Host–Guest Complexes with Water-Soluble Macrocyclic Polyphenolates Including Induced Fit and Simple Elements of a Proton Pump[1]

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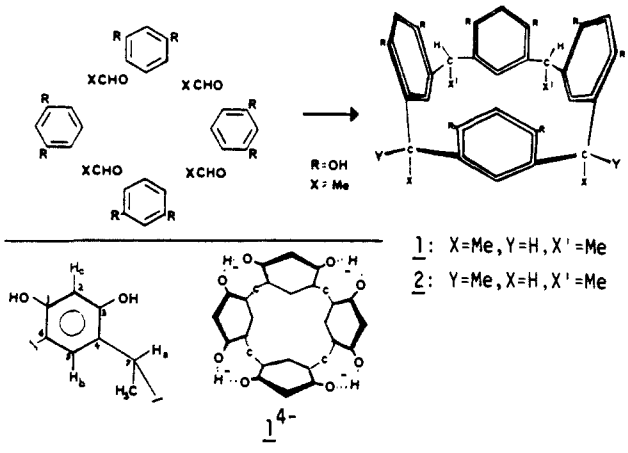
Abstract: The cyclophanes **1** and **2** obtained from condensation of 4 mol of resorcinol and 4 mol of acetaldehyde bind ammonium compounds with association constants between 10 and 10^5 M^{-1} in alkaline solutions, in spite of their open bowllike structure. The binding energy is correlated to the Coulomb attraction as a function of the charge-separating distance. The association rates are almost diffusion controlled, and the dissociation rates reflect the binding constants. Bis(trimethylammonium) compounds act as ditopic substrates, forming RS_2 complexes. Complexation-induced ^1H NMR shifts are assigned to electrostatic rather than to anisotropy effects of the phenolic rings. The stabilizing effect of hydrogen bonds between the phenols is visible in pK_s values, which in comparison to resorcinol are lower for the removal of the first protons but much higher for removal of the remaining protons. The configurational isomer **2** shows three different forms, A, B, and C, as a function of pH; only one of these (B) is capable of complexing ammonium derivatives. Addition of ammonium guest compounds to C reversibly leads to B, which must absorb two protons from the solution in order to form hydrogen bonds, thus representing a simple element of a proton pump.

The condensation of phenols with aldehydes, studied already over 100 years ago by Adolf von Baeyer,[2a] provides probably the most simple entry into macrocyclic ring compounds. The products, e.g., from resorcinol and acetaldehyde, have been studied by numerous workers,[2] and recently also by NMR spectroscopy[2e,f] and by X-ray crystallography.[2g,h] While the conformations of the resulting configurational isomers **1** and **2** have been firmly established in the form of their octaesters,[2e] the phenols themselves have only recently been analyzed and were found to lead to interesting host–guest complexes in solution.[3] Structurally related cyclophanes from para-substituted phenols and formaldehydes,[4] termed calixarenes by Gutsche,[5] show interesting inclusion compounds in the solid state;[5] their very limited solubility explains why only recently a relatively weak complexation in solution has been reported.[6,7] In this paper we present a detailed analysis of the complexes formed with isomer **1**[3] as well as with **2** and of the conformational changes accompanying both deprotonation and guest binding with **2**. The latter observations provide also an example for proton release upon guest binding via an induced-fit mechanism.



Host 1. Acidity and Structure. Preparation and separation of the epimers **1** (all-cis) and **2** (cis–trans) were carried out at described by Högberg.[2e,f] NMR spectra of **1** (R = OH) in DMSO show eight phenolic protons besides four sharp signals for the other different hydrogen atoms and six ^{13}C NMR signals (Table I), indicating a (possibly time averaged) symmetry for **1** as proposed already by Högberg[2f] for a corresponding octaester conformer. Addition of NaOD in mixed aqueous solvents leads to distinct changes at 2 equiv of NaOD for only three protons signals, whereas four proton and six carbon absorptions show an inflection at 4 equiv of NaOD/1 mol of **1** (Figure 1). Further addition of NaOD does not affect the observed shifts; a separate experiment with excess $NaOCD_3$ in a CD_3OD solution demonstrates that the remaining four protons in the tetraphenolate **1** (R = O^-/OH) are not removed by this strong base. A comparison of the deprotonation-induced shifts (DIS) in **1** and resorcinol **3**, in which both protons are dissociated (Table I), reinforces the final structure of a tetraphenolate from **1**, as the observed suitable DIS values are almost exactly twice as high in **3** (Table I). The deprotonation ^{13}C shifts for **3** show only one inflection point with 2 equiv of NaOD, in line with literature results on related phenols.[8a]

The NMR results are only compatible with the formation of a tetraphenolate structure **1**, which contains four equivalent units

(1) Host–Guest Chemistry, part 15; part 14: Schneider, H.-J.; Kramer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) (a) Baeyer, A. v. *Ber. Dtsch. Chem. Ges.* **1872**, *5*, 25. (b) Niederl, J. B.; Vogel, H. J. *J. Am. Chem. Soc.* **1940**, *62*, 2512. (c) Zinke, A.; Ziegler, E. *Ber. Dtsch. Chem. Ges. B* **1944**, *77*, 264. Zinke, A.; Ott, R.; Garanna, F. H. *Monatsh. Chem.* **1958**, *89*, 135. Zinke, A.; Kretz, R.; Leggewie, E.; Hössinger, K. *Monatsh. Chem.* **1952**, *83*, 1213. (d) Erdtman, H.; Haglid, F.; Ryhage, R. *Acta Chem. Scand.* **1964**, *18*, 1249. Erdtman, H.; Högberg, A. G. S.; Abrahamson, S.; Nilsson, B. *Tetrahedron Lett.* **1968**, 1679. (e) Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498. (f) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046. (g) Nilsson, B. *Acta Chem. Scand.* **1968**, *22*, 732. (h) Palmer, K. J.; Wong, R. Y.; Jurd, L.; Stevens, K. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *B32*, 847. (i) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826. (j) Cram, D. J.; Karbach, S.; Kim, H.-E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229. Also see further references in these papers.

