Cyclophanes as Neutral Receptors for Quaternary Ammonium and Iminium Cations in Chloroform Solution

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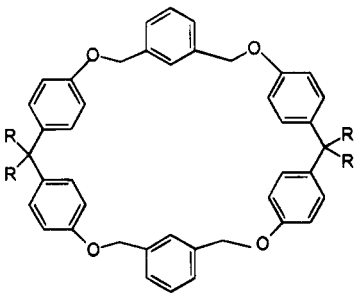
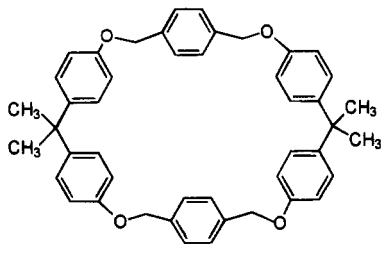
Complexation of quaternary ammonium guests by negatively charged cyclophane hosts in aqueous solution has been extensively studied in recent years.[1] Less common, yet well documented, is the binding of quaternary ammonium cations by neutral hosts in lipophilic media.[2-6] Here electrostatic cation–anion attractions are absent, and solvophobic effects can hardly provide a major driving force for binding. Positive interactions between host and guest are believed to arise from the attraction between the positive charge of the guest and the electron-rich faces of the aromatic rings (cation–π interaction).[2] Earlier examples of neutral macrocyclic hosts capable of forming inclusion compounds with ammonium ions are provided by Dougherty's ethenoanthracene-based cyclophane[2] and Collet's cryptophanes.[3] More recent examples include various calixarenes[4,5] and homocalixarenes.[6]

We report here the binding properties of cyclophane **1a** toward the quaternary salts **3–8** in chloroform solution. The macrocyclic analogues **1b,c** and **2** were also investigated for comparison purposes.



1a R,R = -$(CH_2)_5$-
1b R = -CH_3
1c R = -H



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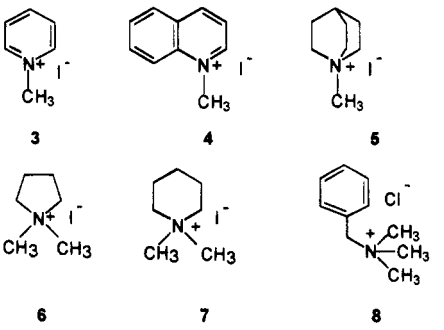
Addition of varying amounts of **1a** in the concentration range from 1 to 20 mM to solutions of the quaternary salts **3–8** in $CDCl_3$ at 30 °C caused regular and reproducible upfield shifts ($\Delta\delta$) of the ^{1}H NMR resonances (300 MHz) of the cations of increasing magnitude on increasing the host concentration. In addition to the methyl protons, changes of the resonances of other protons were monitored whenever possible. These were the α-CH and β-CH of **3**, the α-CH and γ-CH of **4**, and the α-CH_2 of **5–8**. The magnitude of the upfield shifts in the titrations of the iminium ions **3** and **4** was significally larger than that observed with the ammonium ions **5–8**. In no case



3 **4** **5**

6 **7** **8**

were observed separate signals for free and complexed guest, showing that complexation was fast on the ^{1}H NMR time scale. Translation of the titration experiments into estimates of the binding constants K was straightforward in the cases of **3–5**, for which plots of $\Delta\delta$ against host concentration showed an unmistakable negative curvature. In these cases the data could be fitted to a good precision to eq 1, where the binding constant K and

$$\Delta\delta = \frac{\Delta\delta_\infty K[H]}{1 + K[H]} \qquad (1)$$

the upfield shift of the guest fully saturated by the host ($\Delta\delta_\infty$) were treated as adjustable parameters in a nonlinear least-squares fitting procedure. From statistical analysis of the fitting procedure, from comparison of the data obtained from different protons, and from duplicated experiments, we estimate the determined K values to be reliable to ±20% (±0.1 kcal in $\Delta G°$).

Titration of the ammonium ions **6–8** showed chemical shift changes comparable to those found with **5**, but plots of $\Delta\delta$ vs [H] were decidely linear, as predicted by eq 1 whenever the product $K[H]$ is negligible with respect to 1. Thus, the ^{1}H NMR titration experiments provide evidence for the involvment of cations **6–8** in association equilibria with host **1a** that are most likely of the same nature as that observed with **5** but not such as to allow an estimate of the equilibrium constants. The results of our binding studies are summarized in Table 1. An example of a titration curve is reported in Figure 1.

