MS m/e 376 (M^+), 321, 279. Exact Mass Calcd for $C_{21}H_{28}O_2S_2$: 376.1529. Found: 376.1538.

Preparation of Compound 52. 9-BBN (0.5 M in THF, 2.9 mL, 1.4 mmol) was added to a solution of **51** (R = OAc) (256 mg, 0.68 mmol) in THF (10 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the above solution were added $PdCl_2$(dppf) (31 mg, 0.043 mmol), methyl β-bromomethacrylate (197 mg, 11 mmol), DMF (15 mL), and powdered K_2CO_3 (496 mg, 3.6 mmol) and H_2O (630 mg, 35 mmol) at room temperature. The reaction mixture was heated at 50 °C for 16 h. After the mixture was cooled to room temperature, water was added. The reaction mixture was extracted with ether, and the extract was washed with brine and dried over $MgSO_4$. Usual workup and silica gel chromatography gave 200 mg (77%) of **52**: IR ($CHCl_3$) 1730, 1700, 1420, 1360, 1260 cm^{-1}; ^1H NMR δ 0.99 (3 H, d, J = 7), 1.12 (3 H, d, J = 7), 1.78 (3 H, s), 2.29 (3 H, s), 1.30–3.10 (17 H, m), 3.71 (3 H, s), 5.09 (1 H, s), 6.70 (1 H, t, J = 6), 6.99 (1 H, br s), 7.17 (1 H, br s); MS m/e 476 (M^+), 416. Exact Mass Calcd for $C_{26}H_{36}O_4S_2$: 476.2053. Found: 476.2068.

Preparation of Compound 53. DIBAL (1 M in CH_2Cl_2, 2.3 mL, 2.3 mmol) was added to a solution of the compound **52** (110 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) at −78 °C under argon. The reaction mixture was warmed to 0 °C over 3 h and quenched with water. The mixture was extracted with methylene chloride, and usual workup produced a dihydroxy compound, which was acetylated with acetic anhydride (0.5 mL), pyridine (1 mL), and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine under usual conditions: yield, 99 mg (87%); IR ($CHCl_3$) 1720, 1360, 1220 cm^{-1}; ^1H NMR δ 0.97 (3 H, d, J = 7), 1.11 (3 H, d, J = 7), 1.60 (3 H, s), 2.05 (3 H, s), 2.28 (3 H, s), 1.30–3.15 (17 H, m), 4.44 (2 H, s), 5.08 (1 H, s), 5.31 (1 H, t, J = 6), 6.98 (1 H, br s), 7.16 (1 H, br s). Exact Mass Calcd for $C_{27}H_{38}O_4S_2$: 490. Found: 490.2200. A solution of the above diacetoxy compound (80 mg, 0.16 mmol) in THF (1 mL) was added a mixture of BF_3OEt_2 (0.08 mL) and HgO (69 mg, 0.32 mmol) in aqueous THF (15% H_2O, 2 mL) at room temperature. The reaction mixture was stirred for 20 min, diluted with ether, and extracted with ether. The extract was washed with brine and dried over $MgSO_4$. Concentration and purification by silica gel chromatography gave the compound **53** (44 mg 69%): IR ($CHCl_3$) 1725, 1690, 1360, 1210, 1110, 900 cm^{-1}; ^1H NMR δ 0.95 (3 H, d, J = 7), 1.13 (3 H, d, J = 7), 1.56 (3 H, s), 2.01 (3 H, s), 2.32 (3 H, s), 1.45–3.20 (11 H, m), 4.37 (2 H, s), 5.29 (1 H, t, J = 6), 7.36 (1 H, br s), 7.53 (1 H, br s), 9.89 (1 H, s); MS m/e 400 (M^+), 358, 330, 298, 189. Exact Mass Calcd for $C_{24}H_{32}O_5$: 400.2250. Found: 400.2255.

Preparation of Methyl Ester 54. A mixture of **53** (44 mg, 0.12 mmol), freshly prepared active MnO_2 (189 mg, 2.3 mmol), acetic acid (11 mg, 0.18 mmol), and sodium cyanide (27 mg, 0.55 mL) in MeOH (3 mL) was stirred at room temperature for 6 h. After filtration and evaporation of methanol in vacuo, water was added to the residue. The residue was extracted with ether, and the extract was washed with brine and dried over $MgSO_4$. Concentration and purification with silica gel afforded a mixture of acetoxy methyl ester and phenolic methyl ester. The above methyl ester mixture was acetylated under usual conditions to give 40 mg (85%) of methyl ester **54**: IR ($CHCl_3$) 1720, 1710, 1370, 900 cm^{-1}; ^1H NMR δ 0.99 (3 H, d, J = 7), 1.14 (3 H, d, J = 7), 1.60 (3 H, s), 2.06 (3 H, s), 2.34 (3 H, s), 1.22–2.00 (9 H, m), 2.72 (1 H, m), 3.04 (1 H, m), 3.89 (3 H, s), 4.40 (2 H, s), 5.31 (1 H, t, J = 6), 7.53 (1 H, s), 7.75 (1 H, s); MS m/e 430 (M^+), 398, 356, 328, 219. Exact Mass Calcd for $C_{25}H_{34}O_6$: 430.2355. Found: 430.2359.

Dihydroxyserrulatic Acid (1). A mixture of the compound **54** (30 mg, 0.07 mmol) in 1 M aqueous NaOH (2 mL) and MeOH (3 mL) was heated at 70 °C for 5 h. The mixture was acidified with 6 M HCl and concentrated in vacuo. The residue was extracted with ether, and the extract was washed with brine and dried over $MgSO_4$. Evaporation in vacuo and chromatography with silica gel gave 13 mg (60%) of (±)-dihydroxyserrulatic acid, which was identified with the ^1H NMR an authentic sample.

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Cyclophane–Arene Inclusion Complexation in Protic Solvents: Solvent Effects versus Electron Donor–Acceptor Interactions

Stephen B. Ferguson, Elizabeth M. Sanford, Eileen M. Seward, and François Diederich*

Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024-1569. *Received January 25, 1991*

Abstract: This paper describes a comprehensive ^1H NMR analysis of the inclusion complexation of neutral 2,6-disubstituted naphthalene and para-disubstituted benzene derivatives by cyclophanes. The major attractive host–guest interactions in these complexes are π–π-stacking and edge-to-face aromatic–aromatic interactions. Individual studies investigate relative binding strength as a function of (i) the electronic properties of the guests, (ii) the nature of the solvent, and (iii) the nature of the cyclophane hosts. For these investigations, two new tetraoxa[*n*.1.*n*.1]cyclophanes with eight methoxy groups ortho to the aryl ether linkages were synthesized. A comparison between different cyclophanes shows that functional groups attached to the aromatic rings increase binding strength if they deepen the cavity without perturbing the apolar character of the binding site. Electron donor–acceptor (EDA) interactions control the relative stability of cyclophane–arene inclusion complexes in CD_3OD and $(CD_3)_2SO$. Generally, electron-deficient guests form the most stable complexes with the electron-rich cyclophanes. Deviations from the EDA model in these solvents are best explained by unfavorable complexation-induced changes in the solvation of the guest functional groups. In water, such solvation effects may dominate, thus masking contributions of EDA interactions to the relative complexation strength. Electronic host–guest complementarity determines the relative association strength in water only if guest functionalities retain their favorable solvation in the complexes formed. In binary aqueous solvent mixtures, overall complexation strength increases with the amount of water added and follows a linear free energy relationship with the empirical solvent polarity parameter $E_T(30)$.

Introduction

The role of aromatic–aromatic interactions, and in particular π-donor–π-acceptor interactions in stabilizing synthetic host–guest complexes has attracted considerable interest in recent theoretical[1] and experimental molecular recognition studies.[2-12] Advances have been made in defining the contributions of individual terms, which include electrostatic interaction, polarization interaction,

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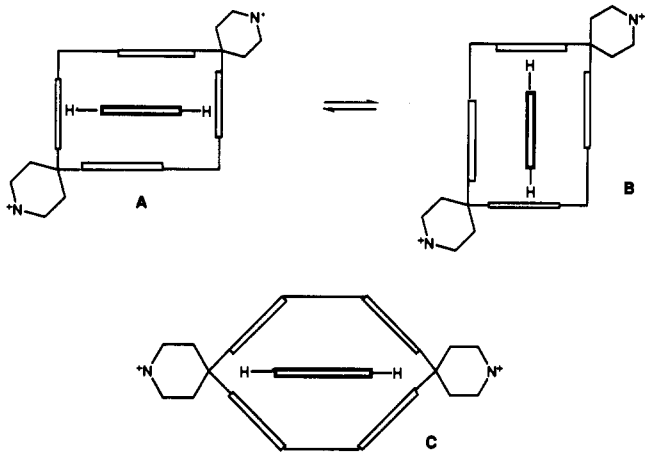
Scheme I

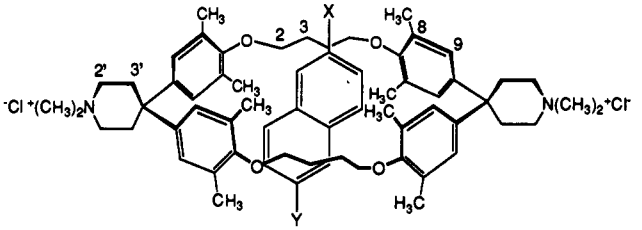


charge-transfer interaction, and dispersion energy, to the total interaction energy in electron donor–acceptor (EDA) complexes.[13-15] A variety of experimental studies suggest that EDA forces may contribute to specific complexation in biological systems.[16,17]

