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Bis-phenol A Cyclophanes: Synthesis, Crystal Structures and Binding Studies

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Abstract

The synthesis and structural characterisation of three new macrocyclic bis-phenol A cyclophane ethers are described. The solid state structures of two of the cyclophanes were determined by single crystal X-ray diffraction. Cyclophane **3** crystallises in the orthorhombic space group *P*bca with unit cell dimensions of a = 11.533(7), b = 29.383(8), c = 14.927(8) Å and cyclophane **4** in the monoclinic space group $P2_1/n$ with cell dimensions of a = 11.585(4), b = 11.839(2), c = 18.866(2) Å, β = 94.48(2)°.The X-ray crystal structures reveal distorted conformations, thus supporting the weak binding of quats in solution observed by the NMR studies. In the crystalline state both macrocycles were found to form self-complementary dimers held together by weak intermolecular π-π and CH-π interactions. The binding behaviour towards a series of tetralkylammonium cations was determined by ^{1}H NMR titration in $CDCl_3$ solution. The interactions between the hosts and the quats were clearly detectable but too weak to be translated into meaningful equilibrium constants.

Introduction

During recent years cation-π and CH-π interactions have been recognised to play an important role among the various noncovalent interactions which provide the basis for molecular recognition both in biotic and abiotic systems [1, 2]. The large majority of studies on artificial systems involve cyclophane receptors in aqueous media [3]. Recently increasing attention has been paid to studies in organic media, mostly in chloroform and tetrachloroethane, in which the complications arising from the hydrophobic effect, as well as from the electrostatic interactions with the negatively charged solubilising groups of the host are absent [4–13].

With the aim of providing further insights into the scope of the cation-π interaction we have considered cyclophanes **3** and **4** as potential hosts for quaternary ammonium ions. In these cyclophanes the bis-phenol A unit is connected to the electron rich naphthalenedioxy unit. Two acetylenic linkers have the potential of providing additional binding sites via cation-π interactions [1]. CPK models show that cyclophanes **3** and **4** can adopt a nest-like conformation suitable for establishing close contacts between the various π-systems of the host and the tetramethylammonium guest.

Herein we report the synthesis and characterisation, including X-ray crystal structures, of cyclophanes **3** and **4**, together with the evaluation of their binding properties towards a number of quaternary salts in $CDCl_3$ at 30 °C. For comparison purposes, cyclophane **5** was also included in the investigation. A CPK model of **5** suggests that the cavity in the corresponding nest-like conformation is too small to accommodate a tetramethylammonium guest.

Experimental

General procedures

All commercially available compounds were used without further purification. *N*-methyl pyrrolidinium iodide was available from a previous investigation [11]. 4-Chloro-2-butyn-1-ol was prepared according to a literature procedure [14]. *N*-methyl pyridinium and tetramethylammonium picrates were obtained from the corresponding iodide salt by anion exchange with silver picrate.

^{1}H and ^{13}C NMR measurements have been carried out on a Bruker AC300P instrument operating at 300.130 and 75.468 MHz for ^{1}H and ^{13}C, respectively, and TMS was used as an internal standard. ^{1}H NMR titrations were carried out in $CDCl_3$ at 30 ° C according to a published procedure [9].

X-ray crystallographic measurements were carried out using an Enraf-Nonius CAD4 diffractometer with graphite monochromatised MoK_α radiation [$\lambda(MoK_\alpha)$ = 0.71073 Å] and a $\omega/2\theta$ scan mode to 2θ = 50° at 173.0 ± 0.1 K. The cell constants and the orientation matrices for data collection were obtained from a least-squares refinement using the setting angles of 25 carefully centred reflections in the range 18.86° < 2θ < 28.10° for cyclophane **3** and 15.46° <

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$2\theta < 26.26°$ for cyclophane **4**. The data were corrected for Lorentz and polarisation effects. The ψ-scans were collected but not used for absorption correction in either case. The structures were solved by direct methods (SHELXS-97) [15] and refined on F^2 (SHELXL-97) [16]. Hydrogen atoms were calculated to their idealised positions with isotropic temperature factors (1.2 or 1.5 times the C temperature factors) and refined as riding atoms. The naphthalene moiety of cyclophane **4** is disordered over two positions and was refined with site occupation factors of 0.62 and 0.38. The temperature factors of C(35) and C(34B) of naphthalene are restrained to reasonable values by equalising them with the temperature factors of C(35B) and C(34), respectively.

