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Ion-Pair Complexation with a Cavitand Receptor

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Dedicated to Professor Albert Eschenmoser at the occasion of his 85th birthday

Abstract: The capability of resorcinarenes to bind anions within the alkyl feet at the lower rim has been exploited as the starting point for developing a new cavitand able to engulf contact ion pairs of primary ammonium salts in chlorinated solvents with association constants (K_{ass}) in the range of 10^3–$10^4\,\text{M}^{-1}$. Methylene bridges were introduced into the upper rim to freeze the resorcinarene in the cone conformation with the four H_{down} protons converging in the lower pocket, thereby maximizing the CH–anion interactions responsible for the anion binding. Four additional phosphate moieties were introduced into the lower rim in close proximity to the anionic site to provide hydrogen-bonding-acceptor P=O groups and promote cation complexation at the bottom of the cavitand. The binding ability of the synthesized ligands was analyzed by ^{1}H NMR spectroscopy and, when possible, by isothermal titration calorimetry (ITC); the data were in agreement when complementary techniques were used.

Keywords: cavitands · CH–anion interactions · host–guest systems · hydrogen bonds · ion pairs

Introduction

The development of synthetic receptors able to mimic noncovalent interactions in nature and to bind charged species efficiently and selectively is a topic of great interest in supramolecular chemistry. Although in recent years considerable effort has been devoted to the realization of specific cation[1] or anion[2] receptors, more recently attention has been focused on the design of heterotopic ion-pair receptors[3] that feature simultaneous complexation of both cationic and anionic species. These systems are particularly intriguing because of their potential applications in biological processes, environmental protection, and industry, for example, in salt extraction, solubilization, or as membrane transfer agents.[4]

So far, research into ion-pair receptors has mainly been focused on calixpyrroles,[5] calixarenes,[6] and crown ethers coupled with azamacrocycles,[7] which feature NH– and CH–anion interactions for anions and cation–dipole and cation–π interactions for the positively charged species.

Herein we introduce a new cavitand receptor capable of selective ion-pair complexation by a synergistic combination of CH–anion and hydrogen-bonding interactions. Enhancement of the CH–anion interactions by rigidification of the upper rim of the resorcinarene scaffold followed by functionalization of the lower rim with hydrogen-bond-acceptor units has led to the formation of an efficient ion-pair receptor for primary ammonium halides.

Results and Discussion

Our starting point was the observation of several crystal structures of resorcinarene[8] and cavitand[9] complexes formed with charged species in which the anion is included within the alkyl feet pocket at the lower rim due to multiple CH–anion interactions with the H_{down} aromatic hydrogen atoms[10,11] and the $ArCHCH_2$ α-methylene units of the chains.[12] To maximize these interactions, we decided to introduce four methylene bridges into the resorcinarene upper

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rim to form a molecule preorganized in the cone conformation with all H_{down} protons converging inwards without attributing any specific binding property to the resulting shallow cavity.[13] Subsequent functionalization of the lower rim was then devised to insert additional binding motifs in close proximity to the anionic site and thereby promote contemporaneous cation complexation (Figure 1).

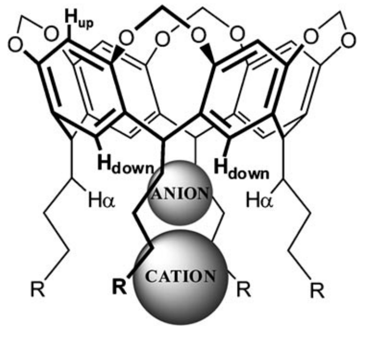
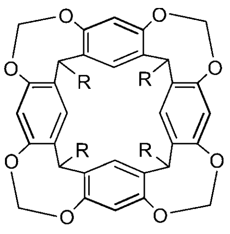


Figure 1. Schematic representation of the target receptor and of the complexation strategy.

Hydrocarbon-footed cavitands 1–3: Theoretical calculations based on PM3 semiempirical methods using SPARTAN08[14] suggested that the target receptor **1**, with four phenyl-ended feet, provided an optimal spatial arrangement for the complexation of tetra-*n*-butylammonium chloride (TBAC) at the bottom of the cavitand bowl. The phenyl groups should bind the cation by additional cation–π interactions,[15] thereby leading to ion-pair complexation.

Receptor **1** was prepared as shown in Scheme 1. First, resorcinarene **7** was obtained by acid-catalyzed condensation between resorcinol and 5-phenylpentanal. Subsequently the upper rim was functionalized with methylene bridges by reaction with bromochloromethane in the presence of K_2CO_3.