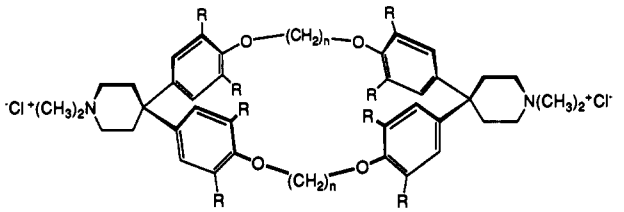
In polar protic solvents and especially in water, solvophobic forces provide a very large favorable contribution to the free energy of apolar binding.[18] In addition, specific solvation effects on host–guest complexation are particularly pronounced in these environments. Previously, we described examples in which specific changes in the solvation of functional groups of either host or guest during the complexation process dramatically influence binding strength.[2b,19] If the energetically favorable solvation of a polar functional group of one of the binding partners is reduced in the complex as compared to the free component, and if no new binding interaction, e.g., host–guest hydrogen bonding, compensates for this loss in solvation energy, a considerable reduction in complexation strength is observed.[2b]

We now address the question of whether, in polar protic environments, weak intermolecular forces such as EDA interactions

Chart I



compete with favorable and unfavorable solvation effects in determining relative host–guest association strength. The water-soluble tetraoxa[*n*.1.*n*.1]cyclophane hosts **1–5** seemed ideally suited



	n	R
1	3	H
2	3	OCH_3
3	4	H
4	4	CH_3
5	4	OCH_3

for such investigations.[20] A variety of neutral 2,6-disubstituted naphthalene and para-disubstituted benzene derivatives with different electronic properties were chosen as guests. According to an EDA model, electron-poor guests should form more stable complexes with these electron-rich cyclophanes than electron-rich guests. Since the water solubility providing quaternary centers of **1–5** are remote from the cavity, investigations into weak EDA interactions are not perturbed by ion–π-system interactions.[21,22]

In the binding conformation, macrocycles **1–5** adopt the shape of a rectangular cavity having four electron-rich aromatic rings as the walls. The substrates generally prefer an axial-type inclusion geometry (Chart I).[2b] This orientation allows highly solvated polar guest substituents to be oriented into the solution, and this should minimize their unfavorable desolvation in the complexes. Naphthalene and benzene guests encapsulated by **1–5** prefer the two orientations A and B (Scheme I) over conformation C.[2b,5,23,24] This is supported by the large upfield complexation-induced ^1H NMR chemical shifts at saturation binding ($\Delta\delta_{sat}$) between 2.0 and 3.0 ppm (Tables III and VI) measured for guest protons located in the cyclophane cavity. In conformers A and B, these protons point directly into the shielding regions of the diphenylmethane benzene rings and therefore move strongly upfield. In contrast, inclusion geometry C should be characterized by smaller upfield shifts since the guest protons in the cavity now point toward the central sp^3 carbon atoms of the diphenylmethane units. We have previously found that, for steric reasons, inclusion complexes between a tetraoxa[7.1.7.1]paracyclophane and the larger arenes pyrene or fluoranthene prefer geometry C and that their protons located in the cavity exhibit upfield shifts of only $\Delta\delta_{sat} \approx 1$–1.5 ppm.[25]

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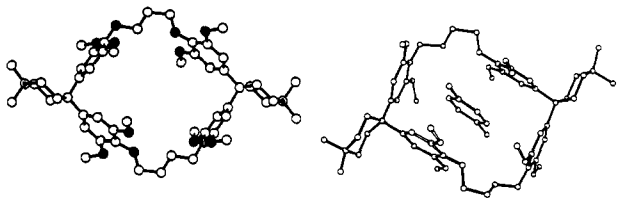


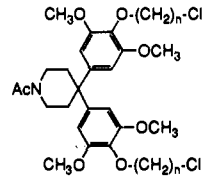
Figure 1. Comparison of the X-ray crystal structure of cyclophane **2** and the current calculated lowest energy conformer of the **2**-*p*-xylene complex in aqueous solution.[20b,24b] The two disordered water molecules in the cavity of the crystalline host are not shown.

In complexes adopting the geometries A and B (Scheme I), two electrostatic interactions are similarly affected by changes in the electronic properties of the guest. Both the attractive π–π-stacking ring interactions and the dipolar edge-to-face interactions should become more energetically favorable with increasing electron affinity of the guest. The edge-to-face interactions are strengthened by an increasing positive polarization of the hydrogen atoms that are oriented into the π-electron clouds of the host benzene rings. These two components of EDA interactions in our complexes cannot be analyzed separately.

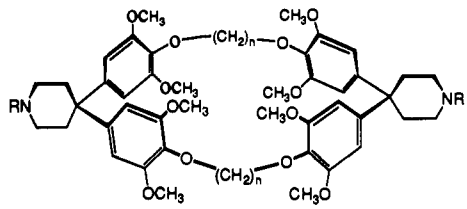
This paper describes the remarkable differences in the physical and complexation properties of the macrorings **3–5**, which only differ by their aromatic substituents ortho to the 1,4-dioxabutane bridges. A variety of ^{1}H NMR binding studies will be presented that analyze the relative contributions of solvent effects and EDA interactions to the stability of host–guest complexes in pure protic solvents as well as in binary aqueous solvent mixtures. The following paper in this issue shows that the formation of arene inclusion complexes by **1–5** and other cyclophanes is enthalpy-driven and analyzes the origin of this driving force.[18b,20b]

Results and Discussion

Role of Substituents at the Aromatic Rings of Cyclophanes. We prepared the two octamethoxy cyclophanes **2** and **5** via the intermediates **6–9** following synthetic routes previously described for **1**, **3**, and **4**.[26] Although the structures of the three [6.1.6.1]cyclophanes **3–5** closely resemble each other, their properties are substantially different.



6a n = 4
6b n = 4



	n	R
7a	4	$COCH_3$
7b	3	$COCH_3$
8a	4	H
8b	3	H
9a	4	CH_3
9b	3	CH_3

Firstly, methyl and methoxy substituents ortho to the bridges in **4** and **5** considerably deepen the cyclophane cavity. The distance between two meta hydrogens is ~4.3 Å, whereas the hydrogen atoms of two *m*-methyl groups in **4** are on average ~6.0 Å apart. The X-ray crystal structure of **2** as the diiodide (Figure 1)[20b] shows that each methoxy group is aligned in the plane of the phenyl ring to which it is attached. This further deepens the cavity, and the average distance between the hydrogen atoms at two *m*-methoxy groups in **5** is ~8.1 Å.

Secondly, the substituents ortho to the bridges have a pronounced effect on the conformation of the macrocycles. In cyclophane **3** without ortho substituents, the torsional angles about the aryl ether C–O bonds are close to 0°, placing the O–CH_2 bonds into the planes of the aromatic rings.[2b] In sharp contrast, for steric reasons, these torsional angles in cyclophanes **4** and **5** are close to 90°. This forces the first CH_2 unit of each ether bridge either into or out of the cavity (Figure 1).[20b]

Thirdly, the critical aggregation concentrations (cac's) of **3–5** differ dramatically in water.[2b,26] The cac of **3** was determined as 1.6×10^{-4} mol L^{-1}. Upon introduction of methyl groups, aggregation becomes even more favorable as shown by the lower cac value of $<2 \times 10^{-5}$ mol L^{-1} for **4**. In contrast, methoxy groups reduce the aggregation tendency, resulting in a high cac value of 1×10^{-2} mol L^{-1} for cyclophanes **2** and **5** as measured by both NMR[20b] and ESR.[27] The cac's of **3** and **4** are too low to perform binding studies in pure water. Therefore, to compare the binding properties of **3–5**, studies were performed in D_2O–CD_3OD (60:40, v/v), where aggregation of these macrocycles does not occur.

Table I. Association Constants K_a and Free Energies of Complexation $\Delta G°$ at 293 K for Complexes of Cyclophanes **3–5** with 1,4-Disubstituted Benzene Guests in D_2O–CD_3OD (60:40, v/v)

guest	host	K_a, L mol^{-1}	$\Delta G°$,[a] kcal mol^{-1}
p-benzodinitrile	**3**	140	−2.89
	4	1580	−4.29
	5	390	−3.48
p-dimethoxybenzene	**3**	95	−2.66
	4	580	−3.72
	5	340	−3.41

[a] Uncertainties of $\Delta G°$ values: ±0.1 kcal mol^{-1}.

Table I shows that the octamethyl host **4** is the best binder, followed by the octamethoxy derivative **5** and then the unsubstituted cyclophane **3**. This sequence, which is observed in all complexation studies performed with the three macrocycles, shows that cavity depth (**3** < **4** < **5**) is not the only factor determining association strength. The methoxy groups deepen the cavity and make **5** a better binder than **3**. However, hydrogen bonding between the methoxy groups and water or methanol molecules, indicated by the large cac of **5**, likely provides favorable solvation to the more polar parts of the cavity, thus reducing the solvophobic driving forces for apolar binding. The absence of such favorable interactions between the solvent and the octamethyl derivative **4** provides a deep cavity having the most apolar character. Such an environment promotes the strongest apolar complexation in protic solvents.

Complexation of 2,6-Disubstituted Naphthalene Derivatives in Methanol. At rapid complexation equilibrium, ^{1}H NMR titrations provided quantitative determination of all association constants reported in this paper. In these titrations, the guest was always maintained at a constant concentration.

A total of 22 2,6-disubstituted neutral naphthalene derivatives were chosen as guests for complexation studies with cyclophane **4** in CD_3OD; binding of some of these derivatives was also investigated with macrocycle **5**. Table II gives the stability constants and the Gibbs free energies of formation for these complexes. Also shown are the solubilities of the various guests in methanol. Upon complexation, the guest is transferred from a solvent cavity to the host cavity. The guest solubility indicates its affinity for the solvent cavity.[28,29] If solvophobic forces are dominant, complexation should become weaker with increasing guest solubility.