(3) See preliminary publication: Schneider, H.-J.; Güttes, D.; Schneider, U. *Angew. Chem.* **1986**, *98*, 635; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 647. The $\Delta G°$ value for the complexation of *n*-Bu_4NBr given there, which should read ≤ 1.3, had been refined (see Table III).

(4) (a) Cornforth, J. W.; D'Arcy-Hart, P.; Nicholls, G. A.; Rees, R. J. W.; Stock, J. A. *Br. J. Pharmacol.* **1955**, *10*, 73. (b) Happel, G.; Mathiasch, B.; Kämmerer, H. *Makromol. Chem.* **1975**, *176*, 3317.

(5) (a) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161. (b) Gutsche, C. D. *Top. Curr. Chem.* **1984**, *123*, 1 and references cited therein. These reviews summarize comprehensively also conformations, NMR spectra, and hydrogen bonds in macrocyclic polyphenols.

(6) Bauer, L. J.; Gutsche, C. D. *J. Am. Chem. Soc.* **1985**, *107*, 6063.

(7) For better water-soluble calixarene derivatives, see: (a) Shinkai, S. *Pure Appl. Chem.* **1986**, *58*, 1523. (b) Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 2409. (c) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981.

(8) (a) See: Agrawal, P. K.; Schneider, H.-J. *Tetrahedron Lett.* **1983**, *24*, 117 and references cited therein. (b) Murto, J. *Ann. Acad. Sci. Fenn., Ser. A2* **1962**, *177*, 1.

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Table I. Deprotonation-Induced NMR Shifts (DIS)[a] in Hosts **1** and **2** and in Resorcinol **3** and pK_s Values[b]

^{13}C NMR

C no.	ϑ_0 (1)	DIS (1)	ϑ_0 (2)	DIS (2)	ϑ_0 (3)	DIS (3)
1.3	152.7	4.8	155.0 154.3	6.2 5.9	158.1	10.0
2	103.6	3.3	104.5	4.7	103.9	6.2
4.6	125.9	0.8	128.5 124.8	−2.3 −3.0	108.8	−0.8
5	125.6	−4.3	128.8 128.6	−2.2 −3.8	132.0	−1.1
7	29.5	0.4	32.7	−0.7		
Me	21.1	0.7	22.1	−0.7		

^{1}H NMR

H no.	ϑ_0 (1)	DIS (1) I	DIS (1) II	ϑ_0 (2)	DIS (2)	ϑ_0 (3)		DIS (3)
a	4.53	0.00	0.05	4.50	−0.22	H1:	6.40	−0.53
b	6.33	*c*	−0.43	6.99 6.42	0.10 −0.01	H2,4:	6.46	*d*
c	7.21	0.10	−0.25	6.34 6.33	−0.33 −0.42	H3:	7.13	−0.31
CH_3	1.62	0.09	−0.07	1.27	−0.15			

pK_s Values

	1	**2B**	**3**	
pK_s (a)	9.4	14.8	11.0	(in acetone-d_6/D_2O, 3/5)[c]
pK_s (b)	11.7		13.6	(in DMF-d_6/D_2O, 1/1)[c]

[a] In ppm, ±0.015 for ^{1}H NMR, ±0.15 for ^{13}C NMR; measured in acetone-d_6/D_2O, 3/5 (v + v), at 300 ± 1 K; ionization step, I; dianion, II, tetraanion; for ^{13}C and with **3** only the step to tetraanion is observable. [b] pK_a values (±0.2) from simultaneous pH measurements, at 300 ± 5 K. [c] Inflection step only at II observable. [d] Proton not detected because of overlapping peaks.

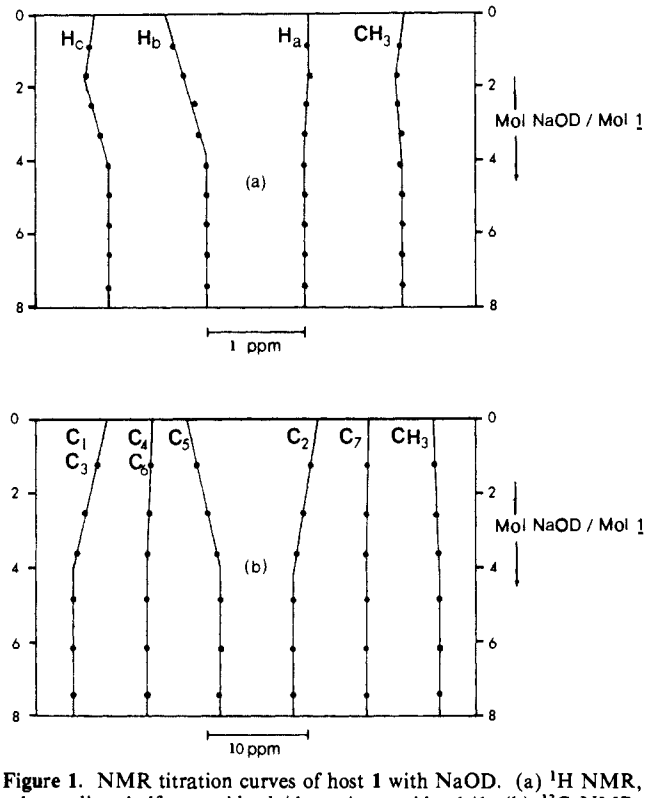

Figure 1. NMR titration curves of host **1** with NaOD. (a) ^{1}H NMR, solvent dimethylformamide-d_6/deuterium oxide, 1/1: (b) ^{13}C NMR, solvent acetone-d_6/deuterium oxide, 5/3.

