, so, if we assume that the loss of entropy on binding due to loss of translational and rotational freedom[5] is about 18 J mol^{-1} K^{-1}, these surface areas correspond to binding constants of roughly 10^4 and 10^{23} M^{-1} for ethyne and cholesterol respectively at 298 K. A hydrophobic receptor for ethyne would need to utilise the entire surface to achieve significant binding, whereas a receptor covering a fraction of the surface of cholesterol could still achieve a respectable affinity. The aim of this study was to gain insight into the binding of small neutral hydrophobic guests to macrocyclic receptors in water, and to find a suitable receptor for alkynes and poly-ynes.

Conjugated acetylenic materials have attracted great interest for a variety of applications,[6] but these highly unsaturated compounds are often unstable, particularly in concentrated solutions, because they tend to polymerise. Polymerisation can be prevented by bulky substituents, but a better way of stabilising poly-ynes might be to protect them by threading them inside macrocycles, to form rotaxanes or pseudorotaxanes. For example polyrotaxane-sheathed carbyne might be a stable material,[6a] whereas this fully sp^1 allotrope of carbon seems too unstable to exist in the pure form,[6b,c] and has no sites where bulky substituents can be covalently appended. This idea lead us to search for a suitable macrocyclic receptor for alkynes and poly-ynes. Alder and Sessions predicted that acetylenes ought to bind in the cavity of [8]beltene.[7] Water-soluble beltenes are challenging synthetic targets,[8] so we decided to start by investigating small Diederich-type spiro cyclophanes.[1a,9] Here we report the synthesis and crystallographic characterisation of two small water-soluble cyclophanes (**1** and **2**), and compare their binding properties with those of larger analogues (**3** and **4**), Stoddart's cyclophane (**5**),[10] α-cyclodextrin (**6a**, α-CD), β-cyclodextrin (**7**, β-CD), 2,6-dimethyl-α-cyclodextrin (**6b**, DM-α-CD) and 2,3,6-trimethyl-α-cyclodextrin (**6c**, TM-α-CD). Preliminary molecular mechanics calculations, and space filling models, indicated that the small cyclophanes **1** and **2** would have similar cavity sizes to [8]beltene, and that they should be able to accommodate acetylenes. We chose to synthesise these cyclophanes with methoxy substituents to increase their water-solubility and to inhibit micelle formation.[9] A cyclophane similar to **2**, but without methoxy substituents, has been reported by Diederich and coworkers.[9b]

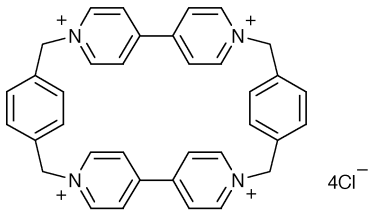
The hydrophobic interactions of all nine receptors with hexane-1,6-diol (**8**) and hexa-2,4-diyne-1,6-diol (**9**) in D_2O were investigated quantitatively by ^1H NMR, in order to compare their affinities for these aliphatic and acetylenic guests. These diols were selected because their high solubility in water makes it possible to measure accurate association constants even for weak complexes. These experiments lead to the unexpected discovery that α-cyclodextrins, particularly DM-α-CD **6b**, have a highly selective preference for the acetylenic diol, and bind **9** better than any of the cyclophanes. Cyclophanes **1** and **2** were found to have very low affinities for both diols. This was explained by an analysis of their crystal structures, allowing us to refine the design criteria for future hydrophobic receptors. The crystal structures of cyclophane **1**, and of its amide precursor **11**, show that this macrocycle behaves as a receptor for the acidic methyl groups of nitromethane and ethyl acetate by virtue of attractive C–H···π interactions.



[8]beltene



1 (n = 1), **2** (n = 2)
3 (n = 3), **4** (n = 4)



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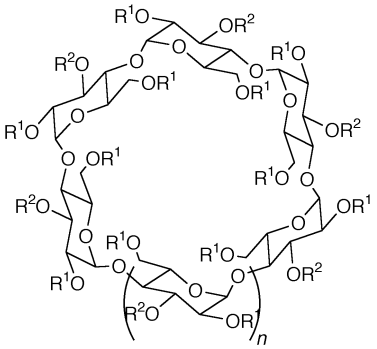
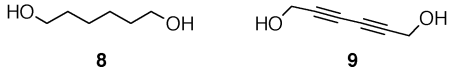


6a α-CD (n = 1, R^1 = R^2 = H)
6b DM-α-CD (n = 1, R^1 = Me, R^2 = H)
6c TM-α-CD (n = 1, R^1 = R^2 = Me)
7 β-CD (n = 2, R^1 = R^2 = H)

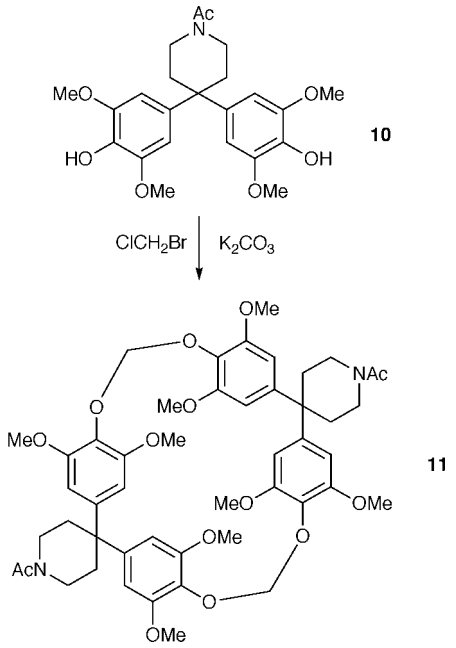


8 **9**

Results and discussion

Synthesis of cyclophanes 1 and 2

The small cyclophane **1** was prepared as shown in Schemes 1 and 2. The conversion of bisphenol **10**[9b,c] into macrocycle **11** was achieved in 38% yield using bromochloromethane, under similar conditions to those developed by Cram *et al.* for the synthesis of carcerands.[11] Elaboration of **11** into the water-soluble cyclophane **1** was achieved by reduction with excess lithium aluminium hydride, to give diamine **12**, followed by quaternisation with ethyl iodide and ion-exchange to the chloride salt.



