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Full papers

Basket-shaped hosts with semi-flexible handles[#]

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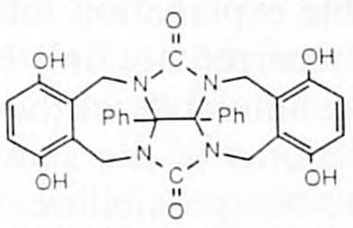
Abstract. Basket-shaped hosts were synthesized starting from the concave building block **4**:



. To this end, oligo(oxyethylene) bridges, containing different aromatic rings, were attached to the 3,6- and 3′,6′-positions of the xylylene rings of **4**. These bridges include 5,6-benzo-1,4,7,10-tetraoxadec-5-ene, 5,6,7-benzo-1,4,8,11-tetraoxaundeca-5,6-diene, 5,6-(2,3-naphtho)-1,4,7,10-tetraoxa-dec-5-ene, 8,9-benzo-1,4,7,10,13,16-hexaoxahexadec-8-ene and 8,9-(2,3-naphtho)-1,4,7,10,13,16-hexaoxahexadec-8-ene chains. Alkali-metal ions and protonated aliphatic or aromatic diamines are bound in these baskets in a 1:1 host/guest ratio. For the metal ions, a clamshell-like or a sandwich-like complex is proposed. Aliphatic diammonium guests are bound in such a way that the methylene chains are wedged in between the *o*-xylylene units of the host, as concluded from the upfield shifts observed in the ^{1}H NMR spectra of the guest CH_2 protons. Free energies of binding of the new hosts with nineteen guests were measured using the picrate extraction technique. The highest $-\Delta G^0$ values were obtained for the complexes with the diammonium salts ($-\Delta G^0$ values up to 13.4 kcal/mol).

Introduction

By building host–guest model systems[1], a better understanding can be gained of the processes occurring in nature, for instance of the interactions between substrate and enzyme or between inhibitor and receptor. *Vice versa*, we can learn from nature how to design enzyme-like catalysts. To achieve this goal it is very important to synthesize well-defined host–guest systems and to study host–guest interactions. Recently, we described a novel versatile building block[2] for the synthesis of various kinds of host molecules, including those which can be used as catalysts[1n]. This building block is **4**, which has an overall concave and rigid structure. The X-ray structure of **4** is given in Fig. 1. Compound **4** is easily accessible in high yield from the inexpensive starting materials urea, benzil, paraformaldehyde and 1,4-benzenediol. Using this building block, we prepared ditopic basket-shaped molecules with two handles (*e.g.* compounds **9d** and **10d**)[2]. The handles of these baskets are formed by oxyethylene chains. In this paper we describe the synthesis and complexing properties of the basket-shaped molecules, compounds **9a-c**, **10a** and **10c**, which have different aromatic rings built into the oxyethylene chains. The effect of these rings on the binding properties of the hosts is discussed.

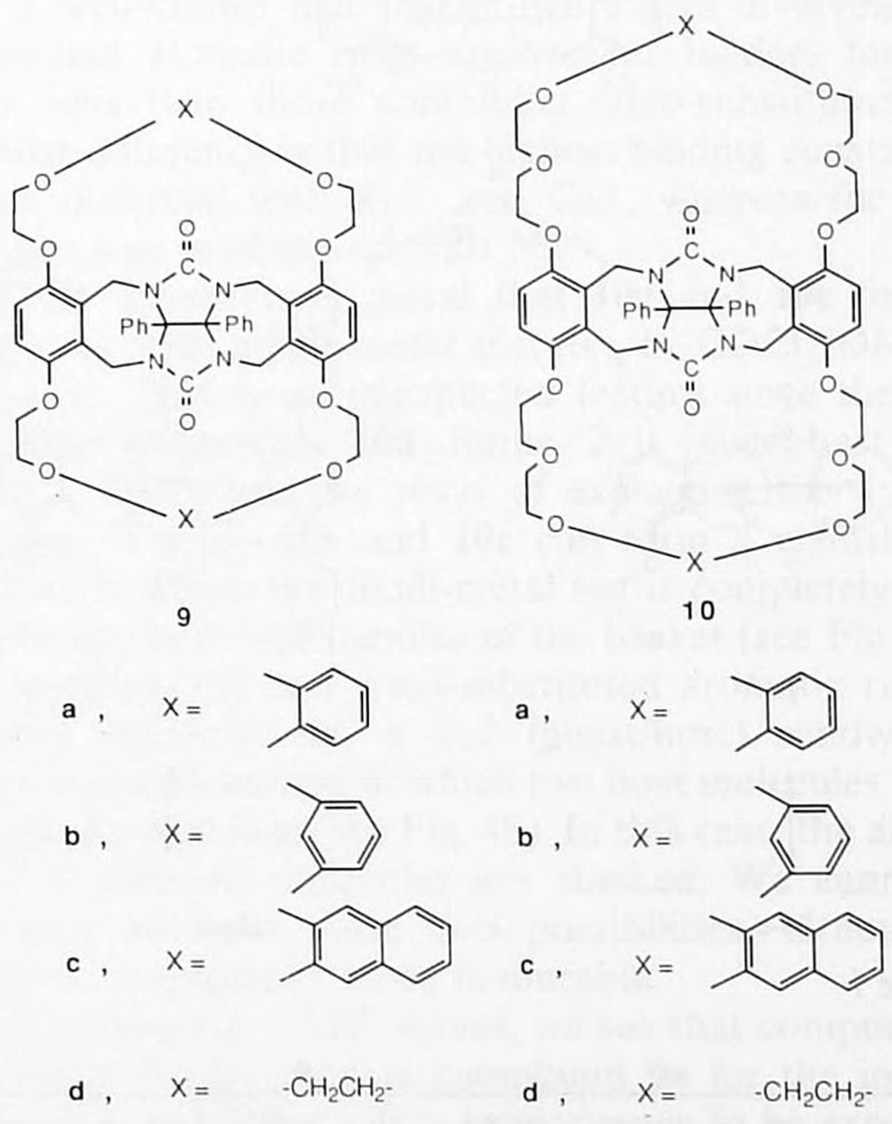


Chart 1

[#] Dedicated to Prof. *W. Drenth* on the occasion of his retirement from the Chair of Physical Organic Chemistry at the University of Utrecht.