Model receptors **2** and **3**, which feature four hexyl or phenylethyl feet, respectively, at the lower rim, were also prepared by known literature procedures.[16] In both of these cases, the binding affinity for TBAC was expected to be lower than in the case of the target receptor **1** because either the stabilizing cation–π interactions were removed (cavitand **2**) or the volume available for the guest was reduced (cavitand **3**).[17]



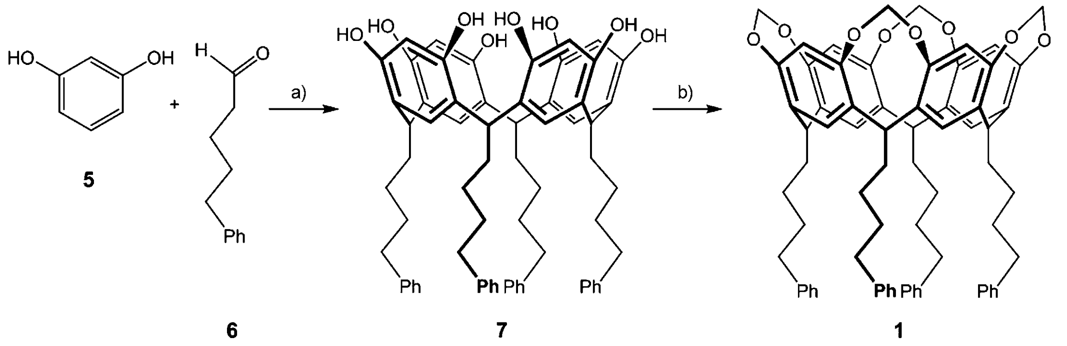
R = **1**: C_4H_8Ph
2: C_6H_{13}
3: C_2H_4Ph

The binding properties of cavitand **1** were examined in $[D_6]$acetone by ^1H NMR titration using TBAC as the guest. The largest complexation-induced change in the chemical shifts of the receptor protons is the downfield movement by +0.78 ppm of the aromatic H_{down} protons (Figure 2), which is indicative of their interaction with a bound chloride anion.[10a] Consistent with this hypothesis is the smaller downfield shift observed for the nearby $ArCHCH_2$ protons of the receptor alkyl chains ($\Delta\delta = +0.45$ ppm). No shifts were observed for the protons of the host phenyl groups or for signals related to the quaternary ammonium guest. Changes were not even observed for the receptor H_{up} or OCH_2O protons and thus cation complexation is excluded at both the lower and upper rims.

Once the 1:1 stoichiometry for the anion complexation had been verified by the continuous variation method (Job plot analysis), the association constant (K_{ass}) was evaluated by monitoring the downfield shift of the H_{down} signal of the receptor (see the Supporting Information for details of the fitting equations used). The low value ($(25 \pm 2)\,\text{M}^{-1}$) found is a result of the energy required to separate the anionic and cationic moieties of the guest.

Control experiments repeated under the same conditions with cavitands **2** and **3** revealed that 1) removal of the phenyl units reduces the association constant (K_{ass}(**2**·TBAC) $= (9 \pm 2)\,\text{M}^{-1}$) and 2) reduction of the alkyl spacer length between the cavitand and the terminal phenyl rings totally suppresses complexation (no TBAC binding was observed with **3**).

The same titrations were conducted with cavitand **1** in $CDCl_3$ and in $[D_6]$DMSO to evaluate the effect of solvent on TBAC complexation. Both solvents completely suppressed anion binding (see Figures S5 and S6 in the Supporting Information), which indicates that both tightly associat-



Scheme 1. Synthesis of target receptor **1**. Reagents and conditions: a) EtOH/HCl, 24 h, RT; 72 h, 80 °C, 71 %; b) $BrCH_2Cl$, dry DMF, overnight, 80 °C, 75 %.

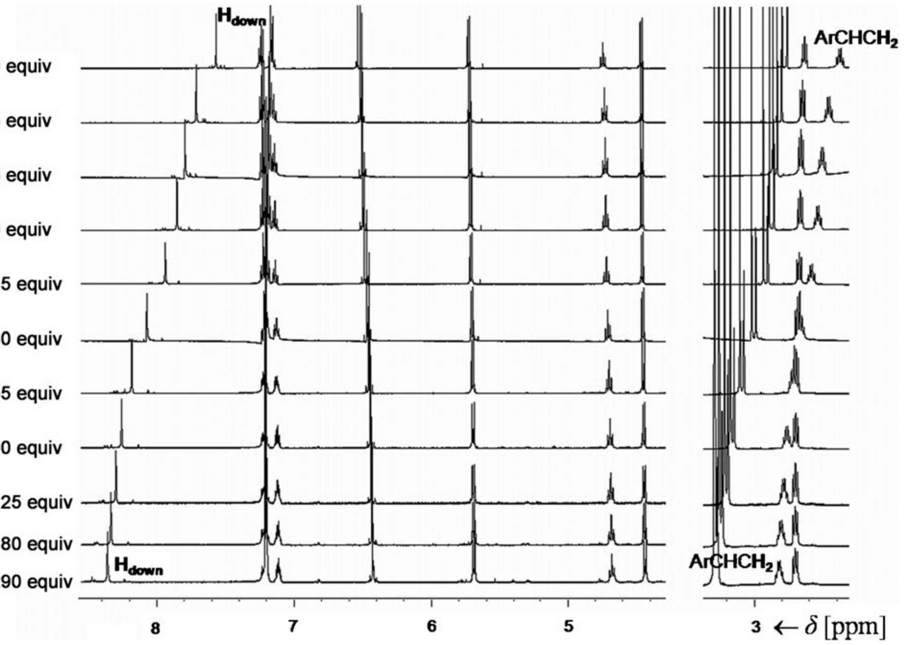


Figure 2. Partial ^{1}H NMR spectra ($T = 25\,°C$) in [D$_6$]acetone recorded during the titration of receptor **1** with TBAC. [**1**] = 2.0 mM.

ed[18] (chloroform) and solvated ([D$_6$]DMSO)[19] ion pairs are unsuitable for cavitand **1**.