10 **11**

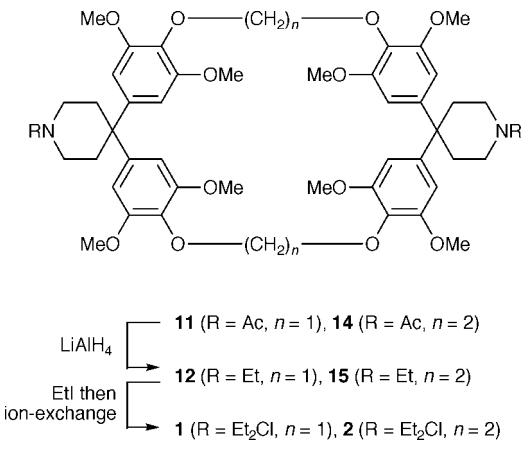
Scheme 1

Cyclophane **2** was prepared by analogy[12] with Diederich's route to a similar macrocycle without methoxy substituents (Schemes 3 and 2). The bisphenol **10** was reacted with excess 1,2-dichloroethane and sodium hydroxide in butanol to give the dichloro-cleft **13** in 55% yield. Coupling of **10** and **13** with caesium carbonate in DMF gave **14** in 42% yield. Reduction to the diamine **15** was achieved in 83% yield using excess lithium aluminium hydride. Quaternisation of **15** with ethyl iodide proved to be surprisingly difficult and the cyclophane dication iodide salt could only be obtained in 40% yield; this compound was recrystallised prior to conversion to the chloride, to remove traces of mono-cationic material.

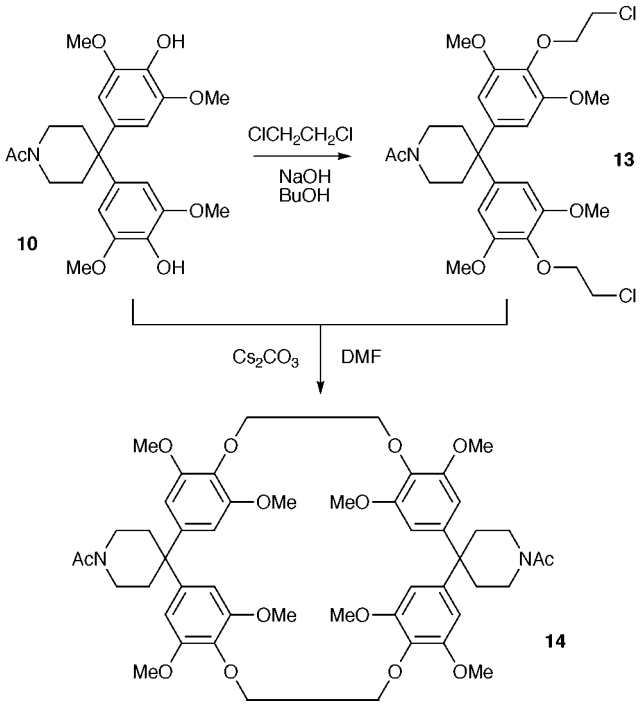
Cyclophanes **3**,[9] **4**[9,13] and **5**,[10] and cyclodextrins **6b**[14] and **6c**,[13] were prepared using published procedures.

Binding studies

The affinities of cyclophanes **1**–**5** (all as chloride salts) and cyclodextrins **6a**–**c** and **7** for hexane-1,6-diol (**8**) and hexa-2,4-diyne-1,6-diol (**9**) in D_2O were measured by ^1H NMR titration at 298 K.[12] Titrations were conducted at constant macrocycle concentration (0.2 to 1.5 mM), monitoring changes in the chemical shift of macrocycle resonances with increasing diol concentration, until a satisfactory level of binding-saturation



Scheme 2



Scheme 3

was reached. The association constants range from *ca.* 1.6 M^{-1} to 1.2 × 10^3 M^{-1} (Table 1). In general the cyclophanes bind both diols more weakly than the cyclodextrins. The cyclophanes and β-CD **7** show a greater affinity for the saturated diol **8**, whereas the α-CDs **6a**–**c** show a strong preference for the acetylenic diol **9**. Our value of 127 ± 6 M^{-1} for the stability constant of the **8**·**6a** complex compares well with that reported by Bastos *et al.* from microcalorimetry (101.4 ± 4.6 M^{-1}).[15] Diols **8** and **9** are extremely soluble in water (solubility limits are *ca.* 1.4 M and 0.4 M respectively at 298 K) which enabled a satisfactory level of saturation (>80%) to be achieved where the binding constant is greater than 10 M^{-1}. Saturations of 60–80% were achieved for **3**, where the binding constants are only 5–10 M^{-1}. Both the binding constants of the smallest cyclophane **1**, and also that between **5** and **8**, are extremely weak and saturations of only *ca.* 30% could be obtained in these cases, so these very weak binding constants must be regarded as almost too weak to measure.

All of the titrations with saturated diol **8**, and most of the titrations with acetylenic diol **9**, gave excellent fits when analysed using the 1 : 1 binding isotherm. For example, Fig. 1 shows binding curves for diols **8** and **9** with α-CD **6a**.

Table 1 Binding constants[a] and cavity radii[b] of macrocycles **1**–**7**

	Binding to **8**	Binding to **9**		Cavity radius[b]
Macrocycle	K_1/M^{-1}	K_1/M^{-1}	K_2/M^{-1}	R_{cav}/Å
1	1.6 ± 0.5	2.1 ± 0.6	—	1.2,[c] 1.2,[d] 1.7[e]
2	23 ± 1	11 ± 2	—	0.2,[c] 0.4[f]
3	7.9 ± 1.2	5.6 ± 1.6	—	2.0[9] [f]
4	79 ± 10	27 ± 3	3 ± 1	2.4[21]
5	2 ± 1	56 ± 3	1.5 ± 1	1.9[22]
6a	127 ± 6	580 ± 20	—	2.0[23]
6b	85 ± 6	1200 ± 100	—	1.8[24]
6c	20 ± 3	380 ± 30	—	1.6[25]
7	75 ± 6	18 ± 2	4 ± 2	2.3[26]

[a] In D_2O at 298 K. [b] See text for definition of cavity radius R_{cav}. [c] Calculated geometry.[18] [d] Crystal structure of **11**. [e] Crystal structure of **1**. [f] Crystal structure of **15**.