and a cyclic hydrogen bond from which the remaining protons dissociate even less than from methanol (pK_s = 15.1[8b]). The particular stability of **1** (R = O^-/OH), which is understandable in view of the possible ideal geometric disposition of the O···H···O arrangement[9] and the cyclic delocalization of the negative charge in the cyclophane, is also visible in the higher acidity of the first four protons to be removed for formation of the tetraanion: potentiometric titrations in two mixed solvents show pK_s values that are lower than the ones of the corresponding resorcinol **3** by 2 units[10] (see Table I). Preassociation by similar hydrogen bonds may also explain why these cyclophanes are easily formed without substantial polymerization, even in the absence of high dilution.

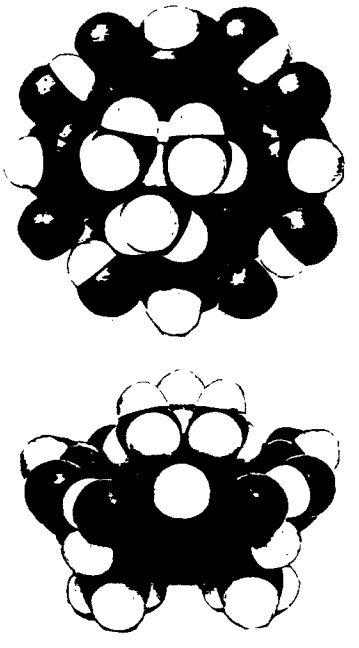

Figure 2. Complex between host **1** and tetramethylammonium chloride.

(9) For a related case of flip-flop hydrogen bonds, see: Saenger, W.; Betzel, C.; Hingerty, B.; Brown, G. M. *Angew. Chem.* **1983**, *95*, 908; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 883.

(10) For related pK_A changes in water-soluble calixarenes, see: Shinkai, S.; Araki, K.; Koreishi, H. *Chem. Lett.* **1986**, 1351. Also ref 7a.

Table II. NMR Shifts of Structures A, B, and C (from Host **2**)[a]

(mol NaOD added):	A 0.0	B 3.5	C 76.0
		^{13}C NMR	
C-1, C-3	155.0 (4 C) 154.3 (4 C)	158.8 (2 C) 157.7 (4 C) 156.9 (2 C)	161.2 (4 C) 160.2 (4 C)
C-2	104.5 (4 C)	111.1 (1 C) 109.6 (2 C) 107.4 (1 C)	109.2 (4 C)
C-4, C-6	128.5 (4 C) 124.8 (4 C)	128.5 (4 C) 127.8 (2 C) 127.4 (2 C)	126.2 (4 C) 121.8 (4 C)
C-5	128.8 (2 C) 128.6 (2 C)	135.0 (1 C) 128.0 (2 C) 123.7 (1 C)	126.6 (2 C) 124.8 (2 C)
C-7	32.7 (4 C)	50.5 (2 C) 50.9 (2 C)	32.0 (4 C)
Me, Me	22.1 (4 C)	21.7 (2 C) 19.5 (2 C)	22.8 (4 C)
		^{1}H NMR	
H-a	4.50 (q, 4 H)[c]	4.65 (q, 2 H)[c] 3.90 (q, 2 H)	4.28 (q, 4 H)[b]
H-b	6.99 (s, 2 H) 6.42 (s, 2 H)	7.26 (s, 1 H) 7.14 (s, 2 H) 7.02 (s, 1 H)	7.09 (s, 2 H) 6.41 (s, 2 H)
H-c	6.34 (s, 2 H) 6.33 (s, 2 H)	6.00 (s, 1 H) 5.97 (s, 2 H) 5.96 (s, 1 H)	6.01 (s, 2 H) 5.92 (s, 2 H)
Me	1.27 (d, 12 H)[b]	1.81 (d, 6 H)[c] 1.73 (d, 6 H)	1.12 (d, 12 H)[b]

[a] Measuring conditions, see Table I; shifts vs TMS (with dioxane as internal reference). Number of atoms from signal areas in parentheses. [b] J = 6.6 ± 0.2 Hz. [c] J = 7.5 ± 0.2 Hz.

Host 1. Complexation. The tetraphenolate **1** binds methylammonium compounds[3] with spectacular high association constants, K (Table III), considering the open bowllike structure of the host (Figure 2). CPK models demonstrate that in such complexes with N^+–Me guest molecules the N^+ atoms lie *above* the rim formed by the upper phenyl parts of the macrocycle. If the binding constants are extrapolated to small electrolyte concentrations (see ref 1), they approach for choline-type substrates micromolecular values that are usually believed to require encapsulation in more closed cavities, such as they occur in protein receptors.[11] The strong complexes with **1** must be due to electrostatic attraction between R_3N^+Me and the anionic macrocycle, which supersedes separation of the ions by water. Hydrophobic or lipophilic interaction contributes only little, as established by the just-measurable association constant with *tert*-butyl alcohol **8** and the nondectability of binding with other electroneutral molecules (see Table III).