Phosphate-footed cavitand 4: The next step was the replacement of the phenyl groups in **1** with four phosphotriester residues, which are well known for their ability to bind positively charged species, such as ammonium cations, through cation–dipole and hydrogen-bonding interactions.[9,20]

The phosphate esters were installed according to the synthetic sequence shown in Scheme 2. First, the hydroxy-footed resorcinarene **8**[16b] was treated with bromochloromethane in the presence of K_2CO_3 to afford methylene-bridged cavitand **9**. This cavitand was then converted into **4** by treatment with trimethyl phosphite and tetrabromomethane.

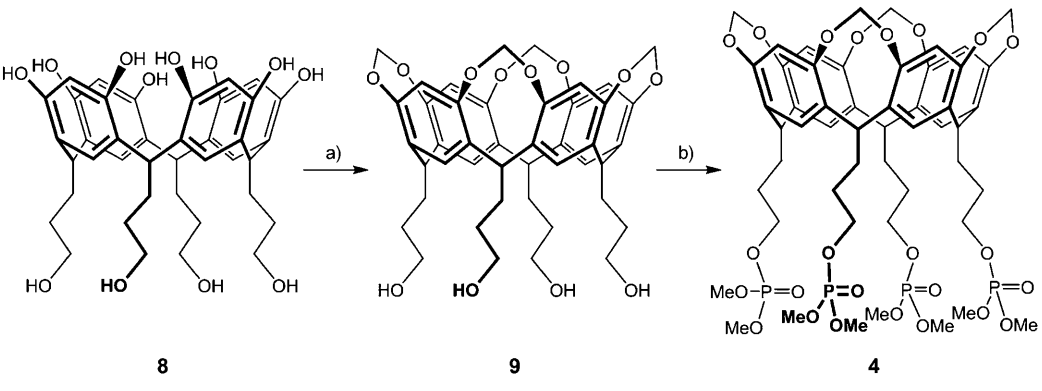
To test the influence of pure cation–dipole interactions in the absence of any hydrogen bonding, cavitand **4** was exposed to three different tetra-*n*-butylammonium salts, namely, the chloride (TBAC), bromide (TBAB), and iodide (TBAI). The changes in the chemical shifts of the diagnostic H_{down} and ArCHCH_2 protons and the K_{ass} values obtained from ^{1}H NMR titrations in [D$_6$]acetone are reported in Table 1. In each case, a 1:1 stoichiometry for the complexation was determined by the continuous variation method.

No significant counterion effect was revealed by comparing the K_{ass} values. Even more compelling is the limited improvement in K_{ass} on moving from cavitand **1** to **4**. A supplementary ^{31}P NMR titration in [D$_6$]acetone was carried out (see Figure S8 in the Supporting Information) to assess the effective role of the phosphate ester units. The recorded change in the ^{31}P NMR chemical shift upon addition of 12 equiv of TBAC to **4** ($c = 3.7$ mM) was negligible ($\Delta\delta = -0.005$ ppm). Thus, the expected cation–dipole interactions between the phosphotriesters and the tetrabutylammonium are negligible and the role of

Table 1. Observed changes in chemical shifts[a] and calculated K_{ass} values in the titrations of **4** with TBA halides.

Guest	$\Delta\delta(H_{down})$ [ppm]	$\Delta\delta$(ArCHCH$_2$) [ppm]	K_{ass} [M^{-1}]
TBAC	+0.88	+0.51	150 ± 30
TBAB	+0.67	+0.48	140 ± 10
TBAI	+0.41	+0.42	73 ± 3

[a] Observed at [**4**] = 3.7 mM and [TBAC] = 575.6 mM, [TBAB] = 643.5 mM, and [TBAI] = 384.1 mM. $\Delta\delta = \delta_{saturation} - \delta_{free}$.



8 **9** **4**

Scheme 2. Synthesis of target receptor **4**. Reagents and conditions: a) BrCH$_2$Cl, dry DMF, overnight, 80 °C, 63 %; b) CBr$_4$, P(OMe)$_3$, 2.5 h, RT; H$_2$O/CH$_2$Cl$_2$, 40 min, RT, 36 %.

cavitand **4** is limited to that of a simple anion receptor. Also in this case, the use of $CDCl_3$ as solvent led to the complete suppression of TBAC complexation, as in the case of **1**.

Because pure cation–dipole interactions did not suffice to bind quaternary ammonium cations, additional hydrogen-bonding interactions were introduced into the system by switching to primary ammonium countercations. *n*-Octylammonium salts were selected because of their solubility in chlorinated organic solvents in which hydrogen bonding is enhanced. In this way, the four P=O moieties of cavitand **4** also acted as hydrogen-bond acceptors.[21] The data for the complexation of **4** with the octylammonium halide (Cl^-, Br^-, and I^-) salt series in $CDCl_3$ at 25 °C are summarized in Table 2.