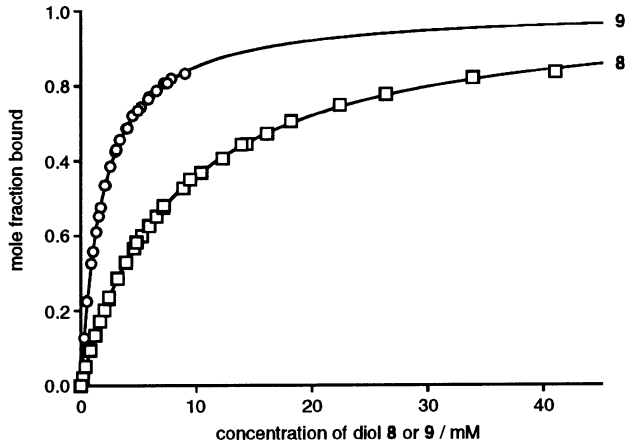
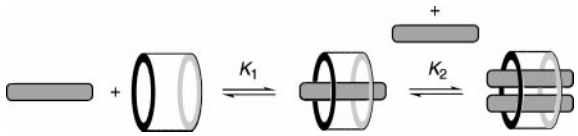


Fig. 1 ^{1}H NMR titration curves for binding of α-CD **6a** with diols **8** and **9** in D_2O, with calculated 1 : 1 binding isotherms. Each curve combines data from two independent titrations. The concentration of α-CD **6a** was 0.25 mM in all four titrations.

However combinations of the slimmer diol **9** with the wider macrocycles **4**, **5** and **7** gave distinctly biphasic curves, which can only be fitted by assuming formation of a weak 2 : 1 complex (Scheme 4). For example Fig. 2 shows a binding curve for diol **9** with β-CD **7**. Values of K_1 and K_2 are given in Table 1.



Scheme 4

The octanol–water partition coefficients, P,[16] of **8** and **9** were measured at 298 K, giving $\log_{10} P$ values of −0.12 ± 0.02 and −0.05 ± 0.02 respectively. Thus **9** is slightly more hydrophobic than **8**, which may contribute towards the higher affinity of this diol for α-CDs **6a**–**c**.

^{1}H NMR titrations were also carried out to explore the interaction of the smallest cyclophane **1** with nitromethane and ethyl acetate (in D_2O at 298 K) because these guests interact with the cavity of **1** in the solid state, as described in the following section, but these guests showed little or no

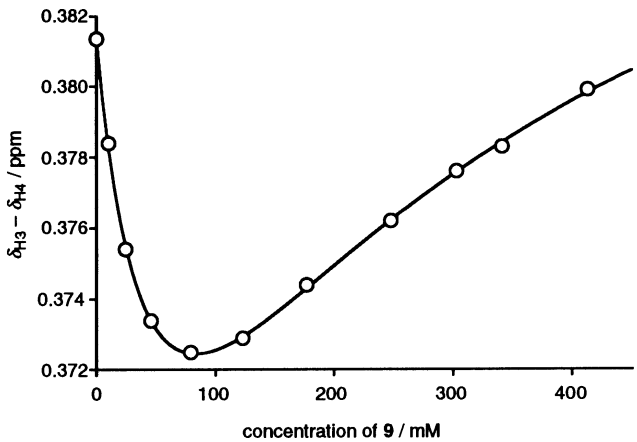


Fig. 2 ^{1}H NMR titration curve for binding β-CD **7** and diol **9** in D_2O, showing the change in the difference in chemical shift between H3 and H4 of the cyclodextrin. The smooth curve is the calculated 2 : 1 isotherm. The concentration of β-CD **7** was 1.3 mM.

binding in aqueous solution ($K \approx 2$ M^{-1} with up to 55% saturation in both cases).

Crystallographic analysis

We attempted to grow crystals of cyclophanes **1** and **2**, and of their synthetic precursors, so as to determine the dimensions of their cavities by X-ray crystallography. The crystal structures of the smaller CH_2-linked cyclophane **1** (as its PF_6^- salt), of its bis(amide) precursor **11** and of the diamine $(CH_2)_2$-linked cyclophane intermediate **15** have been determined and are summarised in Table 2 and Fig. 3 and 4.

Crystals of $\mathbf{1}\cdot(PF_6)_2$ were grown from aqueous nitromethane and the asymmetric unit contains two nitromethane