Synthesis of 2,2-bis[4-(4-tosyloxy-2-butynoxy)phenyl]-propane **2**

The reaction of bis-phenol A (5 g, 22 mmol) with 4-chloro-2-butyn-1-ol (4.7 g, 45 mmol) under N_2 in DMF (40 mL) and in the presence of KOH 85% (2.97g, 45 mmol) at r.t. for 24 h led to the formation of 2,2-bis[4-(4-hydroxy-2-butynoxy)phenylpropane. Crystallisation from ethyl acetate and light petroleum 4:1 afforded 6.2 g, 17 mmol of a pale yellow solid with 75% yield. m.p. 85–86 °C. ^{1}H NMR: δ_H ($CDCl_3$) 6.87 (4H, d, J = 6.6 Hz), 7.17 (4H, d, J = 6.6 Hz), 4.71 (4H, t, J = 1.8 Hz), 4.31 (6H,broad s), 1.65 (6H, s). ^{13}C NMR: δ_C($CDCl_3$) 155.5, 143.9, 7.19 127.8, 114.2, 85.4, 80.8, 56.0, 51.1, 41.7, 31.0. ES-MS: m/z = 388 $(M+Na)^+$. The compound (5.7 g, 15.6 mmol) was transformed into the corresponding ditosylate according to a literature procedure [17]. The crude material was purified by flash chromatography using $CHCl_3$ as eluent. The yield was 41%, 4.3 g, 6.4 mmol of a transparent waxy solid. ^{1}H NMR: δ_H ($CDCl_3$) 7.82-6.76 (16H, m), 4.75 (4H, t, J = 1.7 Hz), 4.55 (4H, t, J = 1.7 Hz), 2.43 (6H, s), 1.65 (6H, s).

General cyclisation procedure

An equimolar solution of the ditosylate **2** (4.18 mmol) and the appropriate dihydroxy naphthalene or hydroquinone in DMF (40 mL) was slowly added over a period of 4 h to the suspension of excess K_2CO_3 (16.7 mmol) in DMF (160 mL) at 75 °C under vigorous stirring. The mixture was kept at this temperature for an additional 4 h. After cooling DMF was distilled off and the residue was washed with 5% KOH solution and extracted with $CHCl_3$. The crude material was purified by flash chromatography on silica gel (toluene with **3** and **4**, $CHCl_3$ with **5**).

Synthesis of cyclophane **3**

Using the above cyclisation procedure, 28% yield, m.p. 118–120 °C, recrystallisation from benzene: methanol (1:1). ^{1}H NMR: δ_H ($CDCl_3$) 6.75-7.71 (14H, m), 4.78 (4H, t, J = 1.7 Hz), 4.70 (4H, t, J = 1.7 Hz), 1.56 (6H, s). ^{13}C NMR: δ_C($CDCl_3$) 153.9, 154.7, 129.1, 127.4, 115.2, 115.1, 109.2, 110.2, 56.2, 55.9, 45.9, 41.6, 30.8. ES-MS: m/z = 490 $(M+H)^+$, 512 $(M+Na)^+$, 528 $(M + K)^+$. *Anal.* calcd. for $C_{33}H_{28}O_4$: C, 81.11; H, 5.78. Found: C, 80.89; H, 5.64.