Table 2. Observed changes in chemical shifts[a] and K_{ass} values in the titrations of **4** with *n*-octylammonium halides.

Guest	$\Delta\delta(H_{down})$ [ppm]	$\Delta\delta(ArCHCH_2)$ [ppm]	$\Delta\delta(P(O))$ [ppm]	K_{ass} [M^{-1}]
$C_8H_{17}NH_3Cl^-$	+0.23	+0.19	+0.20	$(1.5\pm0.2)\times10^3$
$C_8H_{17}NH_3Br^-$	+0.55	+0.49	+0.57	$(2.1\pm0.4)\times10^4$
$C_8H_{17}NH_3I^-$	+0.56	+0.79	+0.96	n.d.[b]

[a] Observed at [**4**]=5.2 mM and $[C_8H_{17}NH_3Cl^-]=414.4$ mM, $[C_8H_{17}NH_3Br^-]=403.1$ mM, and $[C_8H_{17}NH_3I^-]=130.5$ mM. $\Delta\delta=\delta_{saturation}-\delta_{free}$. [b] Data not suitable for the determination of K_{ass}.

The variation in the ^1H NMR chemical shifts upon titration of cavitand **4** with octylammonium bromide are illustrated in Figure 3. In these titration experiments we monitored not only the usual downfield shift of the cavitand H_{down} protons, diagnostic of anion binding, but also the downfield shift of the guest NH resonances, which are indicative of cation hydrogen bonding with the P=O groups (Figure 3).

The presence of NH···O=P hydrogen bonding was confirmed by the corresponding ^{31}P NMR titration in which an upfield shift of the phosphate signal is observed for all three guests (see Figure S17 in the Supporting Information and Table 2).[22]

With octylammonium bromide as the guest, a K_{ass} value one order of magnitude higher than that of the corresponding chloride was determined (Table 2). With the iodide salt, larger variations in the chemical shifts of all diagnostic signals were recorded. However, the corresponding K_{ass} value could not be determined exactly because of a too high standard deviation in the curve fitting, which is a result of the incomplete solubility of octylammonium iodide in $CDCl_3$ at room temperature at the concentrations required for ^1H NMR studies.

The same titrations were repeated with cavitands **1** and **2** in $CDCl_3$ as control experiments. In both cases the cavitand signals were unaffected by the presence of octylammonium chloride (see Figures S10 and S11 of the Supporting Information).

The binding of octylammonium salts by **4** was also monitored by isothermal titration calorimetry (ITC) to overcome the solubility problems[23] as well as to analyze the enthalpic and entropic contributions to complexation (Table 3).

Table 3. Thermodynamic parameters and K_{ass} values for the ITC titration of **4** with octylammonium halides in chloroform at 25 °C.

Guest	ΔH [kJ mol^{-1}]	$T\Delta S$ [kJ mol^{-1}]	ΔG [kJ mol^{-1}]	K_{ass} [M^{-1}]
$C_8H_{17}NH_3Cl^-$	n.d.[a]	n.d.[a]	n.d.[a]	$(1.6\pm0.4)\cdot10^{3[b]}$
$C_8H_{17}NH_3Br^-$	-7.1 ± 0.3	17.1 ± 0.4	-24.2 ± 0.2	$(1.8\pm0.2)\cdot10^4$
$C_8H_{17}NH_3I^-$	-18.3 ± 0.3	8.3 ± 0.2	-26.6 ± 0.8	$(4.7\pm0.4)\cdot10^4$

[a] Data not suitable for thermodynamic evaluation. [b] Qualitative average value.

In the case of octylammonium chloride, the low K_{ass} value, close to the detection limit of the technique,[24] jeopardized a quantitative evaluation. The qualitative estimate obtained ($1200 < K_{ass} < 2000$) is comparable with the value determined by ^1H NMR titration ($1300 < K_{ass} < 1700\ M^{-1}$, Table 2). In the other two cases, the data fitted well a 1:1 binding profile with association constants in the range of $10^4\ M^{-1}$ with a higher affinity for the iodide compound than for the bromide. In this latter case, in which K_{ass} was also determined precisely by ^1H NMR titration, a perfect match of the experimental results was obtained (Tables 2 and 3).

The energetic signatures revealed that the binding is both enthalpy and entropy driven. The observed trend in the en-