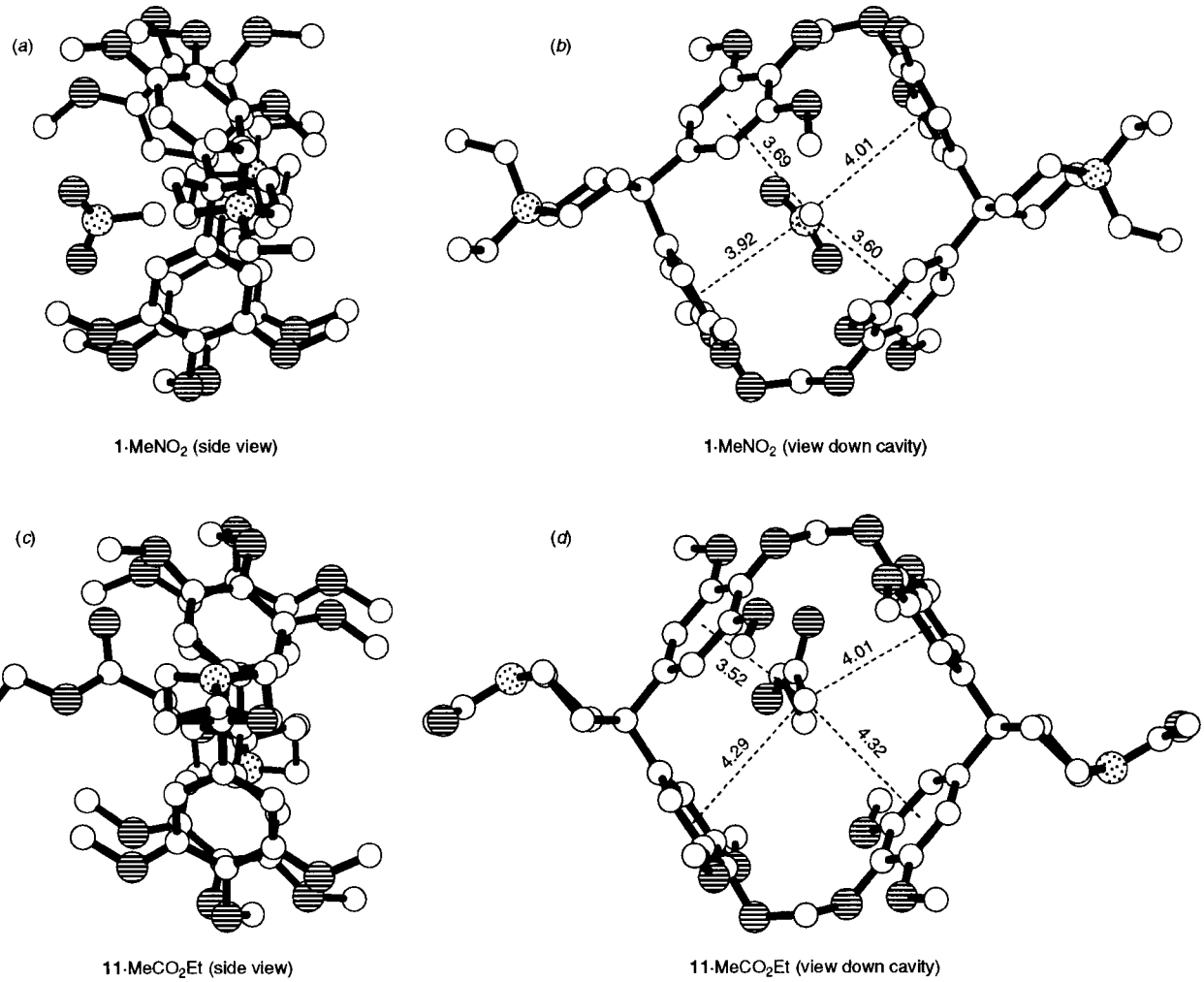


Fig. 3 Structures of $\mathbf{1}\cdot MeNO_2$, (*a*) and (*b*), and $\mathbf{11}\cdot MeCO_2Et$, (*c*) and (*d*), in the solid state. Only the solvent molecule closest to each cyclophane is shown. PF_6^- counter anions (in the structure of **1**) and hydrogen atoms are omitted for clarity. Views (*a*) and (*c*) are exactly perpendicular to views (*b*) and (*d*). Views (*b*) and (*d*) show the distances from the central methyl of the guest to the centroids of each benzene ring.

Table 2 Crystal structure data for **1**, **11** and **15**

Data	**1**	**11**	**15**
Formula	$C_{52}H_{72}N_2O_{12}\cdot 2PF_6\cdot 2CH_3NO_2$	$C_{48}H_{58}N_2O_{14}\cdot 1.5C_4H_8O_2\cdot 0.5CHCl_3$	$C_{50}H_{66}N_2O_{12}$
Formula weight	1329.14	1078.84	887.08
T/K	183(2)	213(2)	213(2)
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$	$P2_1/n$
a/Å	12.263(2)	14.0149(12)	12.446(2)
b/Å	22.3356(13)	12.7542(12)	11.983(2)
c/Å	22.566(2)	17.837(2)	16.456(2)
β/°	94.169(11)	108.711(8)	105.918(12)
U/Å^3	6164.3(13)	3019.8(5)	2363.9(6)
Z	4	2	2
μ(Cu-Kα)/mm^{-1}	1.570	1.97	0.722
Reflections measured	131 67	5311	4973
Independent reflections	125 64	5126	4806
Final $R[I > 2\sigma(I)]$	0.078	0.096	0.065
R (all data)	0.148	0.159	0.073

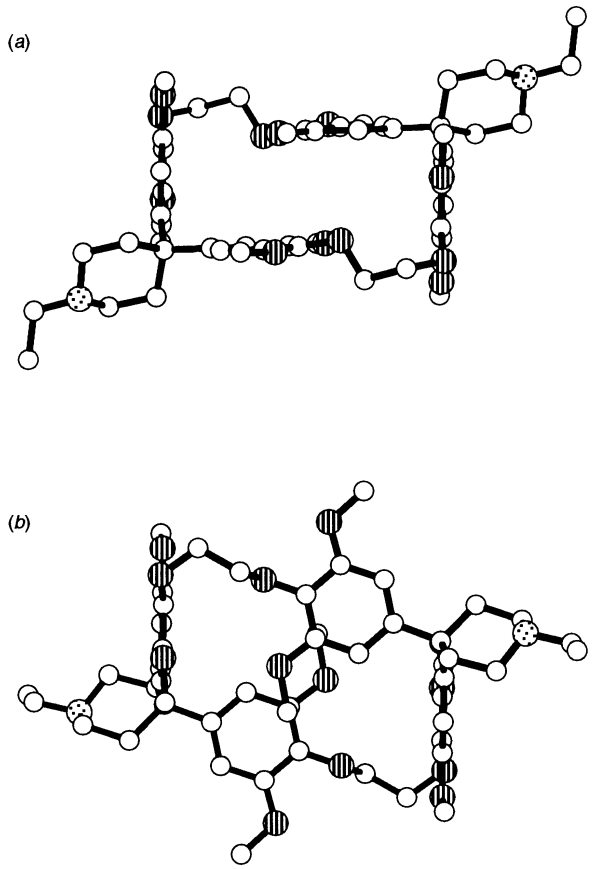


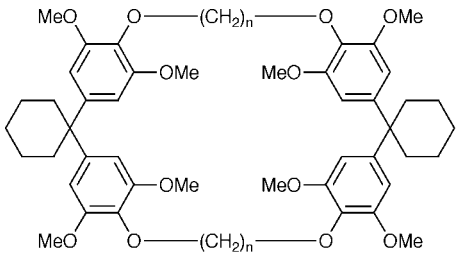
Fig. 4 Two perpendicular views of the structure of **15** in the solid state, showing the collapsed cavity with parallel off-set benzene rings. The distances between the planes of the two closest benzene rings is 3.47 Å, and the centres of these rings are off-set by 4.97 Å.