As there is a pronounced decrease of the complexation free energy $\Delta G°$ with additional CH_2 groups separating the N^+ atom from the anionic ring[3] (Table III), and the residual groups R in $R_3N^+MeX^-$ have little influence on $\Delta G°$ (Table III), an attempt was made to estimate the change in the electrostatic contribution $\Delta G°_{el}$ with the Coulomb equation (1) where q represents the

$$\Delta G°_{el} = \frac{q_1 q_2}{\epsilon r} \qquad (1)$$

atomic charges, ϵ the dielectric constant, and r the average distance

(11) Strong association of ammonium compounds to macrocyclic hosts have been reported for crown ethers and in related spherands, however, in nonaqueous systems in which competition of solvation against intimate ion-pair formation is lacking: Cram, D. J.; Dicker, I. B. *J. Chem. Soc., Chem. Commun.* **1982**, 1219. Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43 and references cited therein. In water, the strongest complexes found so far with methylammonium substrates and an anionic macrocycle show only K = 500 M^{-1}: Dhaenens, M.; Lacombe, L.; Lehn, J.-M.; Vigneron, J.-P. *J. Chem. Soc., Chem. Commun.* **1984**, 1097.

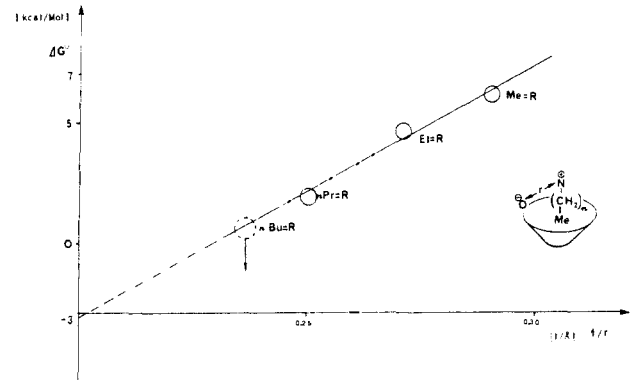

Figure 3. Free complexation energies $\Delta G°$ as a function of Coulomb energy for complexes between host **1** and substrates $[Me(CH_2)_n]_4NCl$ = R_4NCl.

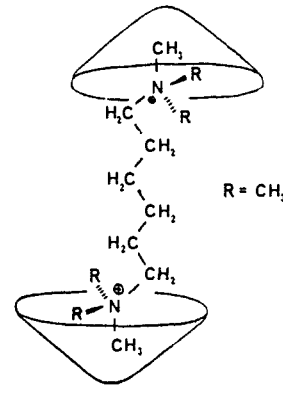

Figure 4. A representative complex between hosts **1** and $Me_3{}^+N(CH_2)_6N^+Me_3$, $2Cl^-$ as ditopic substrate.

from N^+ of the guest to O^- from the host, as estimated from CPK models. Figure 3 shows an approximately linear correlation, the significance of which is visible in the resulting slope giving ϵ = 32, which is a reasonable value for a highly polar medium. The negative $\Delta G°$ value obtained for long distances r (see Figure 3) can be the result of repulsive interactions, which in the observed complexes and their $\Delta G°$ values are overcome by electrostatic interaction.

The large complexation-induced NMR shifts (CIS, Table III), obtained simultaneously with K by nonlinear least-squares fit of NMR titration curves,[1] are in line with the geometry of the complexes as shown in Figure 2. The similar CIS values for N^+–Me protons in all trimethylammonium derivatives (~−2 ppm for **4**, **9**, and **10**) as well as in *N*-methylquinuclidine **12** (−2.5 ppm) indicate that the protons are shielded to the same degree irrespective of being more or less exposed to the host aromatic ring currents (only one methyl group at a time can be immersed in the cavity). The conclusion that an effective charge variation in the guest molecule upon complexation is the dominating source of the observed shielding is also supported by the similar CIS values for $N–CH_2$ in **5**, **9–11**, and **13** (~−1.2 ppm) and CH_3 in **5**, which are the average from protons close and more remote from the cavity. Finally, the small shielding obtained for the electroneutral *tert*-butyl alcohol **8** (0.4 ppm) also indicates the minor contribution of anisotropy effects exerted by the tetraphenolate **1**.

Bifunctional ammonium compounds (**14–17**) can act as ditopic substrates on the host **1** (Figure 4); the N^+Me_3 proton shielding observed upon addition of excess **1** is similar to the monofunctional guests (~−2 ppm, Table IV) and suggests efficient complexation of **14–17**. Attempts to apply the numerical fitting procedures[1] successfully used for the monofunctional substrates failed with NMR titrations for those bifunctional derivatives, in which the N^+ centers are separated by only n = 3 or 4 methylene groups (**16**, **17**); even for **14** (n = 12) and **15** (n = 6) convergence in the simulation was only achieved if the association constants K_1 and K_2 for the possible complexes (**1**·1*S* and **1**·2*S*) where set to be

Table III. Complexation-Induced ^{1}H NMR Shifts (CIS) and Association Constants K Derived from Shift Titrations with Host **1**[a,b]

compd	subst at N	proton	CIS	K^b	K_{av}	$\Delta G°$
4	Me_4	CH_3	1.84	29 ± 6	29 ± 6	6.1
5	Et_4	CH_3	1.19	3.5 ± 0.4	3.4 ± 0.5	4.8
		CH_2	1.18	3.3 ± 0.5		
6	*n*-$Prop_4$	3-CH_3	0.42	0.032 ± 0.005	0.030 ± 0.005	2.0
		2-CH_2	0.42	0.025 ± 0.005		
		1-CH_2	0.42	0.032 ± 0.005		
7	*n*-Bu_4	all H	<0.01	<0.002	<0.002	<0.5
8	Me_3COH	CH_3	0.36	0.007 ± 0.001	0.007 ± 0.001	1.1
9	Me_3, $^1CH_2CH_2OH$ (cholin)	CH_3	2.02	53 ± 10	50 ± 10	6.4
		1-CH_2	1.20	50 ± 15		
		2-CH_2	0.56	46 ± 15		
10	Me_3, *n*-propyl	CH_3	2.03	40 ± 10	40 ± 10	6.3
		1-CH_2	1.2[b]			
		2-CH_2	0.5[b]			
		3-CH_3	0.1[b]			
11	Et_3, CH_2-Ar	CH_3	1.41	2.1 ± 0.1	2.1 ± 0.2	4.5
		CH_3-CH_2	1.21	2.1 ± 0.2		
		Ar CH_2	0.79	2.0 ± 0.2		
12	quinuclidin, *N*-Me	CH_3	2.54		5.2 ± 2.1	5.0
		1-CH_2	1.43			
		2-CH_2	0.72	5.2 ± 2.1		
		3-CH	0.61			
13	carnitin	CH_3	2.07	6.5 ± 0.7	6.5 ± 0.7	5.2
		1-CH_2	1.3[b]			
		CH	0.6[b]			
		3-CH_2	0.1[b]			