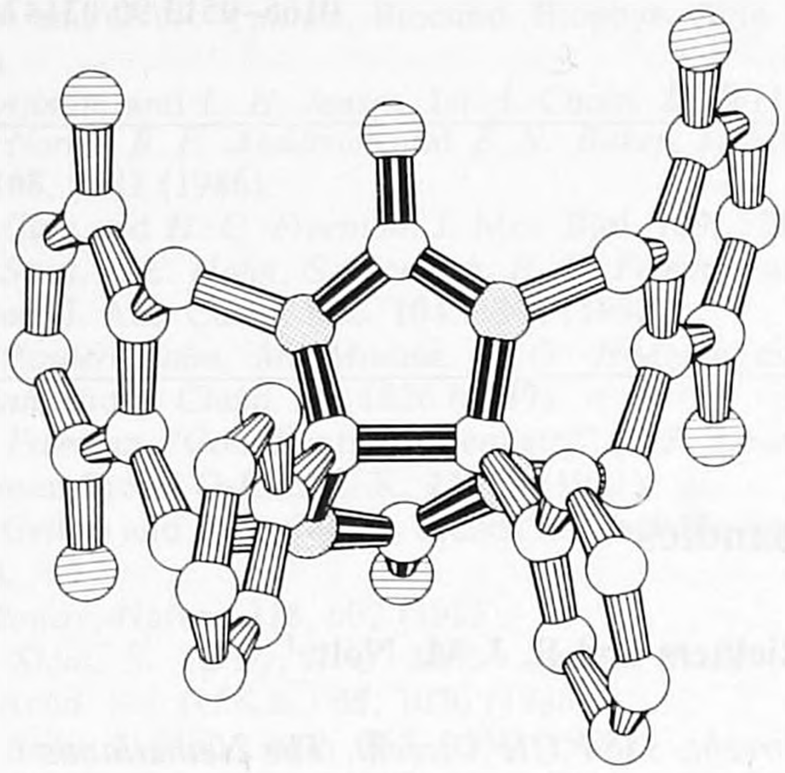


Fig. 1. X-ray structure of **4**. *The overall structure is concave and rigid.*

Results and discussion

Synthesis of the baskets

The synthetic route to compounds **9a-c** and **10a-c** is shown in Scheme 1. Diphenylglycoluril* (**1**) was prepared in almost quantitative yield from urea and benzil[3]. Treatment of compound **1** with paraformaldehyde and sodium hydroxide in DMSO yielded compound **2** (85%)[1m]. Building block **4** was synthesized by treating **2** with an excess of 1,4-benzenediol in 1,2-dichloroethane in the presence of an acidic catalyst (75% yield)[2b]. Compound **3** is formed as an intermediate in this reaction and could be isolated and characterized[1m]. Building block **4** was prepared with four tails, terminated with chlorine groups, by reaction with a slight excess of 1-chloro-2-tosylethane (**5**) and potassium carbonate as a base in DMSO. Compound **7** was obtained in 70% yield. Similarly, treatment of **4** with a slight excess of 1-(2-chloroethoxy)-2-tosylethane (**6**) and powdered KOH as a base in DMSO yielded compound **8** in 74% yield. Compounds **7** and **8** were allowed to react with 2 equivalents of either 1,2-benzenediol, 1,3-benzenediol or 2,3-naphthalenediol in the presence of potassium carbonate as a base in DMSO to yield compounds **9a** (29%), **9b** (20%), **9c** (16%), **10a** (70%) and **10c** (50%). Reaction of **8** with 1,3-benzenediol in the presence of potassium carbonate yielded a product of which the FAB mass spectrum displayed only one intensive signal of the molecular ion $(M + H)^+$ at *m/z* 1063. However, in the ^1H NMR spectrum, two pairs of doublets attributable to the NCH_2Ar protons were visible, suggesting that two isomers of the resulting basket had been formed. The lower-field doublet of each pair lies at δ 5.67 and 5.19 ppm, respectively, whereas the higher-field doublets are masked by the oxyethylene protons. A reasonable explanation for this observation is that ring closure has occurred not only between oxygen atoms of different hydroquinone units of the building block, but also between oxygen atoms of the same hydroquinone unit. In Fig. 2a and b, the two possibilities of ring closure of **8** with 1,3-benzenediol are presented. The doublet at 5.19 ppm can be ascribed to the NCH_2Ar protons of the isomer in Fig. 3b. These protons lie in the shielding zone of the 1,3-benzenediol ring. It is remarkable that ring closure of **8** with 1,2-benzenediol proceeds regioselectively over two rings, whereas ring closure with 1,3-benzenediol yields a mixture of isomers. Attempts to synthesize basket-like compounds from **7** and **8**, using *para*-substituted aromatic rings in the same way as described above, failed.

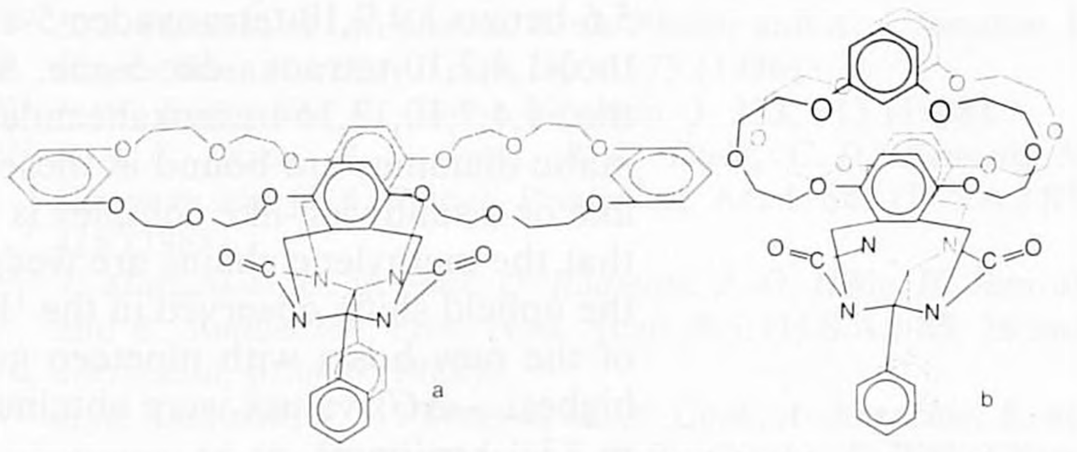
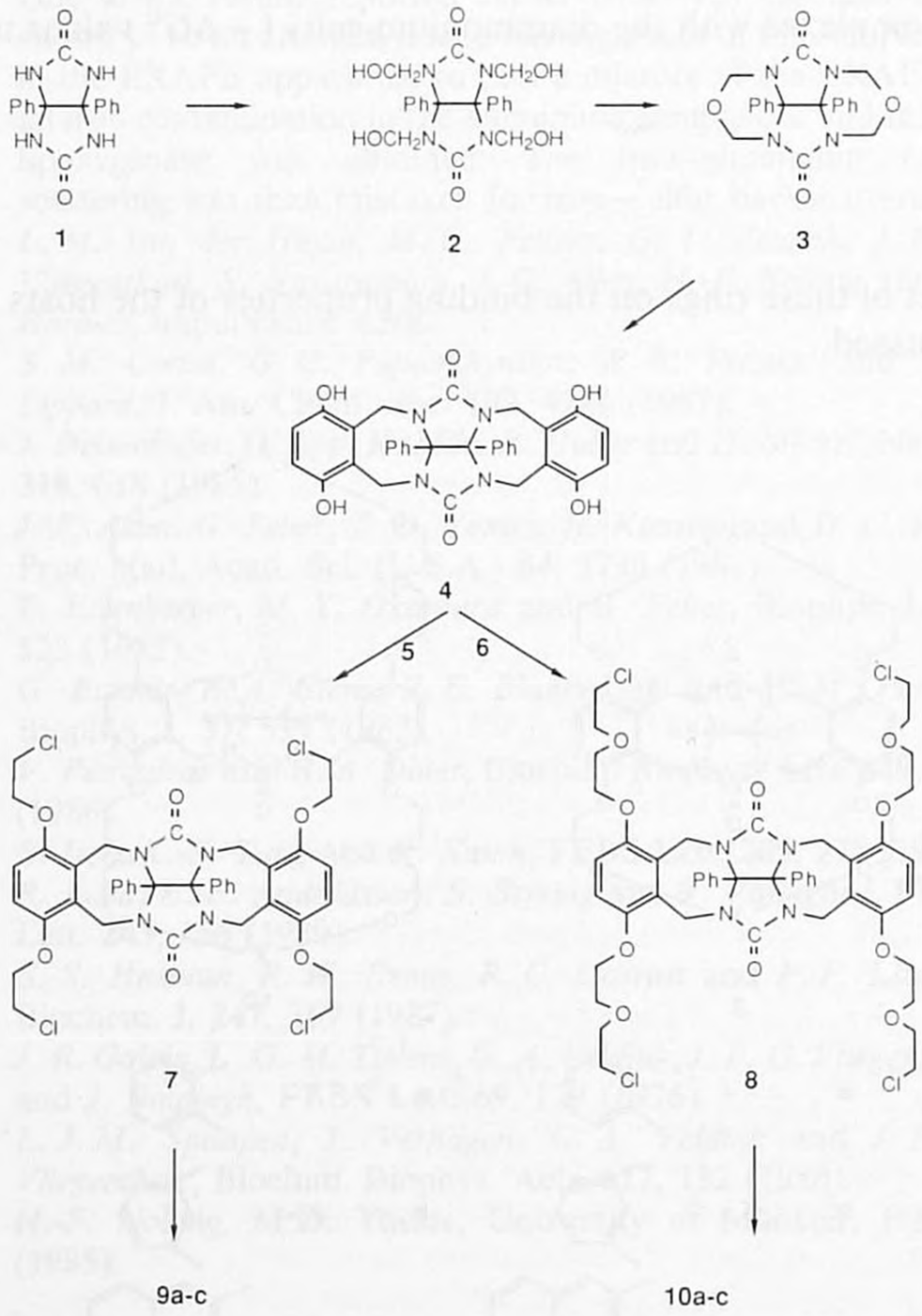