solvent molecules and one cyclophane molecule. The cyclophane adopts a conformation with an open, slightly conical, cavity with the wider rim cupping the methyl of a nitromethane solvent molecule, as shown in Fig. 3(*a*) (side view) and 3(*b*) (view down cavity). The other nitromethane molecule and the counter anions do not appear to interact strongly with the cyclophane and are omitted from this figure. The carbon atom of the methyl of the proximate nitromethane is 1.19 Å from the centroid of the cavity (the centroid of the four benzene rings of the cyclophane). The distances of this methyl carbon from the centroids of the four benzene rings are 3.69, 4.01, 3.60 and 3.92 Å (mean 3.80 Å); where these distances are less than the sum of the van der Waals radii (3.7 Å) this indicates a significant C–H···π interaction.[3c,17]

The cyclophane amide **11** was crystallised from chloroform–ethyl acetate and the crystals contained molecules of both solvents. The acetate-methyl of one of the ethyl acetate molecules protrudes into the cavity, as shown in Fig. 3(*c*) (side view) and 3(*d*) (view down cavity); the carbon of this methyl is 1.71 Å from the centroid of the cavity. The distances from this methyl to the centroids of the four benzene rings are 3.53, 4.01, 4.32 and 4.29 Å (mean 4.03 Å); there also appears to be significant C–H···π interaction here, although on average less than in the $\mathbf{1}\cdot MeNO_2$ complex. The conformation of **11** in this crystal structure, and the interaction with the solvent, is similar to that in the crystal structure of **1**, although **11** has a more regular cylindrical cavity. The stronger interaction of nitromethane with **1** reflects the higher acidity of this guest, which boosts C–H···π hydrogen bonding.

Unsolvated crystals of the $(CH_2)_2$-linked cyclophane amine **15** were grown by vapour diffusion of diethyl ether into a solution in chloroform. The cyclophane has a collapsed cavity as shown by the two orthogonal views of the structure in Fig. 4(*a*) and (*b*). The distance between the planes of the two parallel aryl rings, which define the roof and floor of the cavity, is only 3.47 Å [Fig. 4(*a*)], but the centres of these rings are off-set by 4.97 Å, so they do not overlap [Fig. 4(*b*)], which suggests that the preference for this geometry is due to the conformation of the OCH_2CH_2O link, rather than π–π interactions.

The minimum energy conformations of cyclophanes **16** and **17** (which are slightly simplified analogues of **1** and **2**, respectively) were calculated using the MacroModel molecular mechanics program.[18] These calculated structures are almost identical to the crystallographic structures of **11** and **15** respectively, which suggests that the conformations of **1** and **2** in solution are similar to those in these crystal structures. This conformation of **2** has essentially no cavity. The ability of this cyclophane to bind diols **8** and **9** implies that conformations with larger cavities are accessible, but the weakness of the binding shows that there is an energy penalty associated with opening the cavity. This also explains why Diederich and coworkers found that the analogue of **2** without methoxy substituents does not bind benzene, despite the fact that CPK molecular models indicated that benzene should fit well in the cavity.[9b]



16 ($n = 1$), **17** ($n = 2$)

The 'cavity size' of a cyclophane is difficult to quantify,[19] and yet it is a useful quantity for predicting which guests are likely to be accommodated and for comparing cyclophanes with other macrocycles, such as cyclodextrins. Here we define the 'cavity radius', R_{cav}, as the distance from the centroid of the atoms defining the cavity to the van der Waals surface of the atom of the macrocycle nearest to this centroid, as shown in Fig. 5 (for cyclodextrins we use the centroid of the H5 atoms). This definition of cavity radius takes no account of the ability of flexible macrocycles to distort to accommodate guests (except where coordinates are available for host–guest complexes), so R_{cav} is likely to underestimate the cavity size, particularly for the more flexible and less cylindrical cyclophanes.

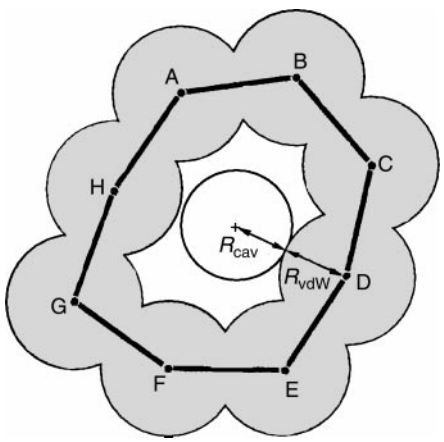


Fig. 5 The cavity radius R_{cav} for a cavity defined by atoms A–H is the distance from the centroid of these atoms (the central cross) to the centre of the nearest atom (D), minus the van der Waals radius of that atom R_{vdW}.

Values of R_{cav} for macrocycles **1**–**7**, calculated using Bondi van der Waals radii[20] are listed in Table 1. Comparison of these cavity radii with the van der Waals radius of an sp^1 acetylenic carbon (1.70–1.77 Å) shows that **1** is probably just too narrow to accommodate an acetylene. **1** has a fairly rigid open cavity, so it cannot expand to accommodate guests, so although there is a clear cupping interaction with guest methyl groups in the crystal structures of $\mathbf{1}\cdot MeNO_2$ and $\mathbf{11}\cdot MeCO_2Et$, **1** shows almost no affinity for diols **8** or **9**, which would have to pass right through the centre of the cavity. According to our molecular mechanics calculations[18] [8]beltene has an R_{cav} value of 1.5 Å, which suggests that the prediction that this macrocycle will bind acetylene needs to be re-examined.