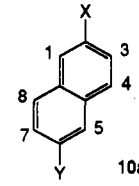


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Table II. Association Constants K_a and Free Energies of Complexation $\Delta G°$ for Complexes of Cyclophanes **4** (at 303 K) and **5** (at 293 K) with 2,6-Disubstituted Naphthalene Guests in CD_3OD[a]

host	guest	X	Y	K_a, L mol^{-1}	$\Delta G°$, kcal mol^{-1}	solubility, mol L^{-1}	σ_p^+
				Donor–Donor Guests			
4	**10a**	CH_2OH	CH_2OH	20 ± 5	−1.80 ± 0.17	2.5×10^{-2}	
	10b	OH	OH	23 ± 5	−1.90 ± 0.16	2.5×10^{-1}	−0.92
	10c	NH_2	NH_2	27 ± 5	−1.97 ± 0.11	2.6×10^{-2}	−1.30
	10d	OCH_3	OCH_3	53 ± 5	−2.39 ± 0.06	1.2×10^{-2}	−0.78
	10e	CH_3	CH_3	67 ± 5	−2.53 ± 0.05	9.3×10^{-2}	−0.31
	10f	SCH_3	SCH_3	162 ± 10	−3.06 ± 0.04	1.4×10^{-2}	
				Donor–Acceptor Guests			
4	**10g**	NH_2	NO_2	105 ± 15	−2.79 ± 0.09	1.2×10^{-2}	
	10h	OCH_3	NO_2	111 ± 10	−2.83 ± 0.05	2.5×10^{-2}	
	10i	OCH_3	Br	117 ± 10	−2.87 ± 0.06	5.7×10^{-2}	
	10j	OCH_3	CN	119 ± 10	−2.88 ± 0.06	1.1×10^{-1}	
	10k	OCH_3	COOH	134 ± 25	−2.95 ± 0.13	4.1×10^{-2}	
	10l	OH	CN	167 ± 20	−3.08 ± 0.09	2.4×10^{-1}	
				Acceptor–Acceptor Guests			
4	**10m**	$COCH_3$	$COCH_3$	64 ± 10	−2.51 ± 0.08	1.7×10^{-2}	
	10n	$OCOCH_3$	$OCOCH_3$	109 ± 10	−2.83 ± 0.06	1.1×10^{-2}	
	10o	$COOCH_3$	$COOCH_3$	188 ± 10	−3.15 ± 0.03	2.1×10^{-3}	+0.48
	10p	COOH	COOH	210 ± 15	−3.22 ± 0.05	3.6×10^{-4}	+0.42
	10q	NO_2	NO_2	216 ± 15	−3.24 ± 0.05	4.0×10^{-4}	+0.79
	10r	CN	CN	272 ± 15	−3.38 ± 0.04	1.2×10^{-3}	+0.66
	10s	$CONEt_2$	$CONEt_2$	<10	>−1.3	8.2×10^{-2}	
	10t	$CONH_2$	$CONH_2$	29 ± 5	−2.07 ± 0.16	7.1×10^{-4}	
	10u	SO_2NH_2	SO_2NH_2	40 ± 5	−2.22 ± 0.08	1.7×10^{-3}	
	10v	OSO_2CH_3	OSO_2CH_3	91 ± 10	−2.72 ± 0.08	2.5×10^{-3}	
5	**10d**	OCH_3	OCH_3	12 ± 3	−1.47 ± 0.20		
	10j	OCH_3	CN	31 ± 5	−2.00 ± 0.10		
	10r	CN	CN	78 ± 5	−2.54 ± 0.05		

[a] Also shown are the solubilities of the guests in methanol as well as selected Hammett substituent parameters σ_p^+ for the functionality in symmetrically substituted naphthalenes.

The relative stability of the majority of complexes between cyclophanes **4** and **5** with naphthalene derivatives (Table II) can be nicely interpreted in terms of an EDA interaction model. Specific differences in functional group solvation are the source for observed exceptions to the model. According to the EDA model, host **4** with its four trialkyl-substituted anisole units provides electron-rich cavity walls and should form the most stable complexes with electron-deficient guests. This is indeed observed, and the highest complex stability is measured for the acceptor–acceptor substituted derivatives **10o–10r**. Considerably less stable complexes are formed by the donor–donor guests **10a–10e**, while the complexes of compounds **10g–10l**, having one donor and one acceptor substituent, demonstrate an intermediate stability. A comparison between complex **4·10a** formed by a donor–donor guest and complex **4·10r** with an acceptor–acceptor guest shows that differences in free energy of complexation can be as large as 1.6 kcal mol^{-1}.

Although cyclophane **5**, with its four trialkoxybenzene rings, is a stronger electron donating host than **4**, the complexes of acceptor–acceptor guests do not demonstrate additional relative stability. For example, the differences in stability between the complexes of 2,6-dicyanonaphthalene (**10r**) and 2,6-dimethoxynaphthalene (**10d**) formed by **4** ($\Delta(\Delta G°) \approx 1.0$ kcal mol^{-1}) and by **5** ($\Delta(\Delta G°) \approx 1.1$ kcal mol^{-1}) are very similar.

Linear free energy relationships such as the Hammett equation[30] often provide insight into molecular interactions that are at the origin of physical properties. Figure 2 shows a very good correlation ($R = 0.947$) between the Hammett substituent parameter σ_p^+ for the guest functionality in symmetrically substituted guests and the free energies for complexation by cyclophane **4**. This correlation only holds for those complexes that follow our EDA model.

The analysis of the association constants in terms of guest solubilities suggests no general trends. Although donor–acceptor guests have solubilities equal to or greater than the donor–donor guests, complexes of the former are more stable. The least soluble derivatives are both some of the best (**10o–10r**) and some of the poorest binding (**10t–10v**) acceptor–acceptor guests. The best binder in the category of donor–acceptor guests **10l** also shows the highest solubility, whereas the most soluble acceptor–acceptor guest **10s** is the poorest binder in the category of acceptor–acceptor guests.

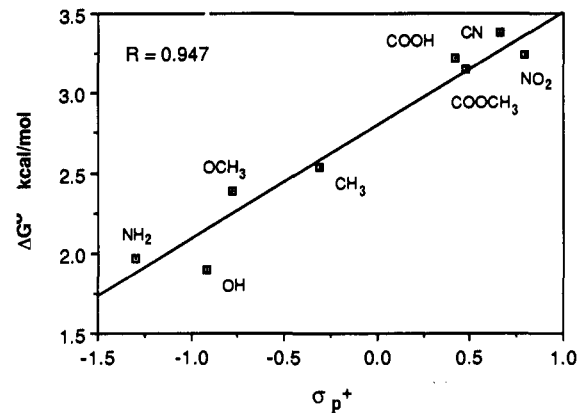


Figure 2. Linear free energy relationship that correlates the free energy of complexation between **4** and donor–donor and acceptor–acceptor substituted naphthalenes with the σ_p^+ parameter of their substituents.

The acceptor–acceptor guests **10s–10u**, in particular, form complexes with stabilities that deviate strongly from those expected on the basis solely of the EDA model. Their amide functionalities undergo favorable multiple hydrogen bonding to the solvent, resulting in large stable solvation shells. In the complexes of these substrates, apparently the apolar cavity walls of **4** interfere with an intact solvation shell of the amide residues. These functional groups are better solvated in the bulk than in the inclusion complexes, and therefore, the overall measurable complexation strength is reduced by a loss in solvation energy. To avoid effects from specific functional group solvation in the evaluation of EDA interactions in protic solvents, it is best to assess the binding of

(30) Johnson, C. D. *The Hammett Equation*; Cambridge University Press: Cambridge, 1973.

Table III. Complexation-Induced Shifts $\Delta\delta_{sat}$ (ppm, Positive Value Indicates Upfield Shift) Calculated for Saturation Binding (A) of Guest Protons and (B) of Host Protons in Complexes Formed by Host 4 and 2,6-Disubstituted Naphthalenes in CD_3OD, T = 303 K

(A) Guest Protons

guest	X	Y	1-H	3-H	4-H	5-H	7-H	8-H
10d	OCH_3	OCH_3	1.57	0.91	1.94			
10e	CH_3	CH_3	1.79	0.85	1.78			
10q	NO_2	NO_2	1.88	1.01	2.29			
10r	CN	CN	2.47	0.82	1.89			
10h	OCH_3	NO_2	1.46	0.72	2.20	2.01	1.27	2.23
10j	OCH_3	CN	1.47	0.60	1.74	2.44	1.27	2.21

(B) Host Protons

guest	X	Y	3-H	CH_3-8	3'-H	2'-H	2-H	9-H
10d	OCH_3	OCH_3	0.47	0.20	−0.19	−0.09	0.98	−0.23
10e	CH_3	CH_3	0.63	0.23	−0.18	−0.08	1.22	−0.29
10h	OCH_3	NO_2	0.31	0.18	−0.13	−0.04	0.65	−0.20
10j	OCH_3	CN	0.45	0.20	−0.21	−0.08	0.91	−0.28
10o	$COOCH_3$	$COOCH_3$	0.30	0.15	−0.11	−0.05	0.59	−0.17

nonprotic guests, e.g., 2,6-dimethoxynaphthalene (**10d**) and 2,6-dicyanonaphthalene (**10r**), which shows ~1 kcal mol^{-1} more stability for the complex of the acceptor–acceptor guest.

^{1}H NMR spectroscopy provides experimental evidence for the strong hydrogen bonding of the amides **10s–10u** to methanol. Whereas the dissociation of the complexes formed by **4** and guests **10d–10r** occurs fast on the 500-MHz ^{1}H NMR time scale, leading to sharp resonances at 303 K, strong line broadening is observed in the spectra of solutions containing host **4** and guests **10s–10u**. This indicates that decomplexation rates k_{-1} have decreased to near 10^3 s^{-1} if these processes are unimolecular. With association constants $K_a = k_1/k_{-1}$ between 10 and 100 L mol^{-1}, the complexation rates k_1 must be much slower than diffusion controlled for the dissociation to be observed on the ^{1}H NMR time scale. In contrast, we had previously found that apolar arenes bind to tetraoxa[*n*.1.*n*.1]cyclophanes with near diffusion controlled rates.[2b] The relatively slow complexation of 2,6-disubstituted naphthalenes with carboxamide and sulfonamide residues reflects the higher energies of activation needed to partially desolvate the substituents upon penetration of the guest into the narrow cyclophane cavity. Peak broadening is also observed, although to a lesser extent, in the complex solutions of two other hydrogen-bonding guests, diamine **10c** and dicarboxylic acid **10p**.