[a] From measurements in D_2O (0.5 M NaOD) at 298 ± 1 K with dioxane or methanol as internal reference. Anions Y, Br^- (for **4–7**, **10**), Cl^- (**9**, **11**, **13**), I^- (**12**); a control experiment with **5**, Y = Br^-, I^- showed ΔCIS < 0.002 ppm. CIS values (±0.01) in ppm, K in 10^3 M^{-1} units, $\Delta G°$ in kcal/mol. [b] Protons not reported were not analyzable due to overlapping peaks and/or due to line broadening; CIS values for such protons were partially obtained from single measurements at 99 ± 1% complexation. [c] CIS values of <0.01 ppm with [**1**] = 0.1 M observed for all protons of toluene, *p*-nitrophenol, *p*-aminobenzoic acid, 6-aminobenzoic acid, 4-aminobutanoic acid, indicating K < 0.002 or $\Delta G°$ < 0.5.

Table IV. Complexation of Bifunctional Ammonium Compounds $Me_3{}^+N(CH_2)_nN^+Me_3$ with Host **1**[a]

compd	δ_0	CIS_{exp}	CIS(1:1)	CIS(1:2)	K
14, n = 10	3.09	2.01[e]	1.32	2.06	90[c]
15, n = 6	3.10	2.09[e]	1.34	2.05	10[c]
16, n = 4[b]	3.13	1.98[e]			
17, n = 3[b]	3.19	2.05[e]			
10[d]			2.03		40

[a] See footnote *a* to Table III. CIS_{exp}, largest CIS (observed with **1** = 0.1 M). [b] No convergence with computer fit; see text. [c] Error estimated by simulation ~±100%; see text. [d] Included from Table III for comparison. [e] 95% complexation.

Table V. Dynamics of the Reaction between Host **1** and Cholin Bromide **9** by Simulation of **9**-Methyl Proton Line Shapes[a]

pf	$W_{1/2}$(calcd)	$W_{1/2}$(obsd)	pf	$W_{1/2}$(calcd)	$W_{1/2}$(obsd)
0.05	10.4	12.1	0.94	14.4	16.1
0.10	40.9	42.3	0.95	10.4	10.5
0.90	40.9	36.4	0.98	2.7	3.0

[a] Half-height line width $W_{1/2}$ (Hz) as calculated with $k_{diss} = 2 \times 10^3$ s^{-1} (best fit) for different concentrations of free substrate S_f; pf = $[S_f]/[S_{total}]$; measurements at 0.1 < pf < 0.9 not possible because of too large $W_{1/2}$. Conditions $0 < [\mathbf{1}] < 1 \times 10^{-3}$, $1 \times 10^{-4} < [S] < 2 \times 10^{-4}$, 0.5 M NaOD, 298 ± 1 K. The $W_{1/2}$(obsd) values are corrected by substraction of $W_{1/2}$ for dioxane as internal reference.

equal. The values obtained for the other two unknown parameters CIS(1:1) and CIS(1:2) as well as the constant K agree approximately, however, with the values predicted from the monofunctional compounds. In particular, CIS = ~−1.3 ppm for the 1:1 complex reflects the average of one complexed and one uncomplexed site. Obviously, a separation by at least six methylene groups is necessary until the complex formation with the trimethylammonium groups can be treated as the one with the simpler substrates.

The dynamics of the complex dissociation are visible in the substantial line broadening, particularly of the methyl proton signals with the methylammonium derivatives S = **4**, **9**, **10**, **12**, and **13**. In fact, disappearance of these signals in the noise limited NMR-shift titrations to concentration ranges in which either little or much complexation is observed (see the Experimental Section). For the same reason, the analysis of the observed line shapes, carried out with cholin bromide **9**, was restricted to complexation degrees below 15% and above 85% (Table V). With proper concentration ratios[12a] of **1** and **9**, Lorentzian line shapes were observed and simulated,[12b] which can be characterized by their half-height width $W_{1/2}$ (Table V). On the basis of the different populations (pf) of the free substrate (S_f), which is calculated from the known equilibrium constant K, the best agreement between experiment and theory was obtained for a S_f, lifetime of $\tau = 2 \times 10^{-4}$ s (Table V). The corresponding rate constant for dissociation $k_d = 1/\tau = 5 \times 10^3$ s^{-1} gives by division with K a rate of association constant of $k_a = 2.5 \times 10^8$ mol^{-1} s^{-1}. Such diffusion-controlled rates have also been reported for other host–guest complexes[13] as well as for many protein receptors.[14,15]

Host 2. Base Effects and Conformations. The epimer **2** shows an entirely different behavior compared to **1** upon addition of sodium hydroxide. The ^{1}H NMR spectra of the electroneutral

(12) (a) Cf: Freeney, J.; Batchelor, J. G.; Albrand, J. P.; Roberts, G. C. K. *J. Magn. Reson.* **1979**, *33*, 519. (b) The program used is based on the classical uncoupled A–B exchange formalism, see: Gutowsky, H. S.; Holm, R. H. *J. Chem. Phys.* **1950**, *25*, 1228. Newmark, R. *J. Chem. Ed.* **1983**, *60*, 45.