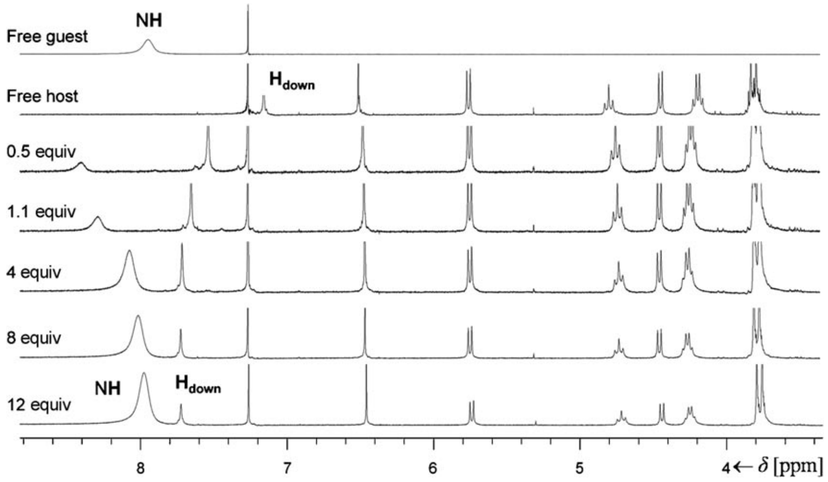


Figure 3. Partial ^1H NMR spectra (T=25 °C) in $CDCl_3$ recorded during the titration of receptor **4** with octylammonium bromide. In the titration, the host concentration was kept constant at 5.2 mM.

thalpic contribution can be rationalized by recalling that, in apolar solvents, the recognition of ion pairs increases with a reduction in the electrostatic interactions between the anion and cation.[25] The opposite entropic trend can be attributed to the different degree of solvation in the ion-pair series, which decreases with decreasing charge density of the anion ($Cl^- > Br^- > I^-$).[26] Because extensive guest desolvation is required for ion-pair binding by **4**, the release of more structured solvent molecules leads to a higher entropic desolvation gain. The two terms partially balance each other in the resulting ΔG values. The positive $T\Delta S$ contribution to the complexation free enthalpy implies that the entropy losses due to conformational freezing of the host upon binding, and to the reduction in translational freedom in the newly formed complexes, are more than compensated by the desolvation of both components.

Conclusion

CH–anion interactions coupled with hydrogen bonding to P=O groups have been exploited to realize the efficient ion-pair cavitand receptor **4** for primary ammonium halides. The key feature characterizing the host is the presence of a preorganized pocket for anion binding in close proximity to four hydrogen-bond-accepting P=O groups. The introduction of the four phosphate units changes completely the cavitand complexation properties, transforming the weak anion binder **1** in acetone into the strong ion-pair receptor **4** in chloroform.

The search for optimal cation-binding units has shown that hydrogen bonding is more effective than cation–π and cation–dipole interactions in apolar media.

The experimental K_{ass} values determined by ^1H NMR titrations have been validated by complementary ITC titrations. The finding that the complexation is also entropy driven can be attributed in part to the preorganization of the anion pocket, which does not undergo major conformation changes upon complexation. Thus, entropic losses from host–guest complexation do not compensate for the gains from the partial desolvation of the bound ion pairs.

Experimental Section

General: All commercial reagents were ACS reagent grade and used as received. CH_2Cl_2 was dried by distillation over CaH_2 according the standard procedures. Dry DMF (DMF puriss. ≥99.5 % (GC), over molecular sieves) and dry pyridine (Pyridine absolute, over molecular sieves, H_2O ≤0.005 %) were purchased from Aldrich and used as received; dry diethyl ether (Diethyl ether purum ≥99.8 %(GC), over molecular sieves) was purchased from Fluka and used as received. Silica gel column chromatography was performed by using silica gel 60 (Fluka 230–400 mesh ASTM) and alumina chromatography was performed by using MP Alumina B, Akt. I (MP Biomedicals Germany GmbH). ^1H NMR spectra were obtained with a Varian Gemini 300 (300 MHz) or Mercury 300 (300 MHz) spectrometer. All chemical shifts (δ) are reported in ppm relative to the proton resonances resulting from incomplete deuteriation of the NMR solvents. ^{31}P NMR spectra were obtained with a Varian Mercury 300 (121 MHz) spectrometer. Electrospray ionization (ESI) MS experiments were performed on a Bruker maXis ESI-Q-TOF spectrometer and EIMS were recorded on a Waters Micromass AutoSpec Ultima spectrometer. Melting points were determined by using a Büchi B-540 capillary melting point apparatus.

ITC studies were performed by using an isothermal titration Microcal VP-ITC microcalorimeter thermostatted at 25 °C. Experimental titration curves were analyzed with the MicroCal Origin 5.0 program. ΔH, ΔS, and K_{ass} values were calculated as the average of a set of independent experiments; the ΔG value is given by: $\Delta G = \Delta H - T\Delta S$.

The standard deviations for ΔH, ΔS, and K_{ass} were calculated from Equation (1) where n is the number of independent experiments, x_i is the value recorded in the i experiment, and $\bar{x}$ is the average value for x. The standard deviation for ΔG was calculated according to Equation (2).

$$\sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})}{n-1}} \tag{1}$$

$$\delta(\Delta G) = \sqrt{\{[(\partial G/\partial K_{ass})\delta(K_{ass})]^2\}} = \sqrt{[(-RT\delta(K_{ass})/K_{ass})^2]} = RT\delta(K_{ass})/K_{ass} \tag{2}$$

The enthalpies of dilution of the hosts and guests were determined in separate experiments, being negligible. All the measurements were carried out by titrating a solution of the host (in the cell) with a solution of the guest (in the syringe).