Cyclophanes **3** and **4** are clearly large enough to accommodate diols **8** and **9**, but they bind more weakly than the α-CDs **6a**–**c**. This may reflect the preference of these cylindrical guests for the more circular cavities of the cyclodextrins. Stoddart's cyclophane **5** ($R_{cav} = 1.9$ Å) seems slightly too narrow to accommodate the alkyl chain of the aliphatic diol **8** (radius ≈ 2.0 Å), but just wide enough to accommodate the slimmer acetylenic diol **9** (radius ≈ 1.7 Å). This cyclophane has a rectangular cavity, so one or two molecules of diol **9** can be accommodated.

Conclusions

We have prepared and characterised two new water-soluble spiro-cyclophanes **1** and **2**. Cyclophane **1** is the smallest possible cyclophane of this series, yet it has a well defined open cavity, which is larger than that of **2**. Cyclophane **1** binds the methyl group of nitromethane by C–H···π interaction in the solid state, but it does not interact significantly with these guests in aqueous solution, and its cavity is too small to form pseudorotaxane-type complexes, even with very slim guests such as diol **9**. It would be interesting to explore the interaction of this cyclophane with soft metal cations.[27] Cyclophane **2** has a collapsed cavity in the solid state; it binds diols **8** and **9** weakly in solution, indicating that its cavity can open, albeit reluctantly. The larger Diederich-type cyclophanes **3** and **4** bind weakly to **8** and **9** because of their poor shape-complementarity for these slim cylindrical guests. Stoddart's cyclophane **5** shows no significant binding to the saturated diol **8**, but it does form weak 1 : 1 and 1 : 2 complexes with the narrower acetylenic diol **9**. The α-cyclodextrins **6a**–**c** all bind quite strongly to **9**, and weakly to **8**. β-Cyclodextrin binds both diols more weakly than α-CD, and forms a 2 : 1 complex with **9**. Dimethyl α-CD **6b** shows a remarkably high affinity for **9** ($K = 1.2 \times 10^3$ M^{-1}); this macrocycle may be useful for encapsulating and stabilising acetylenic materials.

Experimental

General techniques

All reactions were carried out under a dry inert atmosphere (nitrogen or argon). ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz respectively (Bruker AM-500), on solutions in $CDCl_3$ at 298 K, unless otherwise stated. Microanalyses were carried out in the Dyson Perrins Laboratory. All chromatography was carried out using Merck Kieselgel 60 μm. Light petroleum refers to the fraction boiling in the range 60–80 °C. DM-α-CD **6b** was prepared using Takeo's method.[14] TM-α-CD **6c** was prepared from α-CD **6a** using NaH/DMSO followed by methyl iodide.[13] Cyclophanes **3** and **4** were prepared using published procedures.[9,12]

1′,1″-Diacetyl-5,9,13, 15,21,25,29,31-octamethoxydispiro[1,3,17,19-tetraoxa[3,1,3,1]-paracyclophane-0,4′:26,4″-bispiperidine] (11)

A solution of 1-acetyl-4,4-bis(3′,5′-dimethoxy-4′-hydroxyphenyl)piperidine **10** (4.0 g, 9.3 mmol) and bromochloromethane (1.55 g, 12.0 mmol) in acetonitrile (200 mL) was slowly added to a suspension of potassium carbonate (15 g, 107 mmol) in refluxing acetonitrile (500 mL), over 12 h. Heating was continued for a further 96 h, then the solution was cooled and the inorganic residues removed by filtration. Purification by flash column chromatography (eluting with a gradient of 0–3% methanol in chloroform) gave **11** as a white solid (1.56 g, 38%), mp 270 °C; R_f (dichloromethane : methanol, 20 : 1) 0.61; ^{1}H NMR: δ 6.21 (s, 8H, ArCH), 5.75 (s, 4H, OCH_2O), 3.67–3.65 (m, 4H, NCH_2), 3.56 (s, 24H, OCH_3), 3.49–3.46 (m, 4H, NCH_2), 2.24–2.23 (m, 8H, NCH_2CH_2), 2.07 (s, 6H, $C(O)CH_3$); ^{13}C NMR: δ 169.2, 152.6, 141.7, 134.8, 105.2, 98.6, 56.4, 45.4, 43.6, 38.5, 36.9, 35.8, 21.3; IR (KBr): ν 1646 cm^{-1} (C=O); MS (APCI$^+$): m/z (%) 888 (100) [MH$^+$].

1′,1″-Diethyl-5,9,13, 15,21,25,29,31-octamethoxydispiro[1,3,17,19-tetraoxa[3,1,3,1]-paracyclophane-10,4′ : 26,4″-bispiperidine] (12)

Lithium aluminium hydride (337 mg, 8.9 mmol) was added to a suspension of amide **11** (400 mg, 0.45 mmol) in THF (60 mL). The mixture was stirred at room temperature for 24 h, then ethyl acetate (3 mL) was added and stirring continued for 1 h. Sodium hydroxide (10% solution, 2 mL) was added and the solid material removed by filtration, the solid being washed with chloroform. The combined organic extracts were dried over $MgSO_4$ and the solvent then removed. The residue was recrystallised twice from ethyl acetate–light petroleum to give the amine **12** as a white solid (291 mg, 75%), mp 258 °C; ^{1}H NMR: δ 6.25 (s, 8H, ArCH), 5.76 (s, 4H, OCH_2O), 3.53 (s, 24H, OCH_3), 2.52–2.42 (bs, 8H, CH_2), 2.39–2.30 (m, 12H, CH_2 and NCH_2CH_3), 1.05 (t, $^3J = 7.2$ Hz, 6H, NCH_2CH_3); ^{13}C NMR: δ 152.1, 142.5 (broad), 134.2, 105.3, 98.4, 56.2, 52.4, 50.2, 45.4, 36.6, 12.1; MS (APCI$^+$): m/z (%) 861 (33) [M$^+$ + 2H], 859 (100) [M$^+$].