Synthesis of cyclophane **4**

Using the above cyclisation procedure, 25% yield, m.p. 164–166 °C, recrystallisation from benzene: methanol (1:1). ^{1}H NMR: δ_H ($CDCl_3$) 6.90–7.36 (14H, m), 4.78 (4H, t, J = 1.5 Hz), 4.72 (4H, t, J = 1.5 Hz), 1.67 (6H, s). ^{13}C NMR: δ_C($CDCl_3$) 154.9, 154.2, 144.1, 128.4, 128.3, 127.8, 118.7, 114.6, 110.3, 83.2, 56.7, 55.3, 41.6, 31.4. ES-MS: m/z = 490 $(M+H)^+$, 512 $(M+Na)^+$. *Anal.* calcd. for $C_{33}H_{28}O_4$: C, 81.11; H, 5.78. Found: C, 81.32; H, 6.02.

Synthesis of cyclophane **5**

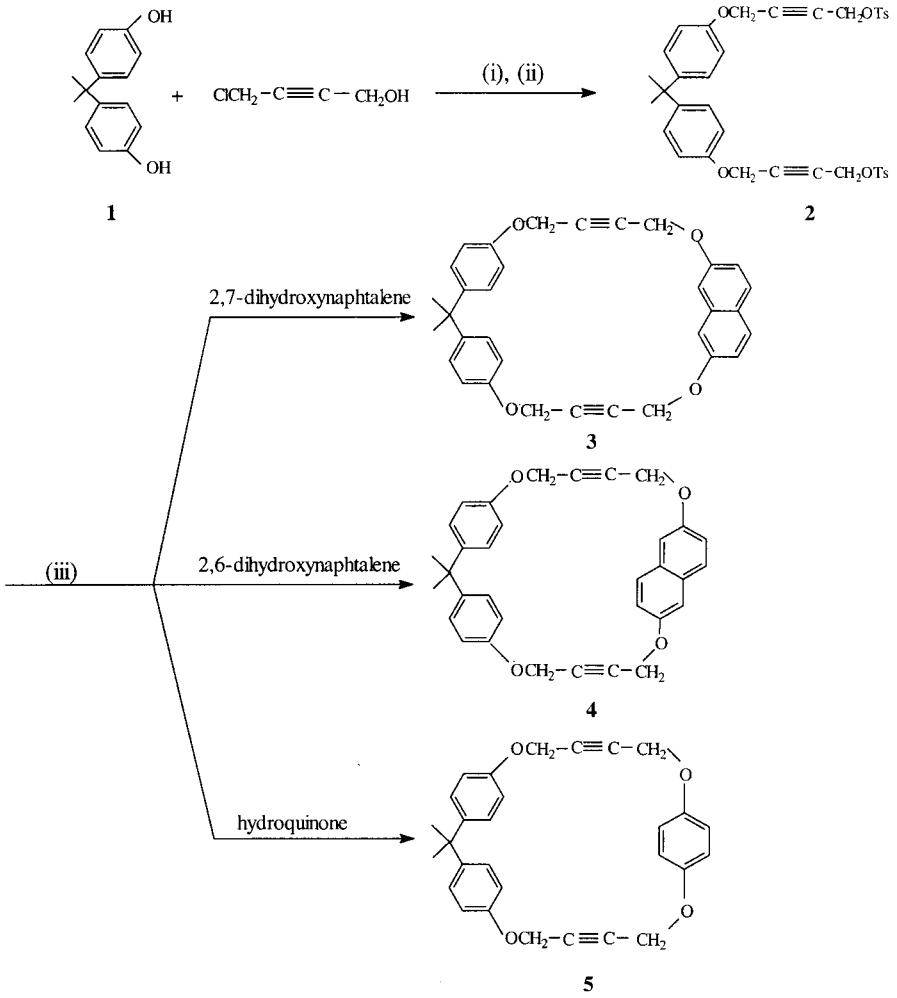
Using the above cyclisation procedure, 17% yield, m.p. 176-178 °C. The product was not recrystallised but used after purification by flash chromatography on silica using chloroform. ^{1}H NMR: δ_H ($CDCl_3$) 6.86–7.26 (8H, m), 6.67 (4H, s), 4.73 (4H, t, J = 1.7 Hz), 4.62 (4H, t, J = 1.7 Hz), 1.60 (6H, s).^{13}C NMR: δ_C($CDCl_3$) 127.7, 117.4, 115.1, 57.6, 55.3, 31.0. ES-MS: m/z = 440 $(M+H)^+$, 462 $(M+Na)^+$, 478 $(M+K)^+$. *Anal.* calcd. For $C_{29}H_{26}O_4$: C, 79.42; H, 5.98. Found: C, 79.62; H, 6.18.