Fig. 2. Two ways of ring closure of **8** *with resorcinol. Ring closure has occurred between different 1,4-benzenediol units (a) and over one 1,4-benzenediol unit (b)*

Ring closure of **7** to **9** proceeds in a much lower yield than does ring closure of **8** to **10**. This is probably caused by a template effect of the potassium cation. The larger rings of compounds **10** (**10a** can be compared with benzo-21-crown-7) are a better match with the potassium ion than are the rings of compounds **9** (**9a** can be compared with benzo-15-crown-5). Furthermore, the fact that the yield decreases on going from *ortho*- to *meta*- to *para*-substituted aromatic rings in compounds **9** and **10** can be explained on the basis of a template effect. The absence of any template effect could be the reason for our failure to obtain basket-like compounds with *para*-substituted aromatic rings. For the reaction of **7** with hydroquinone, the strain in the product could also be one of the reasons for this failure. The phenomenon that closure of **8** with 1,2-benzenediol proceeds regioselectively over two rings, whereas ring closure with 1,3-benzenediol yields a mixture of isomers, is remarkable. We also ascribe this to a template effect of the potassium ion. Ring-closure reactions with compound **7** al-



Scheme 1

* Tetrahydro-3a,6a-diphenylimidazo[4,5-*d*]imidazole-2,5(1*H*,3H)-dione.

ways take place between two different 1,4-benzenediol units since, according to CPK models, the chains are too short to bridge one unit. This fact was supported by the ^{1}H NMR data of the product which reveal only one pair of doublets. Compounds **9a-c** and **10a-c** are baskets with a rigid framework and semi-flexible handles. Compounds **10a-c** are somewhat more flexible than compounds **9a-c**.

Complexation of alkali-metal ions and ammonium ions

Compounds **9** and **10** are able to complex alkali-metal ions and ammonium ions. By ^{1}H NMR chemical-shift experiments, we determined the stoichiometry of complexation for most of the complexes[2b,4]. Small portions of solid alkali-metal picrate salts were added to a solution of host **9** or **10** in $CDCl_3$/DMSO-d_6 3:1, v/v) and the changes in chemical shifts of signals of the host against the guest/host ratio were plotted. It was found that **10a** forms exclusively 1:1 complexes with alkali-metal picrates. The same holds for **10c**. ^{1}H NMR experiments with compounds **9a-c** did not give information about the stoichiometry because the shifts were too small to be detected.

The association constants (K_a) and free energies of complexation ($-\Delta G^0$) between hosts **9a**, **9b**, **10a**, **10c** and Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $H_3NH_3^+$, t-$BuNH_3^+$ picrates in $CHCl_3$ saturated with water were determined by means of the picrate-extraction technique described by *Cram* et al.[5]. For **9c**, $-\Delta G^0$ values could not be determined due to the poor solubility of this compound in $CHCl_3$. In the calculation of the K_a and $-\Delta G^0$ values (Table I), a 1:1 stoichiometry of the complexes was assumed. In Fig. 3, the $-\Delta G^0$ values are plotted against the ionic radii of the complexed alkali metal ions. The values of **9a** and **10a** are compared with hosts **9d** and **10d**, previously prepared by us, in which the 1,2-benzenediol unit is replaced by an oxyethylene unit[2b].

Compound **9a** shows $-\Delta G^0$ values of binding in the order of 6–7 kcal/mol. We believe that the stoichiometry of complexation of metal picrates with **9a** is 1:1, *i.e.* similar to that of compound **9d**[2b]. For a 2:1 (guest/host) stoichiometry, the two K^+ ions would have been at a distance of $\approx$4 Å, which, as judged from CPK models, is an extraordinarily close distance in a binuclear complex[6].

