ARTICLE

OBC
www.rsc.org/obc

Tetrakis(imidazolium) macrocyclic receptors for anion binding†

Wallace W. H. Wong, Matthew S. Vickers, Andrew R. Cowley, Rowena L. Paul and Paul D. Beer*

Department of Chemistry, Inorganic Chemistry Laboratory, University of Oxford, South Parks Road, Oxford, OX1 3QR. E-mail: paul.beer@chem.ox.ac.uk

Received 15th July 2005, Accepted 10th October 2005
First published as an Advance Article on the web 31st October 2005

New (tetrakis)imidazolium macrocyclic receptor systems of variable cavity size have been synthesised by stepwise alkylation reactions of bis(imidazolium) precursor compounds. Proton NMR titration studies reveal the macrocycles to strongly bind halide and benzoate anions, with two receptor systems displaying notable selectivity for fluoride in competitive acetonitrile–water (9 : 1) solvent media.

1. Introduction

Stimulated by the important role negatively charged species play in biological systems, medicine and the environment, interest in the synthesis of new host molecules designed to recognize and sense anions is ever increasing.[1] Positively charged ammonium, guanidinium[2] and neutral amide, urea and pyrrole groups[3] have all been incorporated into various molecular frameworks to produce receptor systems capable of binding anions of diverse sizes and geometries.

The imidazolium moiety has been recently shown to be an effective motif for complexing anions *via* favourable electrostatic interactions and hydrogen bonding.[4] Although various acyclic imidazolium receptors have been described,[5,6] synthetic routes to macrocyclic analogues are rare, especially those containing more than two imidazolium groups.[7] We report here the synthesis of novel tetrakis(imidazolium) and benzimidazolium macrocyclic receptor systems which strongly bind halide and benzoate anions, with two receptors exhibiting notable selectively for fluoride anions in highly competitive aqueous–acetonitrile solvent mixtures.

2. Results and discussion

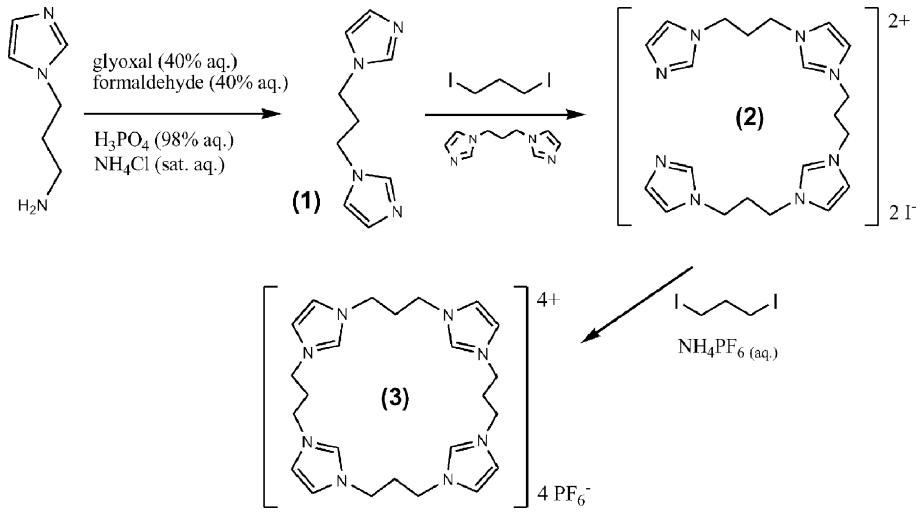
2.1 Syntheses

In an effort to examine the synergy of multiple imidazolium moieties for anion binding, we designed new tetrakis-imidazolium and benzimidazolium macrocyclic receptor systems, which may be considered as calix[4]imidazolium analogues of calix[4]pyrrole.[8] Starting with commercially available imidazole and benzimidazole derivatives, a cascade of simple alkylation reactions was employed to synthesise the macrocycles in good yields.

The synthesis of 1,3-bis(*N*-imidazolyl)propane **1** was achieved by imidazole ring formation starting from commercially available *N*-(3-aminopropyl)imidazole (Scheme 1).[9] The reaction of two equivalents of **1** with 1,3-diiodopropane gave the corresponding imidazole–imidazolium compound **2** in 60% yield. Reaction of **2** with a further equivalent of 1,3-diiodopropane followed by anion exchange with NH_4PF_6 (aq.) gave the cyclised product **3** in 80% yield (Scheme 1). This remarkably high yield for such a cyclised product suggests the iodide counteranions are playing a significant templating role in macrocycle formation. Indeed, chloride and bromide anions have been shown to exhibit a templation role in the synthesis of bis(imidazolium) macrocycles.[10]