In addition to the two aromatic–aromatic interactions defined in the EDA model, other attractive host–guest interactions may be relevant in individual complexes in methanol. The complexes with the dipolar donor–acceptor guests (**10g–10l** in Table II) could be stabilized by additional dipole–induced dipole interactions. Direct interactions between the guest functional groups and the host may also contribute to the free energy of association. The dithioether **10f** forms a more stable complex than the other donor–donor naphthalenes. Since SCH_3 groups are highly polarizable, the complex of **10f** may be stabilized by additional host–guest dispersion interactions.

Information on the geometries of the complexes is obtained by analysis of the complexation-induced changes in the ^{1}H NMR chemical shifts of the host and guest resonances. Table IIIA provides examples for the changes in chemical shift at saturation binding $\Delta\delta_{sat}$ of guest protons in complexes of **4**. Table IIIB shows $\Delta\delta_{sat}$ values for the host protons. All naphthalenes adopt a time-averaged axial or pseudoaxial-type inclusion geometry[2b,31] characterized by specifically high upfield shifts of the guest protons 1-H, 4-H, 5-H, and 8-H. The $\Delta\delta_{sat}$ values in Table IIIA show a clear effect of EDA interactions on the geometry of the complexes formed by the unsymmetric donor–acceptor substituted guests. In the time-averaged geometry, the naphthalene moiety bearing the acceptor substituent is located more deeply in the cavity of **4** than the moiety with the donor substituent.

All solution complexes of cyclophanes **1–5** with naphthalene and benzene derivatives that were analyzed in this study are characterized by the absence of a charge-transfer band in the electronic absorption spectra. Only small bathochromic shifts (2–4 nm), band broadening, and weak hypochromicity are observed in the electronic absorption spectra of the complexed guests as compared to the spectra of the free species. For example, at 67% of saturation binding by **4** in CH_3OH, the absorption bands of **10r** appear at λ_{max} = 330 and 344 nm as compared to 326 and 343 nm in the absence of host.

Table IV. Estimates of Association Constants K_a and Free Energies of Complexation $\Delta G°$ for Complexes of Cyclophane **4** with 2,6-Disubstituted Naphthalenes in $(CD_3)_2SO$, T = 303 K

guest	X	Y	K_a, L mol^{-1}	$\Delta G°$, kcal mol^{-1}
		Donor–Donor Guests		
10c	NH_2	NH_2	0.4	0.5
10d	OCH_3	OCH_3	2	−0.4
10e	CH_3	CH_3	4	−0.8
		Donor–Acceptor Guests		
10k	OCH_3	COOH	3	−0.6
10g	NH_2	NO_2	4	−0.8
10l	OH	CN	7	−1.1
		Acceptor–Acceptor Guests		
10p	COOH	COOH	5	−0.9
10q	NO_2	NO_2	9	−1.3
10o	$COOCH_3$	$COOCH_3$	13	−1.5
10r	CN	CN	16	−1.6

Complexes of 2,6-Disubstituted Naphthalene Derivatives in Dimethyl Sulfoxide. Quantitative titration binding studies involving complexes of **4** and the 2,6-disubstituted naphthalenes in $(CD_3)_2SO$ were not possible due to weak complexation. All K_a's in this solvent are less than 16 L mol^{-1}. To estimate these K_a values and the free energies of formation shown in Table IV, complexes in $(CD_3)_2SO$ were assumed to have geometries similar to those of the complexes in CD_3OD and the calculated $\Delta\delta_{sat}$ values for complexes in CD_3OD were used.[32] The assumption of similar geometries is justified by the strong correlation seen between the $\Delta\delta$ values in $(CD_3)_2SO$ and the $\Delta\delta_{sat}$ values in CD_3OD. For example, for a solution of [**4**] = 2.0×10^{-2} mol L^{-1} and [**10e**] = 5.0×10^{-3} mol L^{-1} in $(CD_3)_2SO$, a degree of complexation of 6.9 ± 0.2% was calculated from the observed shifts of all three guest proton resonances and the saturation shifts in CD_3OD. In the same way, a degree of complexation of 23.5 ± 0.5% was calculated for a similar solution of **4** and **10r**.

While the complexes in $(CD_3)_2SO$ are considerably less stable than those in CD_3OD, the estimated K_a values follow the same trend in both solvents. This provides strong evidence for attractive EDA interactions between host 4 and the electron-deficient naphthalene guests. It is possible that EDA interactions provide

(31) Odashima, K.; Koga, K. In *Cyclophanes*; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic Press: New York, 1983; Vol. 2, pp 629–678.

(32) Diederich, F.; Dick, K.; Griebel, D. *J. Am. Chem. Soc.* **1986**, *108*, 2273–2286.

Table V. Association Constants K_a and Free Energies of Complexation $\Delta G°$ at 293 K for Complexes of Cyclophanes **2** and **5** with 1,4-Disubstituted Benzene Derivatives in D_2O[a]

host	guest	X	Y	K_a, L mol^{-1}	$\Delta G°$, kcal mol^{-1}	solubility,[b] mol L^{-1}	log $P_{octanol}$[c]
				Donor–Donor Guests			
5	**11a**	NH_2	NH_2	$(3.6 \pm 0.4) \times 10^2$	-3.43 ± 0.07	3.4×10^{-1}	−0.33[d]
	11b	OH	OH	$(5.6 \pm 0.4) \times 10^2$	-3.69 ± 0.05	5.1×10^{-1}	0.59
	11c	CH_3	OH	$(3.2 \pm 0.4) \times 10^3$	-4.71 ± 0.09	1.8×10^{-1}	1.94
	11d	CH_3	CH_3	$(9.3 \pm 0.5) \times 10^3$	-5.33 ± 0.04	1.9×10^{-3}	3.15
	11e	OCH_3	OCH_3	$(1.0 \pm 0.05) \times 10^4$	-5.38 ± 0.03	5.8×10^{-3}	2.09[d]
				Donor–Acceptor Guests			
5	**11f**	OH	NO_2	$(2.3 \pm 0.3) \times 10^4$	-5.86 ± 0.08	9.5×10^{-2}	1.91
	11g	CH_3	CN	$(3.0 \pm 0.3) \times 10^4$	-6.01 ± 0.07	1.2×10^{-3}	2.06[d]
	11h	CH_3	NO_2	$(3.0 \pm 0.3) \times 10^4$	-6.01 ± 0.07	2.6×10^{-3}	2.42
				Acceptor–Acceptor Guests			
5	**11i**	NO_2	NO_2	$(7.8 \pm 0.5) \times 10^3$	-5.22 ± 0.04	4.4×10^{-4}	1.46
	11j	CN	CN	$(7.8 \pm 0.6) \times 10^3$	-5.23 ± 0.05	1.0×10^{-3}	0.99[d]
	11k	$COOCH_3$	$COOCH_3$	$(1.2 \pm 0.2) \times 10^5$	-6.81 ± 0.09	2.8×10^{-4}	2.11[d]
				Donor–Donor Guests			
2	**11a**	NH_2	NH_2	$(2.1 \pm 0.3) \times 10^1$	-1.77 ± 0.1	3.4×10^{-1}	−0.33[d]
	11b	OH	OH	$(3.0 \pm 0.3) \times 10^1$	-1.99 ± 0.08	5.1×10^{-1}	0.59
	11d	CH_3	CH_3	$(1.3 \pm 0.1) \times 10^3$	-4.18 ± 0.05	1.9×10^{-3}	3.15[d]
	11e	OCH_3	OCH_3	$(3.7 \pm 0.2) \times 10^2$	-3.45 ± 0.04	5.8×10^{-3}	2.09
				Donor–Acceptor Guests			
2	**11f**	OH	NO_2	$(2.1 \pm 0.2) \times 10^3$	-4.48 ± 0.05	9.5×10^{-2}	1.91
	11h	CH_3	NO_2	$(2.1 \pm 0.1) \times 10^3$	-4.47 ± 0.03	2.6×10^{-3}	2.42
				Acceptor–Acceptor Guests			
2	**11j**	CN	CN	$(1.0 \pm 0.05) \times 10^3$	-4.04 ± 0.03	1.0×10^{-3}	0.99[d]
	11k	$COOCH_3$	$COOCH_3$	$(2.1 \pm 0.15) \times 10^3$	-4.45 ± 0.05	2.8×10^{-4}	2.11[d]

[a] Also shown are the solubilities of the guests in water as well as their Hansch partition coefficients log $P_{octanol}$. [b] Temperatures for solubility measurements: 288 K (**11b**),[34] 298 K (**11d**);[33] all others at 293 K. [c] Reference 35. [d] Calculated log $P_{octanol}$ value; all others are experimental values from ref 35.

almost the entire driving force for the complexation since the donor–donor guests demonstrate almost no binding (Table IV). The difference in Gibbs free energy $\Delta(\Delta G°)$ for complexation of 2,6-dimethoxynaphthalene (**10d**) and 2,6-dicyanonaphthalene (**10r**) in $(CD_3)_2SO$ is ~1.2 kcal mol^{-1}. A value of $\Delta(\Delta G°)$ of ~1.0 kcal mol^{-1} was found in CD_3OD, indicating that similar interactions are responsible for the differential complexation stabilities in the polar protic and the dipolar aprotic solvent.

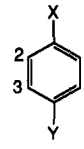
The significant differences in complex stability in $(CD_3)_2SO$ are most likely not due to differences in guest solubilities because all the naphthalene derivatives have large solubilities in this solvent. However, similar to methanol, unfavorable changes in the solvation of guest substituents upon complexation can prevent binding. For 2,6-naphthalenedicarboxamide (**10t**), no complexation-induced shifts of the proton resonances were observed in $(CD_3)_2SO$ even at highest concentrations.