5-Phenylpentan-1-ol: $LiAlH_4$ (3.42 g, 8.98×10^{-2} mol) was suspended in dry diethyl ether (220 mL). The mixture was cooled to 0 °C and a solution of 5-phenylvaleric acid (4.00 g, 2.24×10^{-2} mol) in dry diethyl ether (22 mL) was added dropwise. The mixture was stirred at room temperature for 4 h. The system was then cooled to 0 °C and H_2O (3.4 mL) was slowly added followed by an aqueous 3 M solution of KOH (3.4 mL) and by further H_2O (11.4 mL). The mixture was stirred at 0 °C for 1 h. The crude was filtered and the organic phase dried over $MgSO_4$. The resulting solution was concentrated to dryness to afford 5-phenylpentan-1-ol as a colorless oil (3.14 g, 86 %). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.29$ (t, $^3J(H,H) = 6.0$ Hz, 2 H; H_{ortho}), 7.21–7.18 (m, 3 H; $H_{meta}+H_{para}$), 3.64 (t, $^3J(H,H) = 6.3$ Hz, 2 H; CH_2OH), 2.64 (t, $^3J(H,H) = 7.2$ Hz, 2 H; CH_2Ph), 1.72–1.62 (m, 4 H; $CH_2CH_2OH + CH_2CH_2Ph$), 1.47–1.40 ppm (m, 2 H; $CH_2CH_2CH_2OH$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 142.60$, 128.43, 128.31, 125.70, 62.92, 35.94, 32.67, 31.31, 25.44 ppm; HRMS (EI): m/z: calcd for $C_{11}H_{13}^+$: 146.1095 $[M-H_2O]^+$; found: 146.1090.

5-Phenylpentanal (6): A solution of 5-phenylpentanol (3.14 g, 1.92×10^{-2} mol) in dry CH_2Cl_2 (50 mL) was rapidly added to a suspension of PCC (6.19 g, 2.87×10^{-2} mol) in dry CH_2Cl_2 (60 mL) at room temperature. The mixture turned black becoming homogeneous and then a black solid was deposited on the walls of the flask. The reaction was stirred at room temperature for 3 h. Then the solution was decanted and the black residue was washed several times with CH_2Cl_2. The collected organic phases were partially concentrated and finally filtered through a plug of silica (eluent: CH_2Cl_2) to afford **6** as a pale-yellow oil (2.59 g, 83 %). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 9.76$ (t, $^3J(H,H) = 1.8$ Hz, 1 H; CHO), 7.30 (tt, $^3J(H,H) = 7.2$, $^1J(H,H) = 1.2$ Hz, 2 H; H_{ortho}), 7.22–7.12 (m, 3 H; $H_{meta}+H_{para}$), 2.65 (t, $^3J(H,H) = 7.0$ Hz, 2 H; CH_2Ph,), 2.46 (m, 2 H; CH_2CHO), 1.68 ppm (m, 4 H; $CH_2CH_2CHO + CH_2CH_2Ph$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 202.57$, 141.97, 128.41, 128.12, 125.87, 43.77, 35.66, 30.89, 21.71 ppm; HRMS (EI): m/z: calcd for $C_{11}H_{13}O^+$: 160.0888 $[M-H_2]^+$; found: 160.0880.

Compound 7: A solution of resorcinol (1.76 g, 1.60×10^{-2} mol) in absolute ethanol (16 mL) was cooled to 0 °C and an aqueous 37 % HCl solution (3.3 mL) was added. A solution of **6** (2.59 g, 1.60×10^{-2} mol) in absolute ethanol (15 mL) was slowly added over a 20 min period. The solution was allowed to warm at room temperature and stirred for 1 d. After 24 h, the reaction was slowly heated to 80 °C and stirred at reflux for 3 d. No precipitate formed during this period. The red solution was cooled to 0 °C and added to H_2O (150 mL). The voluminous precipitate was stirred for 20 min and finally collected by filtration to afford the desired resorcinarene **7** as an orange solid (2.88 g, 71 %). M.p. >300 °C (slow decomposition); ^{1}H NMR (300 MHz, [D$_6$]acetone, 25 °C): $\delta = 8.50$ (s, 8H; ArO*H*), 7.56 (s, 4H; ArH_{down}), 7.26–7.13 (m, 20H; $H_{ortho}+H_{meta}+H_{para}$), 6.27 (s, 4H; Ar$H_{\mathrm{up}}$); 4.34 (t, ^{3}J(H,H) = 8.1 Hz, 4H; ArC*H*), 2.59 (t, ^{3}J(H,H) = 5.7 Hz, 8H; C*H*$_2$Ph), 2.32 (m, 8H; ArCHC*H*$_2$), 1.68 (m, 8H; ArCHCH$_2$C*H*$_2$), 1.43 ppm (m, 8H; C*H*$_2$CH$_2$Ph); ^{13}C NMR (75 MHz, [D$_6$]acetone, 25 °C): $\delta = 152.77$, 143.53, 129.13, 129.03, 126.45, 125.49, 125.20, 103.80, 36.66, 34.18, 34.04, 32.22, 28.66 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{68}H_{73}O_8^+$: 1017.5300 [*M*+H]$^+$; found: 1017.5321.