Fig. 3 hows that host **9a** and its relative **9d** have similar

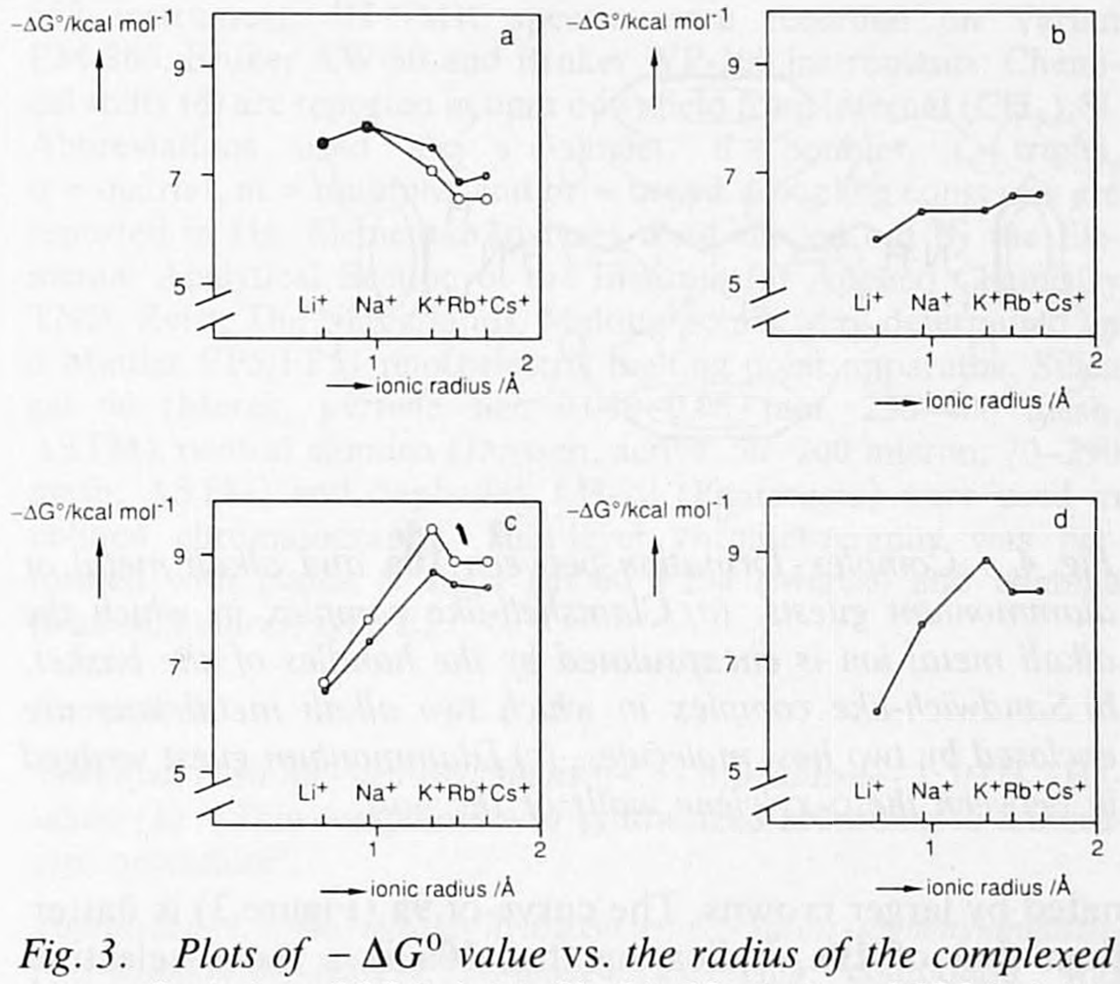


Fig. 3. Plots of $-\Delta G^0$ value vs. *the radius of the complexed cation:* **9a** (●) *and* **9d** (○) *(a);* **9b** *(b);* **10a** (●) *and* **10d** (○) *(c);* **10c** *(d).*

Table I Association constant and free energies of binding of picrate salt guests to hosts at 25 °C in $CHCl_3$ saturated with H_2O.

Host	Cation of guest	$K_a \times 10^{-5}/M^{-1}$	$-\Delta G^0$/(kcal·mol^{-1})	
9a	Li^+	3.8	7.6	(7.6)[a]
	Na^+	6.2	7.9	(7.9)[a]
	K^+	3.2	7.5	(7.1)[a]
	Rb^+	1.2	6.9	(6.6)[a]
	Cs^+	1.4	7.0	(6.6)[a]
	NH_4^+	1.6	7.1	(5.8)[a]
	$CH_3NH_3^+$	1.1	6.9	(6.3)[a]
	t-$BuNH_3^+$	<0.04	<5.0	(<5.0)[a]
9b	Li^+	0.15	5.7	
	Na^+	0.43	6.3	
	K^+	0.44	6.3	
	Rb^+	0.69	6.6	
	Cs^+	0.70	6.6	
	NH_4^+	0.43	6.3	
	$CH_3NH_3^+$	0.16	5.7	
	t-$BuNH_3^+$	<0.04	<5.0	
10a	Li^+	0.58	6.5	(6.6)[b]
	Na^+	2.9	7.4	(7.8)[b]
	K^+	24	8.7	(9.5)[b]
	Rb^+	17	8.5	(8.9)[b]
	Cs^+	15	8.4	(8.9)[b]
	NH_4^+	65	7.9	(8.8)[b]
	$CH_3NH_3^+$	0.45	6.3	(7.3)[b]
	t-$BuNH_3^+$	<0.04	<5.0	(5.5)[b]
10c	Li^+	0.30	6.1	
	Na^+	4.6	7.7	
	K^+	36	8.9	
	Rb^+	24	8.7	
	Cs^+	25	8.7	
	NH_4^+	7.2	8.0	
	$CH_3NH_3^+$	0.66	6.6	
	t-$BuNH_3^+$	<0.04	<5.0	

[a] Free energies of binding of **9d**[2b]. [b] Free energies of binding of **10d**[2b].

binding patterns. In both cases, the highest $-\Delta G^0$ value 7.9 kcal/mol) is observed for Na^+. Except for Li^+ and Na^+, **9a** is a better binder than is **9d**. This is probably due to the fact that **9a** is the more preorganized compound[4,7].

The complexing properties of **9b** are inferior to those of **9a**. It is a well-known fact that crown ethers involving *meta*-substituted atomatic rings are weaker binders for alkali metal ions than those containing *ortho*-substituted rings. Another difference is that the highest binding constants for **9b** are observed with Rb^+ and Cs^+, whereas for **9a** the highest value is observed with Na^+.

^{1}H NMR experiments reveal that **10a** and **10c** form 1:1 complexes with alkali metal picrates in $CDCl_3$/DMSO-d_6 (3:1, v/v). This is an unexpected feature since the corresponding compound **10d** forms 2:1 (guest/host) complexes[2b]. There are two ways of explaining the 1:1 complexation. Firstly, **10a** and **10c** can form a clamshell-like complex in which the alkali-metal ion is completely encapsulated by the folded handles of the basket (see Fig. 4a). In this complex, the two *ortho*-substituted aromatic rings are stacked. Alternatively, a 2:2 (guest/host) sandwich-like complex can be formed in which two host molecules enclose two alkali metal ions (see Fig. 4b). In this case, the aromatic rings of different molecules are stacked. We cannot discriminate between these two possibilities, although the former is entropically more favourable.

When comparing $-\Delta G^0$ values, we see that compound **10a** is a better binder than is compound **9a** for the ions K^+, Rb^+, Cs^+ and NH_4^+. This behaviour is to be expected in that ions with a larger radius are more favourably coordi-