Results

Crystal structure studies for **3** *and* **4**

Colourless single crystals of size 0.50 × 0.40 × 0.30 mm (**3**) and 0.30 × 0.30 × 0.10 mm (**4**) and of suitable quality for X-ray analysis were obtained from toluene. The crystal data are presented in Table 1. The fractional coordinates, bond distances and angles are deposited with the Cambridge Crystallographic Data Centre (deposition numbers 120573 and 120574). The molecular structures, conformations and the numbering schemes of cyclophanes **3** and **4** are shown in Figure 1.

In the crystalline state both cyclophanes **3** and **4** adopt distorted conformations. However, the conformation of cyclophane **3** is more nest-like than the conformation of cyclophane **4**. The reason for the difference in conformations is the twisting of the naphthalene moiety of cyclophane **4** between the phenyl rings thus blocking the cavity. The distortions of cyclophanes may be described by the angles between the naphthalene moiety and the phenyl rings and also by the angles between the phenyl rings. In cyclophane **3** the angle between two phenyl rings is 89.15(7)° and the angles between the naphthalene moiety and the phenyl rings are 56.47(7)° and 72.88(6)°. In cyclophane **4** the respective angle between the phenyl rings is somewhat smaller, i.e. 81.44(7)°. Also the angles between the naphthalene and the phenyls are smaller, 53.99(9)° and 29.6(1)°, leading to a distorted shape of the cavity. In addition to the angles between the planes of the aromatic rings, the torsion angles concerning ether oxygen atoms may be used to define the shapes of the molecules in the crystalline state. Torsion angles C(5)–O(6)–C(7)–C(8) to the phenyl ring C(7)–C(12) are approximately the same in both cyclophanes (10.4(3)° and 9.4(2)°, respectively), but the angles C(21)–O(20)–C(17)–C(16) differ significantly being – 12.3(2)° for cyclophane **3**



Scheme 1. Reagents and conditions used for the preparation of neutral macrocyclic host molecules **3–5**: (i) KOH, DMF, 24 h; (ii) TsCl, KOH, CH_3CN, 20 h; (iii) K_2CO_3, DMF, 75 °C, high dilution.

Table 1. The crystal data for cyclophanes **3** and **4**

Compound	**3**	**4**
Empirical formula	$C_{33}H_{28}O_4$	$C_{33}H_{28}O_4$
Formula weight	488.55	488.55
Crystal system	Orthorhombic	Monoclinic
Space group	Pbca (No. 61)	$P2_1/n$ (No. 14)
a	11.533(7) Å	11.585(4) Å
b	29.383(8) Å	11.839(2) Å
c	14.927(8) Å	18.866(2) Å
β	90 °	94.48(2) °
Volume	5058(4) $Å^3$	2580(1) $Å^3$
Z	8	4
Density (calculated)	1.283 Mg m^{-3}	1.258 Mg m^{-3}
Absorption coefficient	0.083 mm^{-1}	0.082 mm^{-1}
F(000)	2064	1032
Index ranges	$0\leq h\leq 13$; $0\leq k\leq 34$; $-17\leq l\leq 17$	$0\leq h\leq 13$; $0\leq k\leq 14$; $-22\leq l\leq 22$
Reflections collected	8679	4754
Independent reflections	4436	4514
Data/restraints/parameters	4436 / 0 / 336	4514 / 0 / 415
GooF	1.009	0.902
Final R indices [$I > 2\sigma I$]	R1 = 0.0378, wR2 = 0.0946	R1 = 0.0457 wR2 =0.0982
R indices (all data)	R1 = 0.0637, wR2 = 0.1035	R1 = 0.1124 wR2 =0.1125
Largest diff. peak and hole	0.175 and −0.190 e.$Å^{-3}$	0.165 and −0.192 e.$Å^{-3}$