Compound 1: In a dried Schlenk tube, resorcinarene **7** (2.00 g, 1.97×10^{-3} mol) was dissolved in dry DMF (40 mL). Oven-dried K_2CO_3 (2.56 g, 1.97×10^{-2} mol) was added followed by bromochloromethane (5.11 mL, 7.87×10^{-2} mol). The mixture was stirred at 80 °C overnight and then poured into 1 M HCl (150 mL). An orange solid deposited on the walls of the flask. The solution was decanted and the solid dissolved in CH_2Cl_2. The resulting organic solution was dried over $MgSO_4$ and then concentrated to dryness. The crude was finally purified by column chromatography (SiO_2; CH_2Cl_2) to afford cavitand **1** as a white solid (1.57 g, 75 %). M.p. >310 °C (slow decomposition); ^{1}H NMR (300 MHz, [D$_6$]acetone, 25 °C): $\delta = 7.58$ (s, 4H; ArH_{down}), 7.26–7.15 (m, 20H; $H_{ortho}+H_{meta}+H_{para}$), 6.54 (s, 4H; Ar$H_{\mathrm{up}}$), 5.74 (d, ^{3}J(H,H) = 7.5 Hz, 4H; CH$_{\mathrm{in}}$), 4.75 (t, ^{3}J(H,H) = 8.1 Hz, 4H; ArC*H*), 4.47 (d, ^{3}J(H,H) = 7.5 Hz, 4H; CH$_{\mathrm{out}}$), 2.63 (t, ^{3}J(H,H) = 7.5 Hz, 8H; C*H*$_2$Ph), 2.37 (m, 8H; ArCHC*H*$_2$), 1.74 (m, 8H; ArCHCH$_2$C*H*$_2$), 1.45 ppm (m, 8H; C*H*$_2$CH$_2$Ph); ^{13}C NMR (75 MHz, [D$_6$]acetone, 25 °C): $\delta = 155.91$, 143.35, 139.46, 129.16, 129.13, 126.53, 122.89, 117,48, 100.39, 37.31, 36.56, 32.30, 29.88, 28.35 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{72}H_{72}O_8Na^+$: 1087.5119 [*M*+Na]$^+$; found: 1087.5121.

Compound 9: In a dried Schlenk tube, propanol-footed resorcinarene (3.00 g, 4.17×10^{-3} mol)[8b] was dissolved in dry DMF (40 mL). Oven-dried K_2CO_3 (7.00 g, 4.17×10^{-2} mol) was added followed by bromochloromethane (10 mL, 1.67×10^{-1} mol). The mixture was stirred at 80 °C overnight. The solvent was then removed in vacuo and the crude suspended in 1 M HCl (150 mL), filtered, and purified by flash chromatography (SiO_2; CH_2Cl_2/MeOH, 9:1) to afford cavitand **9** as a white solid (2.02 g, 63 %). M.p. >300 °C (slow decomposition); ^{1}H NMR (300 MHz, [D$_6$]acetone, 25 °C): $\delta = 7.61$ (s, 4H; ArH_{down}), 6.51 (s, 4H; ArH_{up}), 5.71 (d, ^{3}J(H,H) = 7.8 Hz, 4H; CH$_{\mathrm{in}}$), 4.56 (t, ^{3}J(H,H) = 7.8 Hz, 4H; ArC*H*), 4.47 (t, ^{3}J(H,H) = 5.1 Hz, 4H; CH$_2$O*H*), 4.39 (d, ^{3}J(H,H) = 7.8 Hz, 4H; CH$_{\mathrm{out}}$), 3.51 (m, 8H; C*H*$_2$OH), 2.40 (m, 8H; ArCHC*H*$_2$), 1.46 ppm (m, 8H; ArCHCH$_2$C*H*$_2$); ^{13}C NMR (75 MHz, [D$_6$]acetone, 25 °C): $\delta = 155.91$, 139.55, 123.43, 117.26, 100.37, 62.33, 37.55, 32.33, 26.93 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{44}H_{48}O_{12}Na^+$: 791.3038 [*M*+Na]$^+$; found: 791.3060.