(13) (a) Sutherland, I. O. In *Applications of NMR Spectroscopy to Problems in Stereochemical and Conformational Analysis*; Takeuchi, Y., Marchand, A. P., Eds.; Verlag Chemie International: Deerfield Beach, 1986; p 1. (b) Rohrbach, R. P.; Rodriguez, C. J.; Eyring, E. M.; Wojcik, J. F. *J. Phys. Chem.* **1977**, *81*, 944 (cyclodextrins). (c) Cramer, F.; Saenger, W.; Spatz, H.-C. *J. Am. Chem. Soc.* **1967**, *89*, 14 (cyclodextrins); (d) Lein, G. M.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1982**, 301 (spherands).

(14) See: Fersht, A. *Enzyme Structure and Mechanism*; W. H. Freeman: San Francisco, 1977; p 130.

(15) For a recent use of the tetraphenolate **1** for the inhibition of cholineacetate hydrolysis, see: Schneider, H.-J.; Schneider, U. *J. Org. Chem.* **1987**, *52*, 1613.

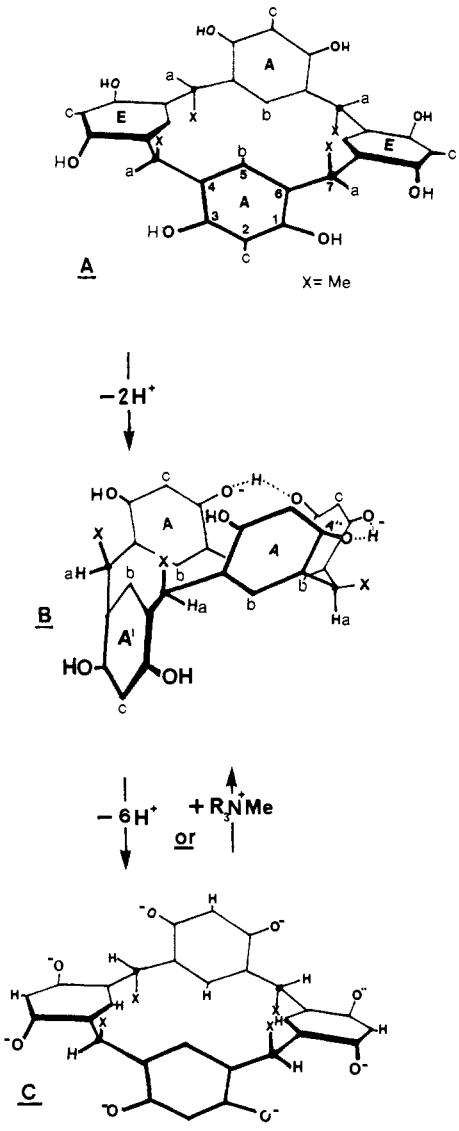

Figure 5. Structures of 2A–C.

octaphenol **2** has six signals, its ^{13}C NMR spectrum nine signals (structure A, Table II, Figures 5 and 6). This is in line with a conformation containing 2 + 2 equivalent benzene rings that—similarly to corresponding octaesters[2f]—are oriented pairwise equatorially and axially with respect to the macrocyclic plane (conformer A = e,a,e,a). Other than with **1**, addition of 2 mol of NaOD does not lead to resorcinol-like steadily increasing deprotonation shifts but to the appearance of 10 new ^1H and 16 new ^{13}C NMR signals. These as well as the observed relative intensities (Figure 6, Table II) indicate a conformation B (a,a′,a′,a″) in which only two benzene (a′) moieties are equivalent. An excess of NaOD finally produces again six new ^1H and nine new ^{13}C signals, which suggest a C conformation with e,a,e,a-oriented aromatic rings, similar to A but distinct by the charges. Thus, there are three structures slowly interconverting on the NMR time scale, which show completely reversible population changes as a function of the concentration ratio [NaOD]/[**2**] or pH (Figure 7).

Inspection of molecular models helps to clarify the observed changes. The electroneutral octaphenol **2** assumes an e,a,e,a conformation A as the cis/trans configuration of methyl substituents X this way avoid the repulsion with the C(1)–OH aromatic groups. The latter interaction (twofold) is then compensated in conformer B (2^{2-}) by formation of 2 $O^-\cdots H\cdots O$ hydrogen bonds, which are only possible in such a near-boat-shaped structure. It then takes a large excess of NaOD to withdraw more protons (Figure 7); this leads not even to an intermediate formation of a stable tetraphenolate: a cyclic boat-shaped structure similar to **1** obviously involves too much repulsion between Me and C-(1)–O. Instead, the octaphenolate C is produced with a symmetry minimizing the Me···C(1)–O^- as well as all electrostatic $O^-\cdots O^-$ repulsions. The independence of the NMR shifts of A, B, and C from the applied NaOD concentration, the observed numbers and the intensities of the NMR signals, and the sequence of their appearance with NaOD addition are in line only with symmetries and structures as proposed (Figure 7). The observed shift differences between A, B, and C also allow us to rule out deprotonation as single source. Thus, the difference of ~20 ppm between the C-7 signals in B (Table II) is far too large in comparison to the corresponding DIS values observed with **1** and rather indicates a difference in the stereochemical environment.