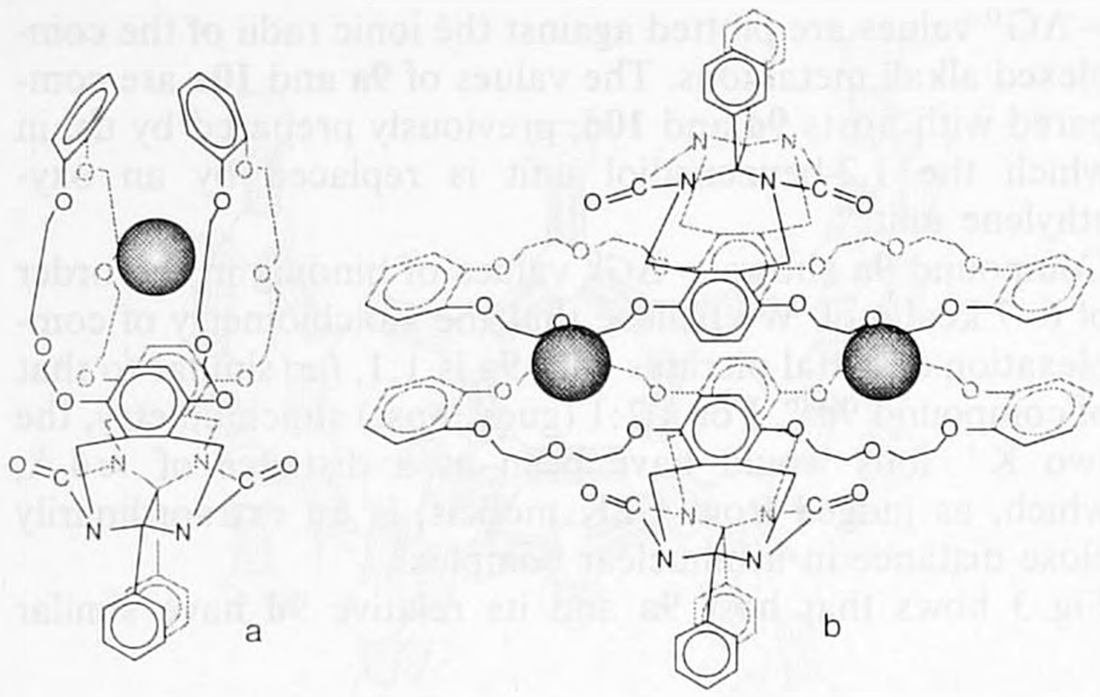


Fig. 4. Complex formation between **10a** *and alkali metal or diammonium guests. (a) Clamshell-like complex in which the alkali metal ion is encapsulated by the handles of the basket. b) Sandwich-like complex in which two alkali metal ions are enclosed by two host molecules. (c) Diammonium guest wedged in between the* o*-xylylene walls of the host.*

nated by larger crowns. The curve of **9a** (Figure 3) is flatter than that of **10a**, indicating that **10a** is a more selective binder than **9a**. The highest binding constant is found for potassium, but there is not much difference with Rb^+ and Cs^+.

The influence of size of the aromatic ring in the bridge [naphthalene (**10c**) instead of benzene (**10a**)] on the free energies of complexation is not very large (Table I, Fig. 3). With the exception of Li^+, the binding pattern of both compounds is similar. There is a difference of about 0.2–0.3 kcal/mol over the total range in favour of **10c**. The slightly better binding property of **10c** can be ascribed to improved stacking of the larger naphthalene rings as compared to the benzene rings (see Fig. 4).

The $-\Delta G^0$ values of **10a** are slightly smaller than those of **10d**. A comparison of the two complexes is not readily made, because of the different stoichiometry of complexation (1:1 for **10a**, 2:1 for **10d**).

For all compounds, the $-\Delta G^0$ values for binding with *t*-$BuNH_3^+$ are very low ($-\Delta G^0 < 5$ kcal/mol). CPK models suggest that steric repulsion by the *tert*-butyl group is probably the reason for this feature. It is almost impossible to position this group at the inside of the host. The low $-\Delta G^0$ value indicates that binding of *t*-$BuNH_3^+$ does not take place at the outside of the host.

For all potassium complexes of compounds **9a-c**, **10a** and **10c**, we determined the position of the major UV/VIS absorption band of the picrate anion in CH_2Cl_2 (Table II). *Inoue* et al.[8] have shown that from the position of this band it is possible to determine whether the picrate anion is present as a separated ion pair ($\lambda \approx 375$ nm) or as a contact ion pair ($\lambda \approx 360$ nm). For compounds **10**, we measured λ_{max} values corresponding to separated ion pairs. This is not surprising since, in these hosts, the K^+ ion is completely encapsulated. For compounds containing *ortho*-substituted aromatic rings (**9a** and **9c**), we find λ_{max} values of 366–367 nm, *i.e.* somewhere between a contact and a separated ion pair. This feature is in line with the fact that the bridges of **9a** and **9c** are short and rigid, making it more difficult to encapsulate the potassium ion. It is surprising to see that **9b** behaves differently in that its λ_{max} value is in the range of a separated ion pair. We hope to resolve this point by means of an X-ray analysis.

Table II Absorption maxima of potassium picrate extracted into CH_2Cl_2 with hosts **9** *and* **10**[a].

Host	λ_{max}/nm
9a	366–367
9b	372
9c	366
10a	372
10c	372

[a] Extraction experiments were carried out with a CH_2Cl_2 solution of the host (10 ml, 0.3 m*M*) and an aqueous solution of potassium picrate (10 ml, 3.0 m*M*).

Complexation of aliphatic and aromatic diammonium salts

Since compounds **9** and **10** have two receptor sites, we investigated the binding of protonated diamines. The stoichiometry of complexation was determined by ^1H NMR chemical shift experiments as described above. These experiments revealed that **10a** and **10c** form 1:1 complexes with aliphatic diammonium dipicrate salts $^+H_3N-(CH_2)_n-NH_3^+$, $n = 3$–9, when $n \geq 5$. With $n = 3$, a 2:1 stoichiometry is found. The salt with $n = 4$ is almost insoluble in the solvent mixture $CDCl_3$/DMSO-d_6 (6:1, v/v). Therefore, a ^1H NMR shift experiment could not be carried out with this guest. On the basis of shift values of the methylene protons of the complexed guest (*vide infra*, Table III), we tentatively propose that this guest forms 2:1 (guest/host) complexes.

Table III ^1H NMR chemical shifts of guests $^+H_3N-(CH_2)_n-NH_3^+$, n = 3–9 added in a 1:1 ratio to **10a**[a].

Guest	Guest chemical shifts/ppm				
	α	β	γ	δ	ε
$^+H_3N-(CH_2)_n-NH_3^+$					
$n = 3$	2.90	2.00			
$n = 4$	2.50	1.31			
$n = 5$	2.48	0.99	0.67		
$n = 6$	2.60	0.57	0.29		
$n = 7$	2.78	1.13	0.32	0.32	
$n = 8$	2.81[b]	1.10[b]	0.76[b]	0.20[b]	
$n = 9$	2.81[b]	1.16[b]	0.83[b]	0.83[b]	0.38[b]

[a] ^1H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 (6:1, v/v) ar 25°C. [b] Tentative assignment.

In the 1:1 complexes, the aliphatic chains are wedged in between the *o*-xylylene* units of the basic building block (Figure 4c). This is concluded from the upfield shifts of the methylene guest protons of the aliphatic diammonium salts when complexed in **10a**. For the complexes formed between **10a** and the aliphatic diammonium ions $^+H_3N-(CH_2)_n-NH_3^+$, $n = 3$–9, the ^1H NMR chemical shift values of the methylene protons in $CDCl_3$/DMSO-d_6 (6:1, v/v) are compiled in Table III.

On the ^1H NMR time scale, the rate of exchange between the complexed and the free aliphatic diammonium salts is

* *o*-Xylylene = *o*-phenylenebis(methylene).

rapid at 25°C. This can be seen from the ^{1}H NMR spectra of a 2:1 mixture of guest to host in that only one set of average signals for the guest protons is visible.