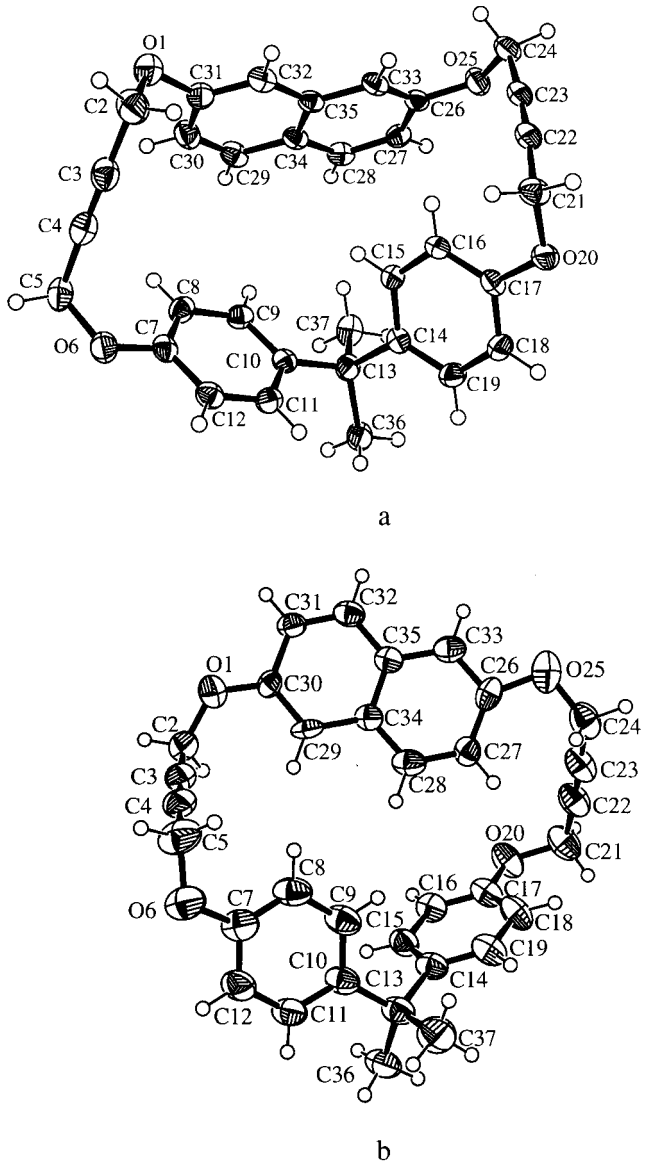


Figure 1. Molecular conformations and the crystallographic numbering scheme of cyclophanes **3** (a) and **4** (b). Anisotropic displacement ellipsoids are drawn at the 50% probability level.