1′,1′,1″,1″-Tetraethyl- 5,9,13,15,21,25,29,31-octamethoxydispiro[1,3,17,19-tetraoxa[3,1,3,1]-paracyclophane-10,4′ : 26,4″-bispiperidinium] dichloride (1)

A solution of amine **12** (200 mg, 0.23 mmol) and ethyl iodide (20 mL) in acetonitrile (50 mL) was heated at 50 °C. After 48 h the mixture was evaporated, but analysis by tlc and MS showed that alkylation was incomplete (*ca.* 10% of the mono quaternised product remaining) so the solid was redissolved in acetonitrile : chloroform (1 : 1, 150 mL) and ethyl iodide (50 mL), and stirred for a further 48 h at 50 °C, until analysis indicated only one product. The solvent was removed and the residue recrystallised from methanol–diethyl ether to give the diiodide salt as a white solid (100 mg, 59%). A portion of this salt (80 mg) was then dissolved in a small amount of methanol : water (1 : 1) and passed through an ion exchange column [Dowex 1X8-400(Cl)], eluting with methanol : water (1 : 1). The solvent was evaporated and the residue recrystallised from methanol–diethyl ether to give dichloride **11** as a white solid (65 mg, 96%), mp 261–263 °C; R_f (methanol : ammonium chloride : nitromethane, 8 : 2 : 1) 0.42; ^{1}H NMR (D_2O, 323 K): δ 6.31 (s, 8H, ArCH), 5.55 (s, 4H, OCH_2O), 3.44 (s, 24H, OCH_3), 3.28–3.18 (m, 16H, NCH_2CH_3 and NCH_2CH_2), 2.53–2.45 (m, 8H, NCH_2CH_2), 1.11 (t, $^3J = 7.2$ Hz, 12H, NCH_2CH_3); ^{13}C NMR (D_2O): δ 151.8, 140.6, 133.4, 104.1, 99.2, 61.7, 56.0, 55.1, 43.6, 31.1, 28.9, 24.7, 6.3; MS (ESI$^+$, + 20 V): m/z (%) 458.3 (100) [M^{2+}].

1-Acetyl-4,4-bis[4-(2-chloroethoxy)-3,5-dimethoxyphenyl]piperidine (13)

A solution of 1-acetyl-4,4-bis(3′,5′-dimethoxy-4′-hydroxyphenyl)piperidine **10** (10 g, 23 mmol) and sodium hydroxide (2.4 g, 60 mmol) in 1-butanol (320 mL) was heated at reflux for 1 h, then 1,2-dichloroethane (45.5 g, 460 mmol) and potassium carbonate (13.8 g, 100 mmol) were added. Heating was continued for 40 h. After cooling the solvent was removed and the residue redissolved in dichloromethane–water. The organic phase was extracted with potassium hydroxide (2 M, 3 × 200 mL), water (3 × 200 mL) and dried over $MgSO_4$. The solvent was removed and the residue purified by flash column chromatography (eluting with a gradient of 0–1% methanol in dichloromethane) to give the product **13** as a pale yellow solid (7.0 g, 55%), mp 110–113 °C; ^{1}H NMR: δ 6.40 (s, 4H, ArCH), 4.16 (t, ^3J = 6.5 Hz, 4H, CH_2Cl), 3.75 (s, 12H, OCH_3), 3.72 (t, ^3J = 6.5 Hz, 4H, CH_2CH_2Cl), 3.66–3.63 (m, 2H, NCH_2), 3.51–3.48 (m, 2H, NCH_2), 2.31–2.26 (m, 4H, NCH_2CH_2), 2.07 (s, 3H, $OCCH_3$); ^{13}C NMR: δ 169.0, 153.2, 142.3, 135.3, 104.9, 72.8, 56.5, 45.8, 43.7, 42.4, 38.7, 37.3, 36.3, 21.5; IR (KBr): ν 1644 cm^{-1} (C=O); MS (APCI): *m/z* (%) 556 (100) [MH^+], 557 (65) [MH^+], 558 (45) [MH^+]; $C_{27}H_{35}NO_7Cl_2$ (556.5): calcd C, 58.28; H, 6.34; N, 2.52; found C, 58.28; H, 6.30; N, 2.41%.

1′,1″-Diacetyl-6,10,14,16,23,27,30,32-octamethoxydispiro[1,4,18,21- tetraoxa[4,1,4,1]-paracyclophane-11,4′ : 28,4″-bispiperidine] (14)

A solution of 1-acetyl-4,4-bis(3′,5′-dimethoxy-4′-hydroxyphenyl)piperidine **10** (0.77 g, 1.8 mmol), dichloride **13** (1.0 g, 1.8 mmol) and caesium carbonate (3.0 g, 9.3 mmol) in DMF (90 ml) was stirred at 100 °C for 4 d. After cooling the solid was removed by filtration and the solvent removed. The residue was dissolved in chloroform (20 mL) and washed with hydrochloric acid (10%, 2 × 10 mL). The solvent was once more removed and the crude product purified by flash column chromatography (eluting with dichloromethane). Recrystallisation from chloroform–diethyl ether gave the bis(amide) product **14** as a white crystalline solid (695 mg, 42%), mp 260–262 °C; ^{1}H NMR: δ 6.34 (s, 8H, ArCH), 4.25 (s, 8H, OCH_2CH_2O), 3.70–3.67 (m, 4H, CH_2N), 3.59 (s, 24H, OCH_3), 3.53–3.50 (m, 4H, CH_2N), 2.31–2.28 (m, 8H, NCH_2CH_2), 2.09 (s, 6H, $COCH_3$); ^{13}C NMR: δ 168.8, 152.9, 141.2, 135.6, 104.9, 70.9, 56.1, 45.2, 43.5, 38.5, 36.6, 35.6, 21.3; IR (KBr) ν 1636 cm^{-1} (C=O); MS (FAB$^+$): *m/z* (%) 915 (100) [MH^+]; $C_{50}H_{62}N_2O_{14}$ (915.0): calcd C, 65.63; H, 6.83; N, 3.06; found C, 65.54; H, 6.94; N, 2.93%.