Complexes of 2,6-Disubstituted Naphthalene Derivatives in D_2O-CD_3OD (60:40, v/v). Complexation studies with host **4** in pure aqueous solution were not possible due to the low cac of the macrocycle. Therefore, binding of several naphthalene guests (**10c–10e**, **10g**, **10k**, **10l**, and **10o–10r**) in an aqueous environment was qualitatively assessed in D_2O–CD_3OD (60:40, v/v) by evaluation of the $\Delta\delta$ values of the guest resonances in solutions with [host] = [guest] = 5.0×10^{-3} mol L^{-1}. A comparison of these values to the $\Delta\delta_{sat}$ values measured in pure CD_3OD indicated that saturation or near saturation binding occurred in each case. If not identical, the $\Delta\delta$ values measured for all guest protons in the complexes in D_2O–CD_3OD (60:40, v/v) are nearly proportional to the corresponding $\Delta\delta_{sat}$ values in pure CD_3OD. We estimate that all complexes have stability constants near $\sim 1 \times 10^5$ L mol^{-1} or higher. The high association strength is a result of the strong solvophobic forces for apolar inclusion complexation that become effective in aqueous environments. In the absence of accurate K_a data, contributions of EDA interactions to the relative stability of the complexes could not be evaluated.

With the weaker binding host **5**, accurate association constants for some naphthalene complexes in the binary solvent mixture were obtained. At 293 K, the association constant and free energy of formation for the **5**·**10d** complex were calculated as $K_a = 4490 \pm 150$ L mol^{-1} and $\Delta G° = -4.90 \pm 0.04$ kcal mol^{-1} and for the **5**·**10j** complex as $K_a = 7160 \pm 650$ L mol^{-1} and $\Delta G° = -5.17 \pm 0.1$ kcal mol^{-1}. The low solubility of naphthalene guests, in particular of the nonprotic acceptor–acceptor guests **10q** and **10r** prevented a more detailed study of EDA interactions in pure water and in the binary aqueous solvent mixture. Therefore, para-disubstituted benzene derivatives were used for comprehensive studies in these aqueous environments.

Complexes of 1,4-Disubstituted Benzene Derivatives in Water. Apolar binding is the most efficient in water as a result of the strong solvophobic driving forces.[18a] At the same time, specific solvation effects involving complexation-induced changes in the solvation of polar functional groups are also larger in D_2O than in CD_3OD or $(CD_3)_2SO$. With 1,4-disubstituted benzenes, solvation effects should be more pronounced than with 2,6-disubstituted naphthalenes because the para substituents do not reach as far out of the cyclophane cavity into the solution. Hence, interactions between guest functional groups and the host substituents at the aromatic rings as well as the corresponding solvation shells should be much more pronounced in the benzene complexes. It was, therefore, uncertain whether the impact of electronic host–guest complementarity and EDA interactions would still be recognizable in the binding data for a series of related benzene complexes. However, we had initially hoped that the strong donor character of hosts **2** and **5** with their four trialkoxybenzene rings would lead to large differences in the stability of complexes formed by electron-rich and electron-deficient guests.

Cyclophanes **2** and **5** form stable complexes with 1,4-disubstituted neutral benzene derivatives in D_2O (Table V).[20b] The complexes of the larger host **5** are more stable than those of the smaller host **2**. In the series of complexes formed by the two macrocycles, relative stabilities are not controlled by EDA interactions. A correlation between association constants and electronic character of the benzene guests does not exist: Some donor–donor and acceptor–acceptor guests like *p*-dimethoxybenzene (**11e**) and *p*-benzodinitrile (**11j**) form complexes of similar stability with **5**. Within one category of guests, e.g., the donor–donor derivatives, large differences in complexation strength are observed. The complex of **5** with *p*-dimethoxybenzene (**11e**) is



11a-l

almost 2 kcal mol^{-1} more stable than the complex of **5** with *p*-diaminobenzene (**11a**). A slight preference for the complexation of dipolar guests is apparent: *p*-Nitrophenol (**11f**), *p*-tolunitrile (**11g**), and *p*-nitrotoluene (**11h**) form among the strongest complexes with both hosts **2** and **5**. The formation of all complexes is strongly enthalpy controlled as shown in the following paper; the complexation enthalpies also do not correlate with the electronic character of the substrates.[18b]

As indicators of the solvophobic driving forces for complexation, Table V includes the solubilities[33,34] and Hansch partition coefficients log $P_{octanol}$[35] of the guests. A positive value of log $P_{octanol}$ indicates that a compound prefers to partition preferentially into octanol rather than into water. A strong general correlation between host–guest association strength and solubility or log $P_{octanol}$ does not exist, although interesting trends are apparent. For example, in the group of donor–donor guests, the substrates with the highest solubilities and smallest log $P_{octanol}$ values *p*-diaminobenzene (**11a**) and hydroquinone (**11b**) form the weakest complexes with **2** and **5**. The substrates with low solubilities and large positive log $P_{octanol}$ values *p*-xylene (**11d**) and 1,4-dimethoxybenzene (**11e**) form more stable complexes. Dimethyl terephthalate (**11k**) with the lowest solubility forms the most stable complexes of all substrates.

As stated before, none of the correlations, neither with the Hansch parameter nor with the guest solubility, are very strong, which indicates the complexity of a binding event in water. Unfavorable changes in the solvation of guest substituents upon complexation undoubtedly represent an important factor governing relative association strength. Other factors, difficult to analyze, are specific favorable interactions, e.g., hydrogen bonding,[18b] or unfavorable interactions between the methoxy groups of the host and the guest functionalities. All three complexes of **2** and **5** with donor–acceptor guests (**11f–11h**) are quite stable despite their high solubility. The stability of the complexes with **11f** is especially noteworthy since this compound has a solubility of almost 1×10^{-1} mol L^{-1}. As discussed above for the binding of donor–acceptor naphthalenes, the high stability of the complexes formed by the dipolar donor–acceptor guests **11f–11h** may indicate a significant contribution of dipole–induced dipole interactions to the association strength. Significant differences in the binding properties of the two octamethoxy hosts **2** and **5** provide some indication for contributions of EDA interactions to the relative binding strength in complexes of the smaller host **2**. For example, the complex of **2** with *p*-benzodinitrile is ~0.6 kcal mol^{-1} more stable than the complex with *p*-dimethoxybenzene. In contrast, the complexes of the larger macrocycle **5** with these two guests possess very similar stability (Table V). The smaller host **2** should form a tighter complex, and therefore, the strongly distance dependent EDA interactions should be more effective than in the complex involving the larger cavity of **5**.

Table VI displays characteristic $\Delta\delta_{sat}$ values calculated for protons of the two binding partners in the complexes of hosts **2** and **5** in aqueous solution. The 1,4-disubstituted benzene derivatives **11a–k** are included axially, and as seen before in the naphthalene series (Table III), donor–acceptor guests prefer complex geometries with the acceptor half more centered in the cavity. There is no apparent correlation between the time-averaged complex geometries deduced from $\Delta\delta$ values and the thermodynamic parameters $\Delta G°$, $\Delta H°$, and $T\Delta S°$ of the complexes.[14,18b]

The data obtained with hosts **2** and **5** indicate that EDA interactions in aqueous solution can be completely masked by solvophobic forces and specific substituent solvation effects. A very different result was obtained with host **1**, which lacks substituents ortho to the cyclophane bridges. The relative stability of these complexes in water at 293 K clearly follows the EDA model (Table VII). Since the cac of **1** is ~2.5×10^{-3} mol L^{-1},[26] the data obtained from binding titrations with varying amounts of host possess a significantly larger error than the other data reported in this paper. Titrations with **1** were executed in concentration ranges below the cac, which afforded a maximum of 70% saturation binding of the stronger binding acceptor–acceptor guests and up to ~40% saturation binding of the donor–acceptor guests, which show intermediate binding affinity. Binding of the donor–donor derivatives is very weak, and complete titrations below the cac were not possible. The stability constants and free energies of formation given in Table VII for these complexes are highest estimates. Even though there are larger error limits, the trends seen are unquestionable. Complexes of acceptor–acceptor guests exhibit association constants between 1000 and 2000 L mol^{-1}, those of donor–acceptor guests demonstrate intermediate stability with K_a values between 400 and 600 L mol^{-1}, and donor–donor guests are only bound very weakly ($K_a \ll 100$ L mol^{-1}). The van't Hoff analysis of a temperature-dependent NMR study for the complex of **1** with 1,4-benzodinitrile provided an enthalpic driving force of $\Delta H° = -6.1 \pm 1.3$ kcal mol^{-1}, partially compensated by a $T\Delta S°$ term at 293 K of -1.8 ± 1.4 kcal mol^{-1}.

Table VI shows that the ^{1}H NMR resonances of the guests, incorporated into the cavity of **1** exhibit complexation-induced shifts similar to those seen in the complexes of **2** and **5**. Interestingly, the host resonances in the benzene complexes of **1** show much weaker shifts than those in the comparable complexes of **2** and **5**. Only the bridge protons 2-H and the aromatic protons 7-H ortho to the bridges show modest complexation upfield shifts. For the **1**·*p*-benzodinitrile complex, the estimated $\Delta\delta_{sat}$ value for 2-H is +0.16 ppm and for 7-H +0.19 ppm; all other shifts, e.g., for the bridge protons 3-H, are smaller than ±0.05 ppm at saturation binding. These shifts are much weaker than those observed for the bridges in **2** or **5** (Table VI). We take these data as an indication for a particular preference of **1** for adopting the complex conformations A/B shown in Scheme I. For these inclusion geometries, CPK model examinations predict only weak upfield shifts of the aliphatic bridges in the host.