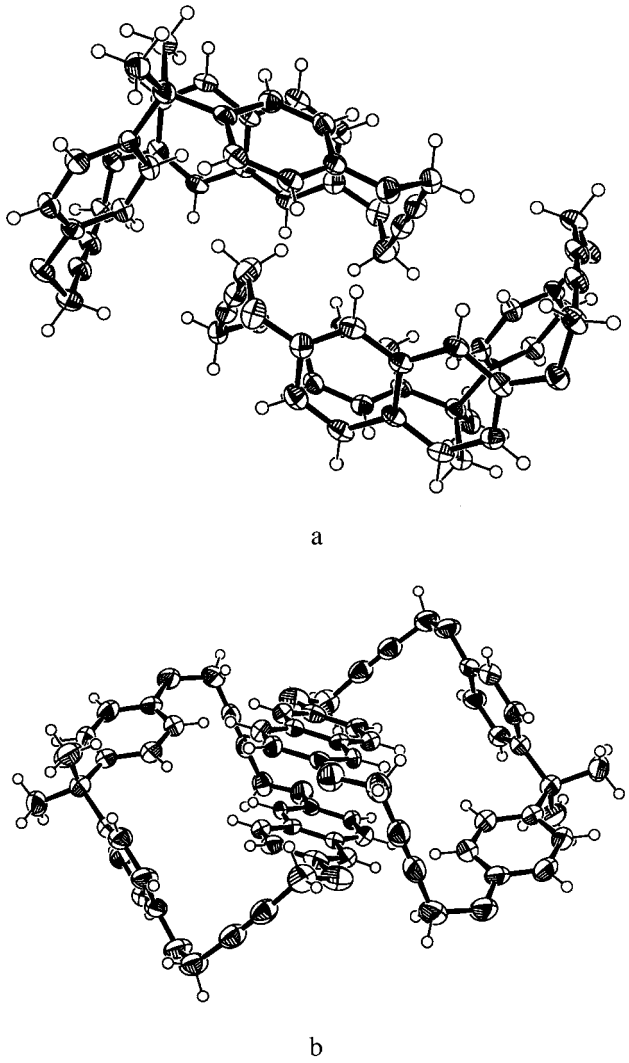


Figure 2. Packing diagram of cyclophanes **3** (a) and **4** (b) showing the dimeric structure in the crystalline state.

and 179.6(2)° for cyclophane **4**. The angles indicate that in cyclophane **3** the phenyl ring C(14)–C(19) is oriented outwards from the cavity while in cyclophane **4** the ring is bent towards the cavity.

Both macrocycles form self-complementary structures (Figure 2), since a dimeric packing motif is observed in the crystalline state. Similar dimeric packing of macrocyclic ethers stabilised by π-π interactions has also been reported earlier [18]. With cyclophane **3** there are several weak interactions varying from 3.4 Å to 3.9 Å between the two molecules forming the dimeric unit. Most of these interactions are π-π interactions between the edge of the naphthalene unit [C(32)–C(35)–C(33)] of one molecule and the triple bond C(3)–C(4) of the other molecule. Similar interactions between the edges of phenyl rings [C(7)–C(12)–C(11) and C(15)–C(16)] and the same triple bond are also observed. Weak electrostatic interactions are observed between oxygen atoms O(1) and O(6) and aromatic rings of the other molecule. CH-π interactions between the carbon C(2) of one molecule and the aromatic rings of the other molecule are also detectable.

With cyclophane **4** the phenyl rings do not participate as much in weak interactions between the dimer forming units as with cyclophane **3**. The main intermolecular interactions involve the naphthalene moiety, the acetylene part C(3)–C(4)–C(5) and the sp^3 carbon C(24) therefore being π-π and CH-π interactions by nature.

NMR binding studies

The binding abilities of **3** and **4** towards a number of quaternary salts were studied by means of the standard ^{1}H NMR titration technique [8]. In the presence of association phenomena, the addition of increasing amounts of a cyclophane host to the solution of a given guest is known to cause regular upfield shifts ($\Delta\delta$) of resonances of the guest. The titration data are generally fitted by means of a non-linear least squares procedure to the standard binding isotherm of Equation (1), where $\Delta\delta_\infty$ represents the limiting upfield shift