The association constants (K_a) and free energies of complexation ($-\Delta G^0$) of the complex formation between compounds **10a** and **10c** and the diammonium dipicrate salts were determined by the picrate-extraction technique in $CHCl_3$ saturated with water at 25°C (see Experimental)[2b]. The values for binding with $^+H_3N-(CH_2)_n-NH_3^+$, n = 3–9, dipicrate salts, *m*- and *p*-xylylenediammonium dipicrate salts and *o*- and *p*-phenylenediammonium dipicrate salts were calculated, assuming 1:1 complex formation, and are presented in Table IV. These values are lower limits because the distribution constants of the uncomplexed salt between the $CHCl_3$ layer and the water layer could not be determined accurately, since the salts are only sparingly soluble in water. For the same reason, we could not measure the K_a and $-\Delta G^0$ values for complex formation between compounds **9** and the diammonium salts. The $-\Delta G^0$ values for these complexes are estimated to be smaller than 9 kcal/mol.

The binding profiles of **10a** and **10c** are very flat. There is a slight increase in K_a value on going to longer CH_2 chains. As judged from CPK models, the maximum chain length for a guest which is completely stretched out in the host is reached for octa- or nonamethylene. The results in Table IV are in line with this observation: the highest $-\Delta G^0$ values are measured for the guest with n = 8–9.

The influence of replacing the benzene group (**10a**) by a naphthalene group (**10c**) on the binding free energy of complexation is not very great. Over the total range of aliphatic diammonium salts, **10c** is only a slightly better binder than **10a**, the values for binding of aromatic diammonium salts being equal. The replacement of the 1,2-phenylene or 1,2-naphthalene group by an ethylene unit has a greater effect on the $-\Delta G^0$ value in that, in such replacement, $-\Delta G^0$ increases by $\approx$2 kcal/mol for the longer aliphatic chains (see Table IV, values in parentheses).

Table IV Association constants and free energies of binding of diammonium dipicrate salts to hosts at 25°C in $CHCl_3$ saturated with H_2O[a].

Host	Cation of guest	$K_a \times 10^{-8}$/ M^{-1} [b]	$-\Delta G^0$/ (kcal · mol^{-1})	
10a	$^+H_3N-(CH_2)_n-NH_3^+$			
	n = 3	0.037	<9.0	(<9.0)[c]
	n = 4	0.16	9.8	(9.8)[c]
	n = 5	0.043	≈9.0	(10.2)[c]
	n = 6	0.21	10.0	(11.5)[c]
	n = 7	1.0	10.9	(12.5)[c]
	n = 8	3.6	11.7	(13.7)[c]
	n = 9	3.7	11.7	(13.7)[c]
	p-xylylenediammonium	0.31	10.2	(11.2)[c]
	m-xylylenediammonium	0.38	10.3	(11.0)[c]
	p-phenylenediammonium	0.44	10.4	(10.6)[c]
	o-phenylenediammonium	2.3	11.4	(12.0)[c]
10c	$^+H_3N-(CH_2)_n-NH_3^+$			
	n = 3	0.038	<9.0	
	n = 4	0.15	9.8	
	n = 5	0.10	9.5	
	n = 6	0.60	10.6	
	n = 7	1.6	11.2	
	n = 8	3.1	11.6	
	n = 9	72	13.4	
	p-xylylenediammonium	2.0	10.1	
	m-xylylenediammonium	0.30	10.2	
	p-phenylenediammonium	0.38	10.3	
	o-phenylenediammonium	2.2	11.4	

[a] See Experimental for methods and equations, [b] The values have been calculated assuming a distribution constant K_d of 1 M^{-1}; they are considered to be lower limits (see Experimental). [c] Free energies of binding of **10d**[2b].

Experimental

General

Unless otherwise indicated, commercial materials were used as received. DMSO and DMF were dried over 4-Å sieves and methanol over 3-Å sieves prior to use. Diethyl ether and toluene were distilled from sodium ketyl while $CHCl_3$ was distilled from $CaCl_2$. FAB mass spectra were recorded on a VG ZAB 2F spectrometer (matrix: 3-nitrobenzyl alcohol and triethyl citrate). IR spectra were recorded on a Perkin–Elmer Model 283 spectrometer. UV/VIS measurements were made using a Perkin–Elmer 555 and 552 instrument. ^{1}H NMR spectra were recorded on Varian EM-360, Bruker AW-80 and Bruker WP-200 instruments. Chemical shifts (δ) are reported in ppm downfield from internal $(CH_3)_4Si$. Abbreviations used are s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Coupling constants are reported in Hz. Elemental analyses were carried out by the Elemental Analytical Section of the Institute for Applied Chemistry TNO, Zeist, The Netherlands. Melting points were determined on a Mettler FP5/FP51 photoelectric melting point apparatus. Silica gel 60 (Merck, particle size 0.040–0.063 mm, 230–400 mesh, ASTM), neutral alumina (Janssen, active, 50–200 micron, 70–290 mesh, ASTM) and Sephadex LH-20 (Pharmacia) were used in column chromatography. Thin-layer chromatography was performed with plates of silica gel 60 F254 (Merck) and alumina (Merck, neutral, type E).

Compounds

*Tetrahydro-3a,6a-diphenylimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione* (**1**). This compound was synthesized according to a literature procedure[3].

*Tetrahydro-1,3,4,6-tetrakis(hydroxymethyl)-3a,6a-diphenylimidazo-[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione* (**2**). This compound was synthesized following a procedure developed in our laboratory[1m].

Compound **3**. This compound was synthesized according to a procedure developed in our laboratory[1m].

Compound **4**. This compound was synthesized according to a procedure developed in our laboratory[2b].

1-Chloro-2-tosylethane (**5**). A mixture of 2.58 g (0.032 mol) of 2-chloroethanol, 7 ml of 2,6-lutidine* and 6.88 g (0.035 mol) of tosyl** chloride was stirred at room temperature for 16 h under a nitrogen atmosphere. Ice was added and the mixture was extracted three times ith diethyl ether. The combined ether layers were washed at 0°C with 2*M* hydrochloric acid, water, a saturated sodium hydrogen carbonate solution and water. They were then dried ($MgSO_4$), filtered over a glass filter with Al_2O_3 (neutral) and evaporated in vacuum. Yield 6.72 g (88%) of **5** as a colourless oil. IR (KBr): 2940, 1595, 1445, 1350, 1180, 1175, 1010 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.61 and 7.16 (2 × d, 4H, ArH, *J* 10 Hz), 4.14 (t, 2H, CH_2OTs), 3.55 (t, 2H, CH_2Cl), 2.38 (s, 3H, CH_3Ar).

1-(2-Chloroethoxy)-2-tosylethane (**6**). This compound was synthesized from 30.1 g (0.24 mol) of 2-(2-chloroethoxy)ethanol, 50.32 g (0.264 mol) of tosyl chloride and 50 ml of 2,6-lutidine as described for **5**. Yield 55.92 g (91%) of **6** as a colourless oil. Since this compound decomposes when it is stored for any length of time, it was used directly in the synthesis of **8**. IR (KBr): 2940, 1590, 1445, 1350, 1180, 1170, 1010, 915 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.61 and 7.16 (2 × d, 4H, ArH, *J* 10 Hz), 4.10 (m, 2H, CH_2OTs), 3.70–3.45 (m, 6H, $CH_2CH_2OCH_2$), 2.43 (s, 3H, CH_3Ar).