Compound 4: CBr_4 (0.79 g, 2.39×10^{-3} mol) was added to a suspension of cavitand **9** (0.30 g, 3.90×10^{-4} mol) in dry pyridine (6 mL) and the mixture stirred at room temp. for 10 min. The suspension was cooled to 0 °C and trimethyl phosphite (0.23 mL, 1.95×10^{-3} mol) was added. The solution was stirred at room temp. for 2.5 h and then H_2O/CH_2Cl_2 (1:1, 10 mL) was added and stirring was continued for 40 min. The solvents were removed in vacuo and the crude was purified by flash chromatography on basic alumina (CH_2Cl_2/EtOH, 96:4). The product obtained was suspended in H_2O and recovered by filtration as a pale-pink solid (0.17 g, 36 %). M.p. >290 °C (slow decomposition); ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 7.57$ (s, 4H; ArH_{down}), 6.56 (s, 4H; ArH_{up}), 5.73 (d, ^{3}J(H,H) = 7.5 Hz, 4H; CH$_{\mathrm{in}}$), 4.61 (t, ^{3}J(H,H) = 7.6 Hz, 4H; ArC*H*), 4.40 (d, ^{3}J(H,H) = 7.5 Hz, 4H; CH$_{\mathrm{out}}$), 4.07 (m, 8H; CH$_2$OP(O)), 3.66 (d, ^{3}J(H,P) = 11.1 Hz, 24H; OCH$_3$), 2.46 (m, 8H; ArCHC*H*$_2$), 1.66 ppm (m, 8H; ArCHCH$_2$C*H*$_2$); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): $\delta = 157.01$, 140.59, 124.82, 119.57, 101.68, 69.57, 56.76, 38.49, 30.98, 27.59 ppm; ^{31}P NMR (121 MHz, [D$_6$]DMSO, 25 °C): $\delta = 2.17$ ppm (s, *P*(O)); IR; HRMS (ESI): *m*/*z*: calcd for $C_{52}H_{68}O_{24}P_4Na^+$ 1223.2943 [*M*+Na]$^+$; found: 1223.2950.

***n*-Octylammonium chloride (10)**:[27] An excess of aqueous 36 % HCl (3 mL) was added to a solution of octylamine (2.00 mL, 1.21×10^{-2} mol) in Et_2O (20 mL). The resulting mixture was stirred at room temp. for 20 min. The solvent was removed under reduced pressure and the product recrystallized from Et_2O (1.98 g, quant.). White solid; m.p. 204–205 °C (lit.:[28a] 197–198 °C); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): $\delta = 8.28$ (br s, 3H; NH$_3$), 2.98 (m, 2H; C*H*$_2$NH$_3$), 1.77 (m, 2H; C*H*$_2$CH$_2$NH$_3$), 1.37–1.27 (m, 10H; (C*H*$_2$)$_5$CH$_2$CH$_2$NH$_3$), 0.87 ppm (t, ^{3}J(H,H) = 6.6 Hz, 3H; CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): $\delta = 40.06$, 31.72, 29.05, 28.97, 27.68, 26.54, 22.59, 14.06 ppm; HRMS (ESI): *m*/*z*: calcd for $C_8H_{20}N^+$: 130.1590 [*M*−Cl]$^+$; found: 130.1584; elemental analysis calcd (%) for $C_8H_{20}NCl$: C 57.99, H 12.16, N 8.45, Cl 21.40; found: C 58.28, H 12.14, N 8.38, Cl 21.25.

***n*-Octylammonium bromide (11)**:[28] An excess of aqueous 47 % HBr (3 mL) was added to a solution of octylamine (2.00 mL, 1.21×10^{-2} mol) in Et_2O (20 mL). The resulting mixture was stirred at room temp. for 1 h. The solvent was removed in vacuo and the product recrystallized from acetone at 0 °C (2.52 g, quant.). White crystals; m.p. 207–208 °C (lit.:[29] 203–206 °C); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): $\delta = 7.93$ (br s, 3H; NH$_3$), 3.04 (m, 2H; CH$_2$NH$_3$), 1.81 (m, 2H; C*H*$_2$CH$_2$NH$_3$), 1.40–1.27 (m, 10H; (C*H*$_2$)$_5$CH$_2$CH$_2$NH$_3$), 0.88 ppm (t, ^{3}J(H,H) = 6.6 Hz, 3H; CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): $\delta = 40.32$, 31.86, 29.19, 29.07, 27.65, 26.71, 22.78, 14.30 ppm; HRMS (ESI): *m*/*z*: calcd for $C_8H_{20}N^+$: 130.1590 [*M*−Br]$^+$; found: 130.1589; elemental analysis calcd (%) for $C_8H_{20}NBr$: C 45.72, H 9.59, N 6.66, Br 38.02; found: C 45.68, H 9.34, N 6.67, Br 37.82.

***n*-Octylammonium iodide (12)**:[29] An excess of aqueous 57 % HI (3 mL) was added to a solution of octylamine (2.00 mL, 1.21×10^{-2} mol) in Et_2O (20 mL). The resulting mixture was stirred at room temp. for 1 h. The solvent was then removed in vacuo and the product recrystallized from hexane (3.05 g, quant.). Pale-yellow solid; m.p. 205–206 °C; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): $\delta = 7.52$ (br s, 3H; NH$_3$), 3.14 (m, 2H; C*H*$_2$NH$_3$), 1.86 (m, 2H; C*H*$_2$CH$_2$NH$_3$), 1.42–1.27 (m, 10H; (C*H*$_2$)$_5$CH$_2$CH$_2$NH$_3$), 0.88 ppm (t, ^{3}J(H,H) = 6.6 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): $\delta = 40.67$, 31.86, 29.20, 29.06, 27.45, 26.82, 22.80, 14.31 ppm; HRMS (ESI): *m*/*z*: calcd for $C_8H_{20}N^+$: 130.1590 [*M*−I]$^+$; found: 130.1584; elemental analysis calcd (%) for $C_8H_{20}NI$: C 37.37, H 7.84, N 5.45, I 49.35; found: C 37.09, H 7.72, N 5.39, I 49.54.

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