Table VI. Complexation-Induced ^1H NMR Shifts (CIS) and Association Constants K with Host **2** (Form B)[a]

compd	subst at N^+	proton	CIS	K	K_{av}	ΔG°
5	$Et_4(Br^-)$	CH_3	1.22	1.45 ± 0.35	1.47 ± 0.3	4.3
		CH_2	1.21	1.50 ± 0.40		
9	$Me_3(Cl^-)$	CH_3	2.11	5.4 ± 0.3	5.4 ± 0.3	5.1
	$^1CH_2CH_2OH$	1-CH_2	1.35[b]	(5.3)[b]		
		2-CH_2	0.70[b]	(6.2)[b]		

[a] See footnote *a* to Table III; measuring conditions as for Table III, except with 0.5 M NaCl instead of 0.5 M NaOH. [b] Measurement at intermediate complexation impossible due to peak broadening and overlapping; CIS values therefore from single measurement at 99 ± 1% complexation; K with these experimental CIS values and one measurement with [**2**] = 1.3 × 10^{-3} M, [**9**] = 6.4 × 10^{-4} M.

The pK_s values could only be determined with form **2B** and not **2A**, since accurate concentration ratios around A:B = 50:50 and higher were not accessible due to excessive line broadening and signal overlapping. The pK_s of 14.8 (Table I), however, observed with **2B** is again in line with the presence of strong hydrogen bonds. Other than with **1**, in which the hydrogen bond forming protons could not be abstracted even by sodium methoxide (see above), deprotonation of **2B** toward **2C** is eased by relaxation of the unfavorable C–X/C–O repulsion in **2B**.

Host 2. Complexation. Forms **2A** (in neutral solution) and **2C** (in strongly basic solution) did not exhibit any changes in the NMR spectra upon addition of methylammonium compounds. In contrast, addition of such guest molecules to **2B** or to **2C** (present in solutions containing smaller NaOH concentrations (Figure 7)), leads to completely reversible variations of both ^1H and ^{13}C NMR spectra, which correspond exactly to the pH dependent B ⇌ C interconversion (Figure 6). Clearly, the semiclosed isomer **2B** is the only form capable of complex formation similar, although weaker, to isomer **1**. The B ⇌ C interconversion thus represents a simple element of a proton pump: addition of a neutral ammonium compound as substrate to a moderately basic solution containing the open form **2C** induces a conformational change toward **2B**. Reversibly, withdrawal of protons from the complex **2B**·**S** leads to a release of the substrate S via removal of the hydrogen bond (which is necessary in stabilizing the highly strained conformation **2B**). The basically allosteric interchange between a hydrogen bond opening and closing at one side and a substrate complexation and release on the other side provides not only a primitive mechanical proton pump but also a simple proton switch for conformational changes.

The quantitative study of **2B** complexes with representative methyl- and ethylammonium derivatives (**5**, **9**, Table VI) furnished complexation-induced NMR shifts that are very similar to corresponding complexes with isomer **1** (Tables VI and III), again pointing to electrostatic effects as major source of the observed shielding variations. As to be expected from the more open form of **2B** compared to **1**, the equilibrium constants showed a distinct decrease (Table VI). This attenuation is less pronounced for the tetraethylammonium compound **5** as compared to **9**, since the change of the charge-separating distances in the complexes with **1** and B is relatively smaller compared to the methylammonium substrate **9**, which brings the positive charge closer to the host charges.

Experimental Section

NMR spectra were recorded with a Bruker AM 400 system at 400 MHz for ^1H NMR (digital resolution, 0.3 Hz) and 100.614 MHz for ^{13}C