Compound **7**. A mixture of 2.81 g (5 mmol) of **4**, 7.04 g (30 mmol) of **5** and 10 g (72.4 mmol) of potassium carbonate in 55 ml of DMSO was stirred at room temperature for 16 h under a nitrogen atmosphere. The reaction mixture was then added dropwise with vigorous stirring to a mixture of 200 ml of doubly distilled water

* 2,6-Dimethylpyridine.
** 4-Toluenesulfonyl.

and 25 ml of diethyl ether. The precipitate was filtered, washed with water (3 times) and diethyl ether (5 times) and dried in vacuum. Yield 2.70 g (70%) of **7** as a white solid; m.p. >220°C (decomp.). IR (KBr): 3055, 3020, 2920, 1720, 1590, 1450, 1350, 1300, 1250 cm^{-1}. ^1H NMR ($CDCl_3$): 7.05 (s, 10H, Ar), 6.45 (s, 4H, ArH), 5.55 (d, 4H, NC*H*HAr, *J* 16 Hz), 4.20–3.55 (m, 20H, OCH_2CH_2Cl, NCH*H*Ar). FAB MS (triethyl citrate): *m/z* 811 $(M+H)^+$.

Compound **8**. Under a nitrogen atmosphere, 2.81 g (5 mmol) of **4** was dissolved in 60 ml of DMSO containing 11.2 g of powdered KOH. After stirring the solution at room temperature for 1 h, 8.57 g (30 mmol) of compound **6** was added. Stirring was continued at room temperature for 10 h. The mixture was then added dropwise, with vigorous stirring, to a mixture of 400 ml of water and 50 ml of diethyl ether. The pH of the solution was maintained between 5 and 7 by adding conc. HCl. The precipitate was filtered, washed with water and diethyl ether (10 times) and dried in vacuum. Yield 3.6 g (74%) of **8** as a white solid; m.p. >210°C (decomp.). IR (KBr): 3055, 3015, 2910, 1720, 1590, 1450, 1350, 1295, 1245, 1130–1070, 735 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.95 (s, 10H, ArH), 6.55 (s, 4H, ArH), 5.45 (d, 4H, NC*H*HAr, *J* 16 Hz), 4.10–3.60 (m, 36H, NCH*H*Ar, $OCH_2CH_2OCH_2CH_2Cl$). FAB MS (triethyl citrate): *m/z* 987 $(M+H)^+$.

Compound **9a**. A mixture of 0.50 g (0.62 mmol) of **5**, 0.17 g (1.54 mmol) of 1,2-benzenediol and 2 g (14.47 mmol) of potassium carbonate in 75 ml of DMSO was heated at 70°C for three days under a nitrogen atmosphere. The reaction mixture was then added dropwise to a double volume of water. The resulting fine precipitate was filtered over infusorial earth, washed with water and diethyl ether, dissolved in chloroform, washed (5 times) with water and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography, first using a short alumina column (eluent $CHCl_3/CH_3OH$, 10:1 v/v) and finally a Sephadex LH-20 column (eluent $CHCl_3$). The product fractions were collected and the solvent was evaporated under reduced pressure to yield 0.16 g (29%) **9a** as a white solid. IR (KBr): 2910, 1710, 1590, 1460, 1250, 1050, 920, 870 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.00–6.80 (m, 18H, ArH), 6.70 (s, 4H, ArH), 5.45 and 3.55 (2×d, 8H, NCH_2Ar, *J* 16 Hz), 4.60–3.95 (m, 16H, OCH_2CH_2O). Anal. calcd. for $C_{52}H_{46}N_4O_{10}$: C 70.42, H 5.23, N 6.32, O 18.04; found: C 69.93, H 5.48, N 6.37, O 18.21%. FAB MS (triethyl citrate): *m/z* 887 $(M+H)^+$.

Compound **9b**. This compound was synthesized from 0.50 g (0.62 mmol) of **5**, 0.17 g (1.54 mmol) of 1,3-benzenediol, 2 g (14.47 mmol) of potassium carbonate and a tiny amount of potassium iodide in 75 ml of DMSO as described for **9a**. The product was purified by chromatography over an alumina column (eluent, $CHCl_3/CH_3OH$, 10:1 v/v). Traces of DMSO were removed by adding a concentrated solution of the product in chloroform to diethyl ether with vigorous stirring. The residue was filtered and dried under high vaccum to yield 0.11 g (20%) of **9b** as a white solid. IR (KBr): 2910, 1710, 1595, 1450, 1250, 1175, 1150, 1060, 875, 760 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.20–6.40 (m, 22H, ArH), 5.75 and 3.75 (2×d, 8H, NCH_2Ar, *J* 16 Hz), 4.60–4.10 (m, 16H, OCH_2CH_2O). Anal. calcd. for $C_{52}H_{46}N_4O_{10}$: C 70.42, H 5.23, N 6.32, O 18.04; found: C 69.92, H 5.03, N 6.25, O 18.80%. FAB MS (triethyl citrate): *m/z* 887 $(M+H)^+$.

Compound **9c**. This compound was synthesized from 0.50 g (0.62 mmol) of **5**, 0.25 g (1.56 mmol) of 2,3-naphthalenediol and 2.0 g (14.47 mmol) of potassium carbonate in 100 ml of DMSO as described for **9a**. The product was purified by chromatography over Sephadex LH-20 (eluent, $CHCl_3$) to yield 0.11 g (16%) of **9c** as a light brown solid. IR (KBr): 3050, 2920, 2880, 1710, 1590, 1500, 1450, 1070 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.0–6.7 (m, 26H, ArH), 5.65 (d, 4H, NC*H*HAr, *J* 16 Hz), 4.8–3.5 (m, 20H, NCH*H*Ar, OCH_2CH_2O). FAB MS (3-nitrobenzyl alcohol): *m/z* 987 $(M+H)^+$.

Compound **10a**. This compound was synthesized from 2.46 g (2.49 mmol) of **8**, 0.65 g (5.9 mmol) of 1,2-benzenediol (recrystalized from toluene prior to use) and 4 g (28.9 mmol) of potassium carbonate in 300 ml of DMSO as described for **9a**. The product was purified by chromatography over Sephadex LH-20 (eluent, $CHCl_3$) to yield 2.11 g (70%) of **10a** as light brown solid; m.p. >210°C (decomp.). IR (KBr) 3050, 2920, 2860, 1700, 1590, 1500, 1130, 1070 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.22 (s, 10H, ArH), 7.05 (s, 8H, ArH), 6.87 (s, 4H, ArH), 5.67 and 3.71 (2×d, 8H, NCH_2Ar, *J* 16 Hz), 4.7–3.3 (s, 32H, OCH_2CH_2O). FAB MS (3-nitrobenzyl alcohol): *m/z* 1063 $(M+H)^+$, 1037 $(M+H-C_2H_2)^+$, 971 $(M+H-C_6H_4O)^+$, 927 $(M+H-C_8H_8O_2)^+$, 901 $(M+H-C_{10}H_{12}O_3)^+$. Anal. calcd. for $C_{60}H_{62}N_4O_{14}$: C 67.78, H 5.88, N 5.27, O 21.07; found: C 66.83, H 6.09, N 5.48, O 21.61%.