The comparison between the octamethoxy hosts **2** and **5** and the unsubstituted system **1** shows that the forces determining relative complexation strength in water can be selected through the host design. The two host systems differ by the presence of eight aromatic ring substituents in **2** and **5**. The absence of functional groups at the aromatic rings of **1** could have a 2-fold effect. First, as a result of differences in torsional angles about the aryl ether C–O bonds (see above), host **1** possibly could form a complex with stronger aromatic–aromatic interactions than the octamethoxy hosts **2** and **5**. The ^{1}H NMR data discussed above provide support for a particular preference of **1** for adopting the complex conformations A/B shown in Scheme I. Second, the methoxy groups in **2** and **5** could interfere with the regaining of a complete solvation shell by the guest functional groups in the complex. This should especially weaken the binding of guests with strongly solvated substituents. Such specific solvation effects are absent in the complexes of **1**. Results in other cyclophane–arene binding studies described by Dougherty et al.[5] and Wilcox et al.[9] support our belief that the interference of the host substituents and their solvation with the solvation of guest functional groups is a very important factor. The cyclophanes described by these researchers do not bear functional groups on their aromatic rings, and the relative strength of inclusion complexation follows the EDA model described above.

Complexes of 1,4-Disubstituted Benzene Derivatives in CD_3OD and D_2O-CD_3OD (60:40, v/v). The previous section clearly demonstrated that solvophobic forces and specific solvation effects rather than EDA interactions determine the relative strength of the complexation between 1,4-disubstituted benzene derivatives

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Table VI. Characteristic Complexation-Induced Shifts $\Delta\delta_{sat}$ (ppm, Positive Value Indicates Upfield Shift) Calculated for Saturation Binding of Guest and Host Protons in Complexes Formed by Hosts **1**, **2**, and **5** and 1,4-Disubstituted Benzene Derivatives in D_2O, T = 293 K

Guest Protons

			Complexes of **1**		Complexes of **2**		Complexes of **5**	
guest	X	Y	2-H	3-H	2-H	3-H	2-H	3-H
11e	OCH_3	OCH_3	1.83		2.19		2.03	
11h	CH_3	NO_2	1.88	1.98	1.73	2.65	1.71	2.33
11j	CN	CN	2.13		2.24		2.09	

Host Protons

	Complexes of **2**				Complexes of **5**			
guest	2-H	3-H	OCH_3	aryl-H	2-H	3-H	OCH_3	aryl-H
11e	0.75	0.27	−0.25	−0.29	0.54	0.10	−0.15	−0.21
11h	0.77	0.28	−0.22	−0.30	0.63	0.11	−0.15	−0.24
11j	0.75	0.24	−0.31	−0.35	0.31	−0.07	−0.19	−0.18

Table VII. Association Constants K_a and Free Energies of Complexation $\Delta G°$ for Complexes of Cyclophane **1** with 1,4-Disubstituted Benzene Derivatives in D_2O, T = 293 K

guest	X	Y	K_a, L mol^{-1}	$\Delta G°$, kcal mol^{-1}
		Donor–Donor Guests		
11a	NH_2	NH_2	<10	<1.3
11d	CH_3	CH_3	<85	<2.6
11e	OCH_3	OCH_3	<85	<2.6
		Donor–Acceptor Guests		
11g	CH_3	CN	420 ± 100	−3.5 ± 0.2
11f	OH	NO_2	600 ± 100	−3.7 ± 0.2
11h	CH_3	NO_2	600 ± 100	−3.7 ± 0.2
		Acceptor–Acceptor Guests		
11i	NO_2	NO_2	1340 ± 200	−4.2 ± 0.1
11j	CN	CN	1520 ± 150	−4.3 ± 0.1
11k	$COOCH_3$	$COOCH_3$	1920 ± 200	−4.4 ± 0.1

and **2** and **5** in water. It was of interest to analyze whether this holds also for methanol and methanol–water mixtures where solvent effects on apolar binding become weaker. Table VIII shows that the binding of benzene derivatives by hosts **3**–**5** dramatically decreases upon changing from pure water to pure methanol. The complexes of the unsubstituted cyclophane **3** and the octamethyl derivative **4** follow the sequence of relative stability expected on the basis of the EDA model in the two methanolic solutions. An interesting trend is observed for the complexes of the octamethoxy cyclophane **5**. In pure water, the relative complex stabilities did not correlate with the electronic properties of the benzene guests, and solvent effects dominated. However, EDA interactions seem to become more relevant with increasing methanol content. In pure D_2O, the complex of 1,4-benzodinitrile (**11j**) is 0.15 kcal mol^{-1} less stable than the complex of 1,4-dimethoxybenzene (**11e**). The situation is reversed in CD_3OD where the complex of **11j** is more stable by ~0.6 kcal mol^{-1}. Similarly, with increasing methanol content, the complexes of hosts **3** and **4** with acceptor–acceptor guests become increasingly more stable than the corresponding complexes of donor–donor guests. The complex between host **4** and *p*-benzodinitrile (**11j**) in CD_3OD is stabilized by 0.85 kcal mol^{-1} compared to the complex formed by *p*-dimethoxybenzene (**11e**) (Table VIII). The analysis of $\Delta\delta_{sat}$ values shows that the geometry of a given host–guest complex is very similar in D_2O, CD_3OD, and the binary mixture.

Linear Free Energy Relationships Predict the Complexation Strength in Binary Solvent Mixtures. In view of the dramatic reduction in complexation strength upon changing from water to methanol (Table VIII), we were interested to see how small changes in binary solvent mixtures affect apolar binding interactions. We investigated the complexation of 1,4-dimethoxybenzene (**11e**) and 1,4-benzodinitrile (**11j**) with host **5** as a function of the composition of binary aqueous solvent mixtures. Cosolvents were CD_3OD, $(CD_3)_2SO$, and 2,2,2-trifluoroethanol. Figure 3A shows how the complexation free energies decrease in a nonlinear way with increasing content of organic cosolvent. Whereas we had previously found that inclusion complexation into a large cyclophane cavity is promoted best by water, followed by CF_3CH_2OH, CD_3OD, and $(CD_3)_2SO$,[18a] the sequence is changed for inclusion into the more narrow binding site of **5**, which is aligned by methoxy groups. Figure 3A shows that the addition of 2,2,2-trifluoroethanol gives the greatest reduction in apolar binding by **5**.

Table VIII. Association Constants K_a and Free Energies of Complexation $\Delta G°$ for Complexes of Cyclophanes **3**–**5** with 1,4-Disubstituted Benzene Derivatives in CD_3OD and D_2O–CD_3OD (60:40, v/v), T = 293 K

host	guest	X	Y	K_a, L mol^{-1}	$\Delta G°$,[a] kcal mol^{-1}
		(A) D_2O–CD_3OD (60:40, v/v)			
3	**11e**	OCH_3	OCH_3	95	−2.66
	11j	CN	CN	140	−2.89
4	**11e**	OCH_3	OCH_3	580	−3.72
	11f	OH	NO_2	1210	−4.13
	11j	CN	CN	1580	−4.29
	11k	$COOCH_3$	$COOCH_3$	4200	−4.87
5	**11e**	OCH_3	OCH_3	340	−3.41
	11f	OH	NO_2	990	−4.02
	11j	CN	CN	390	−3.48
	11k	$COOCH_3$	$COOCH_3$	2080	−4.45
		(B) CD_3OD			
3	**11e**	OCH_3	OCH_3	≪10	≫−1.30
	11j	CN	CN	16	−1.60
4	**11e**	OCH_3	OCH_3	30	−1.99
	11j	CN	CN	130	−2.84
5	**11e**	OCH_3	OCH_3	8	−1.23
	11f	OH	NO_2	10	−1.34
	11j	CN	CN	24	−1.86
	11k	$COOCH_3$	$COOCH_3$	24	−1.86

[a] Uncertainties in $\Delta G°$ ±0.1 kcal mol^{-1} in the binary solvent mixture and ±0.2 kcal mol^{-1} in pure CD_3OD.

For methanol–water mixtures, there exist excellent linear free energy relationships (LFER's) between the free energy of complexation by **5** and $E_T(30)$ (Figure 3B).[18a,36] The linear correlation coefficient for the LFER between $-\Delta G°$ for the **5**·1,4-benzodinitrile complex and $E_T(30)$ was calculated as R = 0.995, for the LFER of the **5**·1,4-dimethoxybenzene complex as R = 0.992. These excellent correlations provide one additional example that apolar binding interactions in inclusion complexes are well reflected by the $E_T(30)$ parameter.[37]

Conclusions

Comprehensive investigations of cyclophane–arene inclusion complexation were undertaken to analyze the relative importance of EDA interactions and solvent effects in various environments. The major attractive host–guest interactions in the complexes

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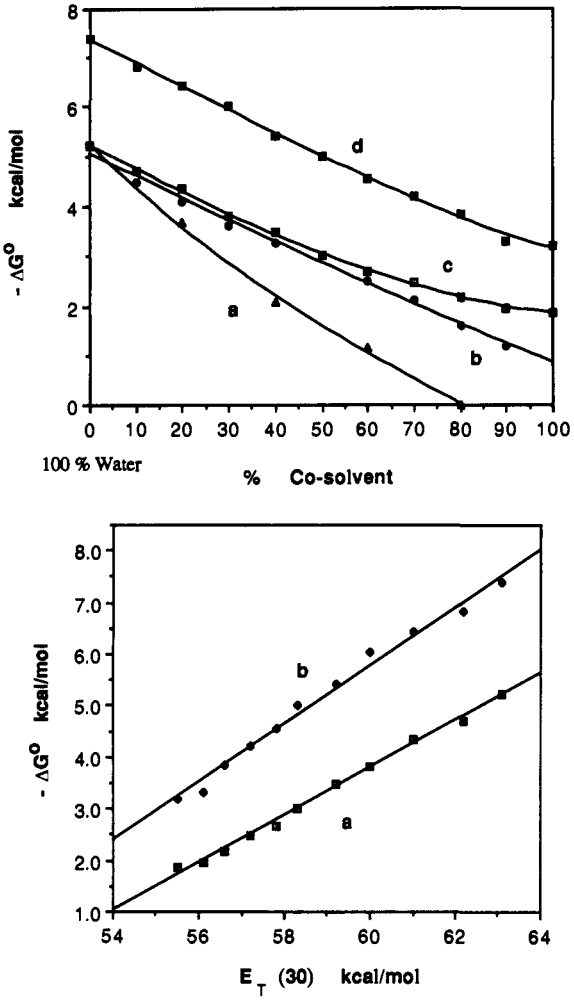