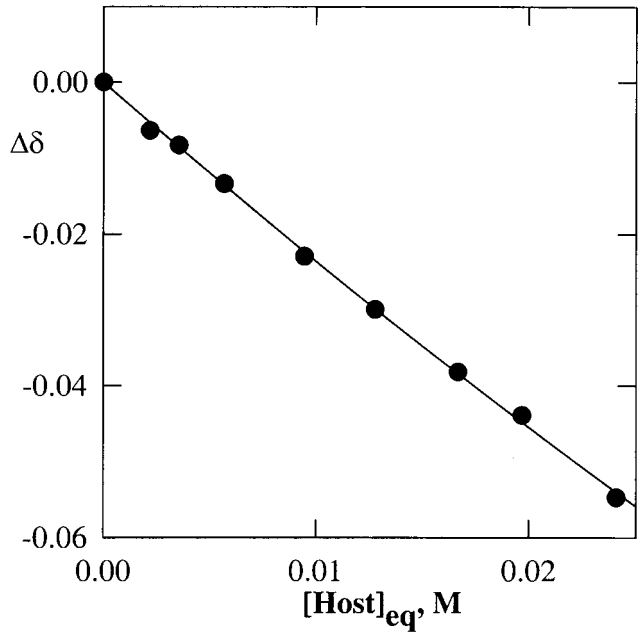


Figure 3. Titration curve of 0.13 mM tetramethylammonium picrate with cyclophane **3** in $CDCl_3$.

and K_{ass} is the equilibrium constant. In the case of cyclophanes **3** and **4** the titrations indeed showed the expected behaviour (Table 2), but plots of $\Delta\delta$ against host concentration were in all cases decidedly linear with no appreciable negative curvature (Figure 3). This clearly indicates that the product K_{ass}[Host], which appears in the denominator of the Equation (1), is small relative to 1 ($K_{ass} < 10$).

$$\Delta\delta = \frac{\Delta\delta_{\infty} K_{ass}[\text{Host}]}{1 + K_{ass}[\text{Host}]} \qquad (1)$$

In the control experiment, the addition of 22 mM of cyclophane **5** caused hardly any appreciable changes of the resonances of *N*-methylpyridinium ($\Delta\delta = -0.003$) and tetramethylammonium ($\Delta\delta = -0.002$) picrates, which are well over one order of magnitude smaller than those measured with either **3** or **4**. This indicates that the chemical shift variations observed during the titrations of quats with **3** and **4** are not due to a medium effect, but are likely to be ascribed to cation-π interactions. However, in all cases binding affinities are too weak to be translated into meaningful equilibrium constants.

Conclusions

This paper describes the synthesis and characterisation of three, new macrocyclic compounds incorporating a bisphenol A unit and an acetylenic moiety. Our idea was that the presence of several electron rich units, namely aromatic rings and triple bonds, could provide multiple binding sites, whereby the stabilising cation-π interactions with quats could be established. ^{1}H NMR measurements showed that the interactions between cyclophanes **3** or **4** and tetraalkylammonium cations are clearly detectable, but weaker than expected. A likely reason for the low binding affinities

Table 2. ^{1}H NMR titration data.[a] Observed upfield shifts ($-\Delta\delta_{obsd}$, ppm)[b] of *N*-Me protons[c] upon addition of cyclophanes **3** and **4** to quaternary salts at 30 °C in $CDCl_3$

Guest	Cyclophane **3**	Cyclophane **4**
Benzyltrimethylammonium chloride	0.028	0.026
N-Methylpyrrolidinium iodide	0.027	0.025
Acetylcholine iodide	0.045	0.042
Tetramethylammonium picrate	0.050	0.044
N-Methylpyridinium picrate	0.059	0.047

[a] Guest concentrations were in all cases < 1mM.
[b] At 22 mM host concentration.
[c] The resonances of other protons were monitored whenever possible and found to exhibit variations comparable to those reported for the *N*-Me protons.

is that the two hosts do not form well pre-organised cavities capable of offering complementary surfaces for the guest cations. This can also be seen from the distorted conformations revealed by the X-ray analysis. Interestingly, some self-complementarity of the host molecules was observed in the crystalline state in which two host molecules form dimeric units mainly via π-π and CH-π interactions.

Acknowledgements

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Supplementary Data

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 120573 and 120574). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK.

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