Attempted synthesis of **10b**. The synthesis was carried out as described for **9a** using 1.02 g (1.03 mmol) of **8**, 0.30 g (2.72 mmol) of 1,3-benzenediol and 3 g (21.7 mmol) of potassium carbonate in 150 ml of DMSO. The product was purified by chromatography over Sephadex LH-20 (eluent $CHCl_3$). Yield 0.86 g (69%) of a light-brown solid. This solid appeared to be a 1:1 mixture of **10b** and the product in which ring closure had occurred between oxygen atoms of the same 1,4-benzenediol unit of **8** (see Figure 2). IR (KBr): 3050, 2920, 2870, 1700, 1580, 1450, 1130, 1070 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.3–6.3 (m, 22H, ArH), 5.67 and 5.19 (2×d, 4H, NC*H*HAr, *J* 16 Hz), 4.6–3.2 (m, 36H, CH*H*Ar and OCH_2CH_2O). FAB MS (3-nitrobenzyl alcohol): *m/z* 1063 $(M+H)^+$, 1037 $(M+H-C_2H_2)^+$, 971 $(M+H-C_6H_4O)^+$.

Compound **10c**. This compound was synthesized from 1.0 g (1.01 mmol) of **8**, 0.40 g (2.5 mmol) of 2,3-naphthalenediol, and 4 g (28.9 mmol) of potassium carbonate in 300 ml of DMSO as described for **9a**. The crude product was purified by chromatography over Sephadex LH-20 to yield 0.65 g (50%) of **10c** as a light brown solid; m.p. >200°C (decomp.). IR (KBr): 3050, 2920, 2870, 1710, 1450, 1130, 1070 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.0–6.6 (m, 26H, ArH), 5.67 and 3.71 (2×d, 8H, NCH_2Ar, *J* 16 Hz), 4.6–3.3 (m, 32H, OCH_2CH_2O). FAB MS (3-nitrobenzyl alcohol): *m/z* 1163 $(M+H)^+$.

Determination of association constants and free energies of complexation

K_a values were determined using the picrate-salt extraction technique from H_2O into $CHCl_3$ at 25°C reported previously by *Cram*[5]. K_a values of complexes involving **9** and **10** and all the 19 picrate guests were calculated and listed (Tables I and IV) as 1:1 complexes. Accordingly, the K_a values have the units M^{-1} (see Tables I and IV). K_a and $-\Delta G^0$ values listed in Table I were calculated from the extraction data as described by *Cram*[5]. For the determination of the K_a and $-\Delta G^0$ values recorded in Table IV, slight changes in the extraction technique of *Cram* had to be made, because of the high K_a values and the low solubility of the diammonium dipicrates in H_2O. Instead of 0.015 M guest and host solutions 0.001 M solutions were used and, instead of 10 µl, 75 µl of the organic phase were transferred to 5-ml volumetric flasks which were then brought to the mark with CH_3CN.

Equations 1–5 were used to calculate the K_a values listed in Table I.

$$K_a = \frac{[M^+ \cdot H \cdot Pic^-]^*}{[M^+ Pic^-]^* \cdot [H]^*} \quad (1)$$

$$K_a = \frac{R^*}{K_d \cdot (1 - R^*) \cdot \{[G_i] - R^* \cdot [H_i]^* \cdot (v^*/v)\}^2} \quad (2)$$

$$K_d = \frac{[M^+ Pic^-]^*}{[M^+] \cdot [Pic^-]} = \frac{A \cdot D_d}{\varepsilon \cdot I \cdot [G_i]^2} \quad (3)$$

$$R^* = ([G]^*/[H_i]^*)_{equil} = A \cdot D^*/(\varepsilon \cdot I \cdot [H_i]^*) \quad (4)$$

$$R_a^* = ([G]^*/[H_i]^*)_{equil} = \frac{\{[G_i] - A \cdot D/(\varepsilon \cdot I)\}(v/v^*)}{[H_i]^*} \quad (5)$$

Equations 4–8 were used to calculate the K_a values listed in Table IV.

$$K_a = \frac{[M^{2+} \cdot H \cdot Pic_2^{2-}]^*}{[M^{2+} Pic_2^{2-}]^* \cdot [H]^*} \quad (6)$$

$$K_a = \frac{2 \cdot R^*}{K_d \cdot (1 - R^*) \cdot (2 \cdot [G_i] - 2 \cdot [H_i]^* \cdot R^* \cdot v^*/v)^3} \quad (7)$$

$$K_d = \frac{[M^{2+}Pic_2^{2-}]^*}{[M^{2+}]\cdot[Pic^-]^2} = \frac{AD_d}{4\cdot\varepsilon\cdot I\cdot[G_i]^3} \quad (8)$$

The starred letters refer to the $CHCl_3$ layer and the non-starred to the H_2O layer. The subscripts i refer to initial concentrations and, when absent, the concentrations are those at equilibrium; M^+ denotes the alkali metal or ammonium cation, M^{2+} the diammonium cation, Pic^- the picrate ion, G the guest, H the host, v the volume; R^* is the ratio $[G]^*/[H_i]^*$ at equilibrium obtained from measurements made on the $CHCl_3$ layer and defined in Eqn. 4; R_a^* equals the ratio $[G]^*/[H_i]^*$ in the $CHCl_3$ layer calculated from measurements made on the aqueous layer at equilibrium and defined in Eqn. 5. A is the observed absorbance of the picrate salt in CH_3CN and ε the extinction coefficient of the picrate salt at 380 nm in CH_3CN. D_d is the factor by which the aliquots taken from the $CHCl_3$ layer are diluted in CH_3CN for the K_d determination; D^* is the factor by which the aliquots taken from the $CHCl_3$ layer are diluted in the R^* determination. D is the factor by which aliquots taken from the aqueous layer are diluted in CH_3CN for the R_a^* determination. The path length for the UV cell is denoted by I. Each of the values of K_a, recorded in Tables I and IV, is the average of values obtained from measurements made on the H_2O and $CHCl_3$ layers. The values based on each layer were in good agreement with each other. The K_d (M^{-1}) and ε values used in Table I were taken from *Cram*[9].

The ε values of the diammonium dipicrate salts are (compound, ε): $^+H_3N-(CH_2)_n-NH_3^+$ $n = 3$–9, 32900 $M^{-1}\cdot cm^{-1}$; 1,2- and 1,4-phenylenediammonium dipicrate, 33000 $M^{-1}\cdot cm^{-1}$; *m*- and *p*-xylylenediammonium dipicrate, 32600 $M^{-1}\cdot cm^{-1}$. The K_d values (M^{-2}) used in Table IV were determined in the same way as described by *Cram*[9] and calculated using Eqn. 8. They ould only be approximately estimated because of he low solubility of the diammonium dipicrates in H_2O. The K_d of 1 M^{-2}, which is used in Table IV for all diammonium dipicrate salts, is an upper value. The real values may be lower.

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