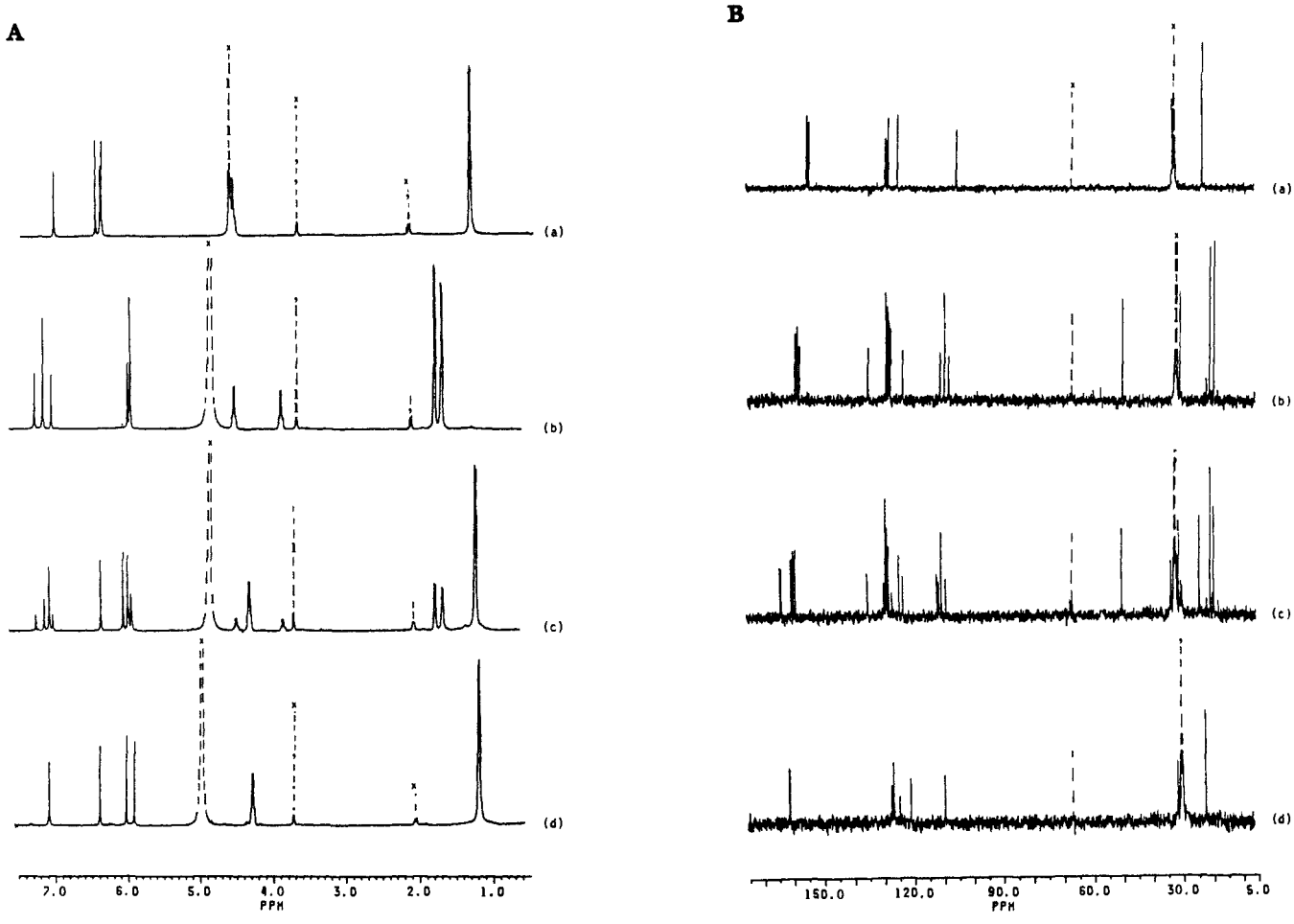

Figure 6. NMR spectra of **2** as a function of NaOD addition. (A) ^{1}H NMR, with moles of NaOD/moles of **2**: (a) 0.0, form A; (b) 3.5, form B; (c) 20.2, form B and C; (d) 76.0, form C. (B) ^{13}C NMR, conditions as with (A) except (c): 14.0 mol of NaOD; *x*: solvent signals.

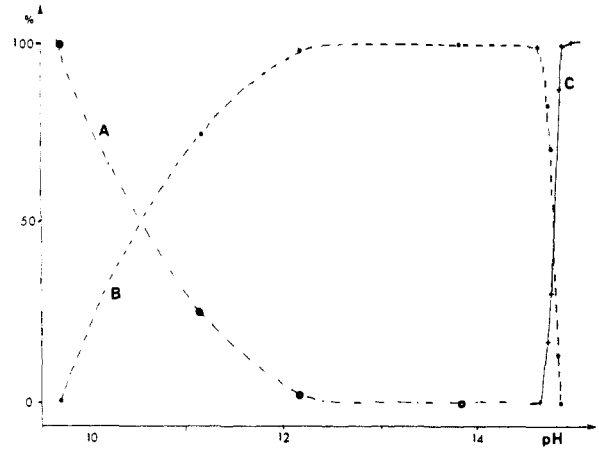

Figure 7. **2**A-C as a function of pH; [%] obtained from ^{1}H NMR signal integration; in acetone-d_6/deuterium oxide, 5/3, at 296 ± 1 K.

NMR (resolution, 3.0 Hz), with methanol or dioxane as internal reference; for the measuring conditions, see the tables.

pH measurements were performed in thermostated cells under nitrogen at 25 ± 0.2 °C with suitable glass electrodes and pH meters. Titrations were carried out by adding 0.1 N sodium hydroxide to ~0.01 M host solutions (other conditions, see Table I). Dissociation constants or pK_a values were obtained by direct potentiometric titration (with **1** and **3**) or by obtaining pH values at 50% deprotonation, which was in turn measured by ^{1}H NMR spectra (with **2B**, **1**, and **3**).

Complexation-induced shifts (CIS) and equilibrium constants *K* were obtained from ^{1}H NMR titration and numerical curve-fitting methods as described previously;[1] in a few cases (see Tables III, IV, VI), experimental CIS values were measured by addition of an excess of host. Initial substrate concentrations S_0 and host stock solution concentrations H_0 were as follows: S_0 2 × 10^{-4} M and H_0 4 × 10^{-3} M for **4**, **9**, **10**, **12**, **13**; S_0 1 × 10^{-3} M and H_0 1 × 10^{-2} M for **5**, **11**; S_0 5 × 10^{-3} M and H_0 1 × 10^{-1} M for **6**, **8**; S_0 5 × 10^{-2} M and H_0 0.5 M for **7**; S_0 1 × 10^{-2} M and H_0 0.1 M for the compounds mentioned in footenote *c* to Table III; for other conditions, see Tables III, IV, VI. Six to eight increments of the host stock solution were added, furnishing total [H]/[S] ratios between 0.5 and 10–20.

Materials. The host compounds **1** and **2** were obtained via literature procedures, with use of propionic acid esters for purification.[2f] Guest compounds were either commercially available or prepared according to the literature given; **16**,[16] **17**,[16] **14**,[17] and **15**[18] were obtained following the procedure given in ref 16.

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Registry No. **1**, 74708-10-4; **2**, 74645-05-9; **4**, 102682-61-1; **5**, 102682-62-2; **6**, 102682-63-3; **7**, 102682-64-4; **8**, 102682-65-5; **9**, 102682-66-6; **10**, 113403-99-9; **12**, 102682-68-8; **13**, 102682-67-7; **14** (1:1), 113404-00-5; **14** (1:2), 113404-04-9; **15** (1:1), 113404-01-6; **15** (1:2), 113404-05-0; **16**, 113404-02-7; **17**, 113404-03-8.

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