In an exploratory investigation carried out in the early part of this work, cyclophanes **1b,c** and **2** were also considered as potential hosts for organic cations. Al-

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Table 1. Stability Constants, Free Energies of Binding, and Limiting Upfield Shifts for the Complexes of Cyclophane 1a with Cationic Guests in $CDCl_3$ at 30° C[a]

guest	K (M^{-1})	$-\Delta G°$ (kcal mol^{-1})[b]	$-\Delta\delta_\infty$ (ppm)[c]
3	18	1.7	2.0 (CH_3), 1.8 (α-CH), 2.1 (β-CH)
4	32	2.1	1.5 (CH_3), 1.6 (α-CH), 2.1 (γ-CH)
5	47	2.3	0.096 (CH_3), 0.098 (α-CH_2)
6	<5	<0.9	0.063 (CH_3), 0.063 (α-CH_2)[d]
7	<5	<0.9	0.040 (α-CH_2), 0.033 (β-CH_2)[d]
8	<5	<0.9	0.025 (CH_3), 0.025 (CH_2)[d]

[a] Guest concentration was 1 mM. [b] 1 cal = 4.184 J. [c] Calculated limiting upfield shifts unless otherwise stated. [d] Upfield shifts observed at host concentrations of about 15 mmol dm^{-3}.

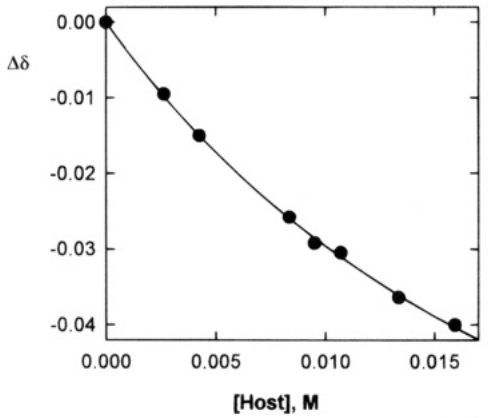

Figure 1. Titration curve of 1 mM *N*-methylquinuclidinium iodide (CH_3 protons) with cyclophane **1a** in $CDCl_3$. Points are experimental, and the curve is calculated.

though the limited solubilities of **1b,c** in chloroform prevented extensive investigation of their binding properties, it was nevertheless clear that some binding occurred with **5** but to a much smaller extent when compared with **1a**. Furthermore, some binding between **1b** and **4** was observed, but the ^1H NMR spectrum of **4** turned out to be completely insensitive to addition of **2** up to a concentration of 26 mM.

There seems to be little doubt that the complexation phenomena described in this work involve inclusion of the organic cations in the cavity of the macrocyclic hosts. It is apparent that the presence of the *p*-xylylene spacers renders the cavity of **2** too large for efficient binding. Inspection of CPK molecular models reveals a substantial degree of conformational looseness in the macrocycles **1a**–**c**. However, the models suggest that the bulky pentamethylene moieties render **1a** somewhat less mobile (more preorganized) than its analogues. The models also show that *N*-methylquinuclidinium ion (**5**), because of its globular shape, is best suited to fill the cavity of **1a** in its extended thoroid conformation (Figure 2). The good complementarity between host and guest is responsible, in our view, for the fact that the complex formed by **5** with **1a** is not only more stable than those formed by the other ammonium ions, but also by the iminium ions. This finding is admittedly unexpected, as strong π-stacking donor–acceptor interactions are likely to operate with the electron deficient piridinium and quinolinium ions[8] and nicely emphasizes the importance of complementarity between host and guest.

Figure 2. Ball and stick computer-drawn model of the complex between cyclophane **1a** and *N*-methylquinuclidinium ion.

Experimental Section

All commercially available compounds were used without further purification. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a 300 MHz spectrometer.

Dispiro[1,10,24,34-tetraoxa[2]metacyclo[2.1]paracyclo[2]metacyclo[2.1]paracyclophane-17,1′:41,1″-dicyclohexane] (1a) and Related Compounds 1b,c and 2. An equimolar solution of 1,3-bis(bromomethyl)benzene (5 mmol) and 1,1-bis(hydroxyphenyl)cyclohexane[7] in DMF (40 mL) was slowly added over 4 h to a suspension of excess K_2CO_3 in DMF (160 mL) at 75 °C under vigorous stirring. When the addition was over, stirring and heating were continued for 4 h. Standard workup, followed by chromatographic elution on silica gel with hexane–chloroform, gave a 10% yield of analytically pure **1a**: mp 288–290 °C; ^1H NMR δ 7.39–6.98 (m, 24H), 5.02 (s, 8H), 2.19 (m, 8H), 1.54 (m, 12H); ^{13}C NMR δ 156.27, 141.38, 137.91, 128.66, 127.96, 126.48, 126.14, 114.38, 69.74, 44.93, 37.06, 26.41, 22.90; ES-MS *m*/*z* 780 $(M + K)^+$. Anal. Calcd for $C_{22}H_{52}O_4$: C, 84.29; H, 7.07. Found: C, 83.92; H, 7.04.

Compounds **1b,c** were synthesized in similar way starting from 1,1-bis(4-hydroxyphenyl)propane (bisphenol A) and bis(4-hydroxyphenyl)methane, respectively, whereas **2** was prepared from bisphenol A and 1,4-bis(bromomethyl)benzene. Spectroscopic and ES-MS data for **1b,c** and **2** were in good agreement with the assigned structures. The purity of all these compounds for which no elemental analysis is provided was judged to be >98% by HPLC analyses: **1b**, mp 245 °C dec; **1c**, mp 218–220 °C; **2**, mp 198–200 °C.

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