1′,1″-Diethyl-6,10,14,16,23,27,30,32-octamethoxydispiro[1,4,18,21-tetraoxa[4,1,4,1]-paracyclophane-11,4′ : 28,4″-bispiperidine] (15)

A solution of the bis(amide) cyclophane **14** (1.0 g, 1.1 mmol) and lithium aluminium hydride (1.1 g, 30 mmol) in THF (150 mL) was stirred at room temperature for 24 h. Ethyl acetate (20 mL) was added and stirring continued for 1 h before adding sodium hydroxide (10%, 20 mL). The mixture was filtered and washed with chloroform, and the combined organic portions dried over $MgSO_4$. The solvent was removed and the crude product recrystallised from ethyl acetate–light petroleum to give the cyclophane **15** as a white solid (808 mg, 83%), mp 208–210 °C; ^{1}H NMR: δ 6.35 (s, 8H, ArCH), 4.24 (s, 8H, OCH_2CH_2O), 3.58 (bs, 24H, OCH_3), 2.52 (bs, 8H, NCH_2), 2.38 (bs, 8H, NCH_2CH_2), 2.34 (q, ^3J = 7.1 Hz, 4H, NCH_2CH_3), 1.06 (t, ^3J = 7.1 Hz, 6H, NCH_2CH_3); ^{13}C NMR: δ 152.7, 142.7, 135.1, 105.0, 70.9, 56.0, 52.4, 50.2, 45.2, 36.2, 12.1; MS (APCI$^+$): *m/z* (%) 887.4 (100) [MH^+]; $C_{50}H_{66}N_2O_{12}$ (886.5): calcd C, 67.70; H, 7.50; N, 3.16; found C, 67.57; H, 7.45; N, 3.00%.

1′,1′,1″,1″-Tetraethyl- 6,10,14,16,23,27,30,32-octamethoxydispiro[1,4,18,21-tetraoxa[4,1,4,1]-paracyclophane-11,4′ : 28,4″-bispiperidinium] dichloride (2)

A solution of the bis(amine) cyclophane **15** (250 mg, 0.282 mmol) in acetonitrile (70 mL) and ethyl iodide (27 g, 0.71 mmol) was stirred at 50 °C for 4 d. Most of the solvent was removed before chloroform was added to precipitate the quaternary ammonium diiodide salt as a yellow solid (136 mg, 40%). A portion of this salt (36 mg, 0.030 mmol) was then dissolved in a small amount of methanol : water (1 : 1) and passed through an ion exchange column [Dowex 1X8-400(Cl)], eluting with methanol : water (1 : 1). The solvent was evaporated and the residue recrystallised from methanol–diethyl ether to give chloride salt **2** as a white solid (24 mg, 79%), mp 281–284 °C; R_f (methanol : ammonium chloride : nitromethane, 8 : 2 : 1): 0.42; ^{1}H NMR (D_2O, 313 K): δ 6.73 (s, 8H, ArCH), 4.32 (s, 8H, OCH_2CH_2O), 3.73 (s, 24H, OCH_3), 3.60–3.56 (bm, 16H, 2 × NCH_2), 2.89 (bs, 8H, NCH_2CH_2), 1.45 (t, ^3J = 6.9 Hz, 12H, NCH_2CH_3); ^{13}C NMR (D_2O, 313 K): δ 152.8, 140.9, 134.7, 104.9, 71.3, 56.3, 55.4, 53.9, 44.0, 29.0, 6.7; MS (ESI$^+$, + 35V): *m/z* (%) 472.8 (100) [M^{2+}]; $C_{54}H_{76}N_2O_{12}Cl_2 \cdot 3MeOH$ (1112.24): calcd C, 61.55; H, 7.97; N, 2.52; found C, 61.65; H, 7.71; N, 2.73%.

Measurement of octanol–water partition coefficients

The diols **8** or **9** (100 mg) were each stirred vigorously at 25 °C in a mixture of water (100 mL) and 1-octanol (100 mL) for 48 h. Stirring was then stopped and the solvent layers allowed to separate. Aliquots of each layer were taken, and analysed as follows. Each value reported is the average of two runs.

Hexane-1,6-diol 8. This was analysed by GC using a Pye 104 oven with a flame ionisation detector linked to a Waters 740 data module. A 1.5 m × 2.5 mm column packed with Carbowax 20M on ChromosorbW was used with nitrogen at 20 psi as the carrier gas. With the column temperature at 212 °C the hexanediol had a retention time of 6.3 min. Injection volumes of 5 μL were used (the linearity of the flame ionisation response was initially confirmed by varying the injection volume). The areas of the peaks obtained were averaged over five runs for each solvent.

Hexa-2,4-diyne-1,6-diol 9. As no suitable peak could be obtained by GC analysis, the lg*P* value was obtained by UV spectroscopy with a Perkin Elmer Lambda 20 spectrometer. 100 μL of the aliquot of each solvent was in turn added to ethanol (2.00 mL) in a 1 cm path length cuvette. The ratio of the absorption in each solvents of the peaks at 245 nm was compared and averaged over five runs.

Binding constants

These were determined by ^{1}H NMR titration in D_2O at 298 K as described previously.[12] Each value in Table 1 is the average of at least two independent measurements; errors were estimated from agreement between values from different resonances on each determination, from the agreement between repeat titrations, and from estimated errors in volumes and masses.

Crystallography

X-Ray diffraction measurements were performed on an Enraf-Nonius MACH3 diffractometer with graphite monochromatised Cu-Kα radiation and $\omega/2\theta$ scan mode. Table 2 summarises the crystal data, data collection, and refinement parameters for cyclophanes **1**, **11**, and **15**. The structures were solved by direct methods with the SHELXS-97 program system[28a] and subjected to full-matrix refinement SHELXL-97.[28b] **11**: single crystals suitable for X-ray analysis were

grown by slow concentration of a solution of **11** in $CHCl_3$: ethyl acetate (1 : 3). **1**: single crystals suitable for X-ray analysis were grown by slow concentration of a solution of $\mathbf{1}\cdot 2PF_6^-$ in $MeNO_2 : H_2O$ (1 : 1). **15**: single crystals suitable for X-ray analysis were grown by diffusion of diethyl ether into a solution of **15** in $CHCl_3$.

CCDC reference number 440/149. See http://www.rsc.org/suppdata/nj/1999/1245/ for crystallogaphic files in .cif format.

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