Figure 3. Complexation in binary aqueous solvent mixtures. (A) Free energy of formation of the **5**·1,4-benzodinitrile complex versus percent (v/v) CF_3CH_2OH (a), $(CD_3)_2SO$ (b), and CD_3OD (c) and of the **5**·1,4-dimethoxybenzene complex versus percent (v/v) CD_3OD (d). To prevent overlap, curve d has been displaced upward on the ordinate by 2 kcal mol^{-1}. (B) LFER between $E_T(30)$ and the free energies of formation of the **5**·1,4-benzodinitrile complex (a) and the **5**·1,4-dimethoxybenzene complex (b) in D_2O–CD_3OD mixtures. Curve b has been displaced upward on the ordinate by 2 kcal mol^{-1}.

formed by 2,6-disubstituted naphthalenes and para-disubstituted benzene derivatives are π–π-stacking and edge-to-face aromatic–aromatic interactions. A comparison between three different cyclophanes shows that a deepening of the cavity by substituents attached to the aromatic rings increases binding strength in protic solvents only if these residues do not perturb the apolar character of the binding site. Studies in D_2O, CD_3OD, and binary mixtures of both solvents show that binding strength decreases monotonously from D_2O to mixtures containing increasing amounts of CD_3OD, to pure CD_3OD. Host–guest association strength in the binary solvent mixtures is predictable from LFER's between the free energy of complexation and the empirical solvent polarity parameter $E_T(30)$.

In $(CD_3)_2SO$ and CD_3OD, electronic host–guest complementarity generally defines relative complexation strength, and the electron-rich cyclophanes form the most stable complexes with electron-deficient guests. If the favorable solvation of guest substituents is reduced in the inclusion complexes as compared to the bulk, binding strength becomes weakened and the EDA model is no longer valid. Such specific substituent solvation effects are particularly pronounced in water, which in addition, provides the strongest solvophobic driving forces for complexation. The electronic host–guest complementarity controls the relative association strength in aqueous solution only if unfavorable complexation-induced changes in substituent solvation are avoided. The relative association strength in benzene complexes of **1** is governed by EDA interactions since the solvation of guest functional groups is not hindered by any host substituents. On the other hand, binding of benzene derivatives by cyclophanes **2** and **5** is largely dominated by solvent effects. The substituents at the aromatic rings of these hosts interfere with the solvation of the guest functional groups in the complex. We believe that the comprehensive investigations described provide significant insight into designing receptor systems. Furthermore, this study demonstrates that strong and selective inclusion complexation in water and other polar protic solvents, where host–guest association is affected by strong solvent effects, must be viewed as a complex multiparameter event and, therefore, be analyzed as such.

Experimental Section

General Procedure. ^1H NMR spectra (293 K) were recorded at 500 MHz in $CDCl_3$ unless specified otherwise. The matrix for FAB spectra was *m*-nitrobenzyl alcohol. Melting points are not corrected. Elemental analyses were done by Spang Microanalytical Laboratory, Eagle Harbor, MI. E. Merck silica gel 60, 0.04–0.063 mm, was used for flash and gravity chromatography. All chemicals were purchased reagent grade and used without further purification. Dimethylformamide (DMF) was dried by standing over basic alumina (E. Merck, activity I) followed by filtration through Celite. Millipore water was used in ion exchange chromatography and in all manipulations involving quaternary ammonium compounds. *N*-Acetyl-4,4-bis(4-hydroxy-3,5-dimethoxyphenyl)-piperidine,[38] dichloride **6b**,[38] and cyclophanes **1**,[26] **3**,[26] and **4**[26] were prepared as previously described.

Solubility Determination. Guest solubilities in Tables II and V were determined by UV/vis spectroscopy by comparing a saturated solution of the compound and a standard of known concentration. Saturated solutions were prepared by stirring powdered material in water (benzene derivatives) or methanol (naphthalene derivatives) for 24 h at 20 °C. Solutions of naphthalene guests were heated to reflux for an initial period of 15 min. The excess of solid guest was removed by filtration.

Binding Studies. ^1H NMR titrations were completed at 360 and 500 MHz. Temperature calibration of each run was made by using the methanol calibration method. The reference peaks for spectra in mixtures were the following: δ 3.312 (CD_2HOD), 4.67 (HDO), 2.490 (CD_3SOCD_2H). All materials were weighed by using either a Sartorius 4503 or a Mettler AT 20 microbalance, and solutions were prepared with micropipettors. In each titration, the total guest concentration was kept constant. If possible, the concentrations of host and guest were chosen to vary the percentage of guest complexation from about 10 to 90%. Two methods for sample preparation were used. Either a gradation of host material was weighed and equal aliquots of stock guest solution were added to each sample or a stock solution of host and a stock solution of guest were made and desired concentrations were achieved by pipetting appropriate amounts of each solution and of pure solvent. Solvent mixtures were made as volume/volume ratios. The association constants of the formed 1:1 complexes were determined from the titration curves by using a computer-assisted nonlinear least-squares curve-fitting procedure described elsewhere in detail together with the programming code.[39]

Synthesis. *N*-Acetyl-4,4-bis[4-(4-chlorobutoxy)-3,5-dimethoxyphenyl]piperidine (6a). The preparation of **6a** followed closely the procedure reported in ref 38 for dichloride **6b**. The reaction of 12.1 g (28 mmol) of *N*-acetyl-4,4-bis(4-hydroxy-3,5-dimethoxyphenyl)piperidine, 66.4 g (520 mmol) of 1,4-dichlorobutane, and 15.9 g (49 mmol) of Cs_2CO_3 afforded 14.4 g (84%) of **6a** as a colorless oil: IR (KBr) ν (C=O) 1649 cm^{-1}; ^1H NMR δ 1.8–1.9 (m, 4 H, OCH_2CH_2), 1.95–2.05 (m, 4 H, OCH_2CH_2), 2.07 (s, 3 H, $NCOCH_3$), 2.25–2.35 (m, 4 H, NCH_2CH_2), 3.5–3.55 (m, 2 H, NCH_2), 3.62 (t, 4 H, J = 6.7 Hz, CH_2Cl), 3.65–3.7 (m, 2 H, NCH_2), 3.74 (s, 12 H, OCH_3), 3.94 (t, 4 H, J = 7.7 Hz, OCH_2), 6.39 (s, 4 H, ArH); MS (EI, 16 eV) m/z (relative intensity) 611 (M^+, 100); HRMS (EI) m/z (M^+, $C_{31}H_{43}Cl_2NO_7$) calcd 611.24164, obsd 611.24166.

1,1″-Diacetyl-8,12,16,18,27,31,35,37-octamethoxydispiro[1,6,20,25-tetraoxa[6.1.6.1]paracyclophane-13,4′:32,4″-bispiperidine] (7a). A solution of 5.64 g (13.1 mmol) of *N*-acetyl-4,4-bis(4-hydroxy-3,5-dimethoxyphenyl)piperidine, 7.99 g (13.1 mmol) of **6a**, and 22.0 g (67.5 mmol) of Cs_2CO_3 in 650 mL of DMF was heated under N_2 at 95 °C for 6 days. The inorganic salts were removed by filtration, and the solvent was evaporated. The residual dark oil was dissolved in CH_2Cl_2, washed with

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10% HCl, and dried over $MgSO_4$. After evaporation of the solvent, the product was purified by flash chromatography with CH_2Cl_2/CH_3OH (97:3). Recrystallization from CH_2Cl_2/ether afforded 1.9 g (15%) of **7a**: mp 288–290 °C (dec); IR (KBr) ν(C=O) 1639 cm^{-1}; ^1H NMR δ 1.8–1.9 (m, 8 H, OCH_2CH_2), 2.08 (s, 6 H, $NCOCH_3$), 2.25–2.35 (m, 8 H, NCH_2CH_2), 3.5–3.55 (m, 4 H, NCH_2), 3.65–3.7 (m, 4 H, NCH_2), 3.70 (s, 24 H, OCH_3), 3.97 (t, J = 6.5 Hz, 8 H, OCH_2), 6.38 (s, 8 H, ArH); MS (EI, 70 eV) m/z (relative intensity) 971 (M^+, 100). Anal. Calcd for $C_{54}H_{70}N_2O_{14}$ (971.2): C, 66.79; H 7.27; N, 2.88. Found: C, 66.74; H, 7.24; N, 2.61.

1′,1″-Diacetyl-7,11,15,17,25,29,33,35-octamethoxydispiro[1,5,19,23-tetraoxa[5.1.5.1]paracyclophane-12,4′:30,4″-bispiperidine] (7b). The preparation described for **7a** was followed: mp 289–290 °C (dec); IR (KBr) ν(C=O) 1636 cm^{-1}; ^1H NMR δ 2.09 (s, 6 H, $NCOCH_3$), 2.11 (qn, J = 6.2 Hz, 4 H, OCH_2CH_2), 2.25–2.35 (m, 8 H, NCH_2CH_2), 3.5–3.55 (m, 4 H, NCH_2), 3.59 (s, 24 H, OCH_3), 3.65–3.7 (m, 4 H, NCH_2), 4.14 (t, J = 6.2 Hz, 8 H, OCH_2), 6.31 (s, 8 H, ArH); MS (EI, 70 eV) m/z (relative intensity) 943 (M^+, 100). Anal. Calcd for $C_{52}H_{66}N_2O_{14}$ (943.1): C, 66.23; H, 7.05; N, 2.97. Found: C, 66.11; H, 7.20; N, 2.93.

8,12,16,18,27,31,35,37-Octamethoxydispiro[1,6,20,25-tetraoxa-[6.1.6.1]paracyclophane-13,4′:32,4″-bispiperidine] (8a). A solution of 1.83 g (1.9 mmol) of **7a** and 4.80 g (85.5 mmol) of KOH in 95 mL of 2-methoxyethanol was heated to reflux for 3 h. Subsequently, half of the solvent was distilled off. Upon addition of 50 mL of H_2O, a solid precipitated, which was collected by filtration and washed with cold water until the washing liquors showed neutral pH: 1.30 g (77%) of off-white **8a**; mp 214–216 °C; IR (KBr) ν(N–H) 3450 cm^{-1}; ^1H NMR δ 1.60 (br s, 2 H, NH), 1.8–1.9 (m, 8 H, OCH_2CH_2), 2.2–2.3 (m, 8 H, NCH_2CH_2), 2.9–3.0 (m, 8 H, NCH_2), 3.69 (s, 24 H, OCH_3), 3.97 (t, J = 6.5 Hz, 8 H, OCH_2), 6.41 (s, 8 H, ArH); HRMS (EI) m/z (M^+, $C_{50}H_{66}N_2O_{12}$) calcd 886.46154, obsd 886.46158.

7,11,15,17,25,29,33,35-Octamethoxydispiro[1,5,19,23-tetraoxa-[5.1.5.1]paracyclophane-12,4′:30,4″-bispiperidine] (8b). The preparation described for **8a** was followed: mp 201–202 °C; IR (KBr) ν(N–H) 3445 cm^{-1}; ^1H NMR δ 1.66 (br s, 2 H, NH), 2.12 (qn, 4 H, J = 6.2 Hz, OCH_2CH_2), 2.25–2.35 (m, 8 H, NCH_2CH_2), 2.9–3.0 (m, 8 H, NCH_2), 3.59 (s, 24 H, OCH_3), 4.15 (t, J = 6.2 Hz, 8 H, OCH_2), 6.35 (s, 8 H, ArH); HRMS (EI) m/z (M^+, $C_{48}H_{62}N_2O_{12}$) calcd 858.43024, obsd 858.430276.

8,12,16,18,27,31,35,37-Octamethoxy-1′,1″-dimethyldispiro[1,6,20,25-tetraoxa[6.1.6.1]paracyclophane-13,4′:32,4″-bispiperidine] (9a). A mixture of 0.951 g (1.10 mmol) of **8a**, 2.04 g (44.3 mmol) of formic acid, and 1.78 g (22.0 mmol) of 37% aqueous formaldehyde was heated to 60 °C. When CO_2 evolution was observed, heating was discontinued. After the CO_2 evolution had ceased, the mixture was heated to 100 °C for 14 h. Upon addition of the cooled reaction mixture into 50 mL of 2 N NaOH, a light brown precipitate formed. The entire mixture was heated to 80 °C for 1 h. After cooling, the brown solid was collected by filtration and rinsed with cold water until the washing liquor showed neutral pH. The product was purified via flash chromatography on silica gel with ethyl acetate/triethylamine/methanol (85:10:5) to give 0.906 g (90%) of solid white product: mp 208–210 °C; ^1H NMR δ 1.8–1.85 (m, 8 H, OCH_2CH_2), 2.23 (s, 6 H, NCH_3), 2.3–2.4 (m, 8 H, NCH_2CH_2), 2.4–2.5 (m, 8 H, NCH_2), 3.69 (s, 24 H, OCH_3), 3.98 (t, J = 6.4 Hz, 8 H, OCH_2), 6.40 (s, 8 H, ArH); MS (EI, 70 eV) m/z (relative intensity) 915 (M^+, 100). Anal. Calcd for $C_{52}H_{70}N_2O_{12}$ (915.1): C, 68.25; H, 7.71; N, 3.06. Found: C, 68.22; H, 7.78; N, 3.06.

7,11,15,17,25,29,33,35-Octamethoxy-1′,1″-dimethyldispiro[1,5,19,23-tetraoxa[5.1.5.1]paracyclophane-12,4′:30,4″-bispiperidine] (9b). The preparation described for **9a** was followed: mp 207–208 °C (dec); ^1H NMR δ 2.12 (qn, J = 6.1 Hz, 4 H, OCH_2CH_2), 2.26 (s, 6 H, NCH_3), 2.35–2.45 (m, 8 H, NCH_2CH_2), 2.45–2.55 (m, 8 H, NCH_2), 3.59 (s, 24 H, OCH_3), 4.16 (t, J = 6.1 Hz, 8 H, OCH_2), 6.34 (s, 8 H, ArH); MS (EI, 70 eV) m/z (relative intensity) 886 (M^+). Anal. Calcd for $C_{50}H_{66}N_2O_{12}$ (887.1): C, 67.70; H, 7.50; N, 3.16. Found: C, 67.88; H, 7.37; N, 3.29.

8,12,16,18,27,31,35,37-Octamethoxy-1′,1′,1″,1″-tetramethyldispiro-[1,6,20,25-tetraoxa[6.1.6.1]paracyclophane-13,4′:32,4″-bispiperidinium] Dichloride (5). A total of 0.362 g (0.260 mL, 3.17 mmol) of methyl fluorosulfonate was added via syringe under N_2 to a solution of 0.480 g (0.525 mmol) of **9a** in 100 mL of $CHCl_3$. After 1 h, diethyl ether (75 mL) was added and the mixture was stirred for 4 h. The precipitated product was collected by filtration. After washing with diethyl ether and drying, 0.550 g (89%) of the bis(fluorosulfonate) was obtained as a hygroscopic white dihydrate: mp 293–294 °C (dec); ^1H NMR (500 MHz, CD_3OD) δ 1.75–1.85 (m, 8 H, OCH_2CH_2), 2.75–2.85 (m, 8 H, NCH_2CH_2), 3.20 (s, 12 H, NCH_3), 3.45–3.55 (m, 8 H, NCH_2), 3.71 (s, 24 H, OCH_3), 3.9–4.0 (m, 8 H, OCH_2), 6.61 (s, 8 H, ArH); MS (FAB) m/z (relative intensity) 930 ($M^+ - 2FSO_3 - CH_3$, 100), 472 ($M^{2+} - FSO_3$, 70). Anal. Calcd for $C_{54}H_{76}N_2O_{12}\cdot F_2S_2O_6\cdot 2H_2O$ (1179.4): C, 55.00; H, 6.84; N, 2.38; S, 5.44. Found: C, 54.85; H, 6.74; N, 2.37; S, 5.45. The bis(fluorosulfonate) was converted in a quantitative yield into the corresponding dichloride **5** by chromatography on Dowex ion exchange resin (Cl^-) using H_2O/CH_3CN (60:40) as the eluant: mp 285 °C (dec); ^1H NMR (500 MHz, D_2O, 295 K) δ 1.35–1.45 (m, 8 H, OCH_2CH_2), 2.6–2.7 (m, 8 H, NCH_2CH_2), 3.02 (s, 12 H, NCH_3), 3.25–3.35 (m, 8 H, NCH_2), 3.51 (s, 24 H, OCH_3), 3.65–3.75 (m, 8 H, OCH_2), 6.52 (s, 8 H, ArH); MS (FAB) m/z (relative intensity) 980 ($M^+ - Cl^-$, 85), 930 ($M^+ - 2Cl^- - CH_3$, 100), 472 ($M^{2+} - Cl^-$, 33). Anal. Calcd for $C_{54}H_{76}N_2O_{12}\cdot Cl_2\cdot 2H_2O$ (1052.1): C, 61.65; H, 7.66; N, 2.66; Cl, 6.74. Found: C, 61.71; H, 7.69; N, 2.67; Cl, 6.62.

7,11,15,17,25,29,33,35-Octamethoxy-1′,1′,1″,1″-tetramethyldispiro-[1,5,19,23-tetraoxa[5.1.5.1]paracyclophane-12,4′:30,4″-bispiperidinium] Dichloride (2). A solution of 95 mg (0.11 mmol) of **9b** in 80 mL of methyl iodide was stirred under N_2 at 20 °C for 15 h. The precipitated diiodide was collected by filtration, washed with diethyl ether, and dried: 125 mg (94%) of the diiodide salt; mp 298–299 °C (dec); ^1H NMR (500 MHz, CD_3OD) δ 2.02 (qn, 4 H, OCH_2CH_2), 2.75–2.85 (m, 8 H, NCH_2CH_2), 3.22 (s, 12 H, NCH_3), 3.45–3.55 (m, 8 H, NCH_2), 3.63 (s, 24 H, OCH_3), 4.11 (t, 8 H, J = 5.8 Hz, OCH_2), 6.55 (s, 8 H, ArH); MS (FAB) m/z (relative intensity) 1043 ($M^+ - I^-$, 85), 915 ($M^+ - H - 2I^-$, 60), 901 ($M^+ - 2I^- - CH_3$, 100). Anal. Calcd for $C_{52}H_{72}N_2O_{12}\cdot I_2\cdot 2H_2O$ (1207.0): C, 51.75; H, 6.35; N, 2.32; I, 21.03. Found: C, 51.70; H, 6.32; N, 2.30; I, 21.02. The diiodide was transformed in a quantitative yield into the dichloride **2** by ion exchange chromatography as described for **5**: mp 285 °C (dec); ^1H NMR (500 MHz, D_2O, 293 K) δ 1.88 (qn, J = 5.9 Hz, 4 H, OCH_2CH_2), 2.6–2.7 (m, 8 H, NCH_2CH_2), 3.02 (s, 12 H, NCH_3), 3.25–3.35 (m, 8 H, NCH_2), 3.45 (s, 24 H, OCH_3), 3.95 (t, J = 5.9 Hz, 8 H, OCH_2), 6.42 (s, 8 H, ArH); MS (FAB) m/z (relative intensity) 952 ($M^+ - Cl^-$, 100), 902 ($M^+ - 2Cl^- - CH_3$, 83), 458 ($M^{2+} - Cl^-$, 60). Anal. Calcd for $C_{52}H_{72}N_2O_{12}\cdot Cl_2\cdot 2H_2O$ (1024.1): C, 60.99; H, 7.48; N, 2.74; Cl, 6.92. Found: C, 61.09; H, 7.36; N, 2.69; Cl, 6.74.

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