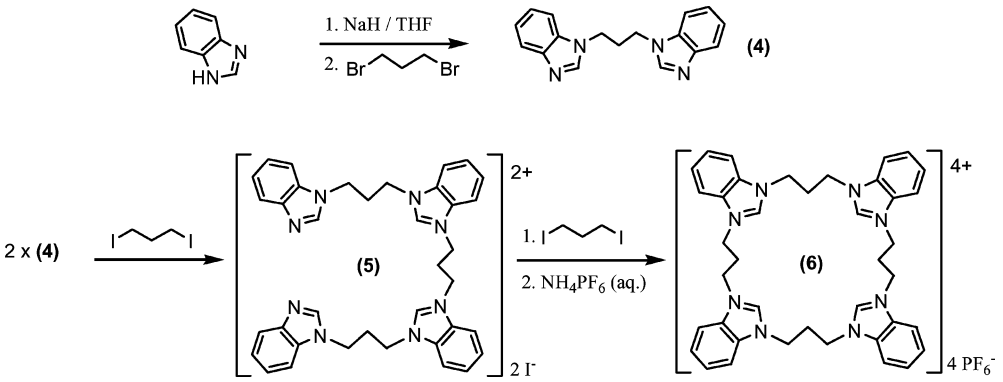
An analogous synthetic procedure was used to obtain tetrakis(benzimidazolium) receptors of three different macrocyclic sizes: **6**, **9** and **11** (Schemes 2–4). Benzimidazole precursors **4** and **7** were obtained from the alkylation of benzimidazole with 1,3-dibromopropane and 1,4-dibromobutane respectively (Schemes 2 and 3). For the synthesis of the four-fold symmetric receptor **6**, two equivalents of **4** were reacted with one equivalent of 1,3-diiodopropane to give **5** in 65% yield (Scheme 2). Precursor **5** was then reacted with a further equivalent of 1,3-diiodopropane to give macrocycle **6** in 31% yield (Scheme 2).

† Electronic supplementary information (ESI) available: Titration data, Job plots, ESMS data. See DOI: 10.1039/b510068b

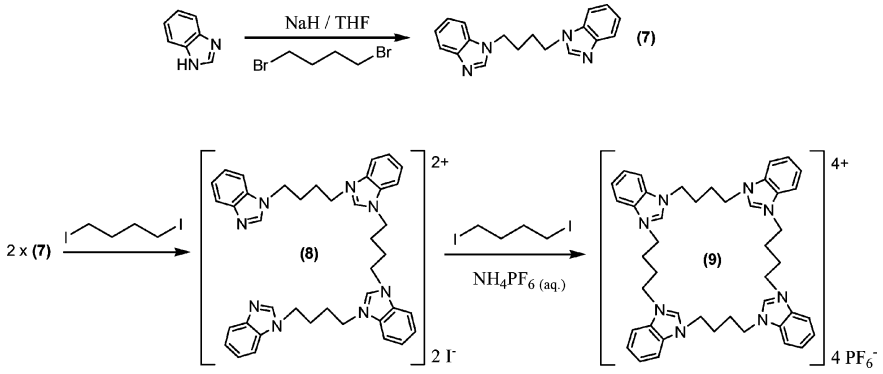


Scheme 1

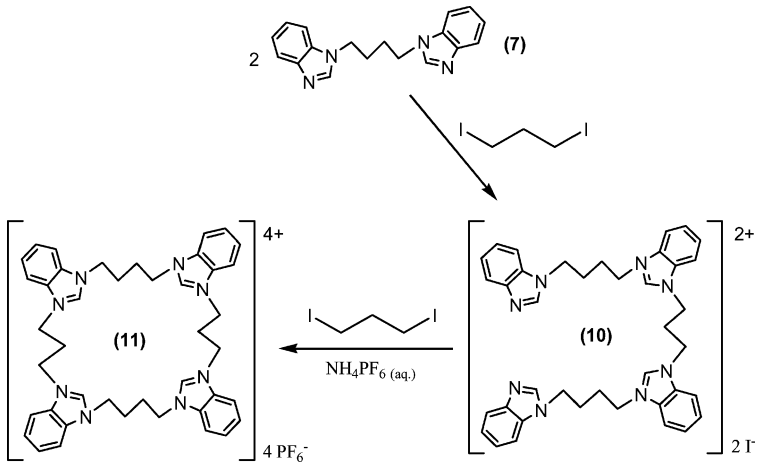
DOI:10.1039/b510068b



Scheme 2



Scheme 3



Scheme 4

Reaction of two equivalents of **7** with 1,4-diiodobutane afforded **8** in 46% yield. The butyl spaced macrocycle **9** was prepared *via* reaction of **8** with 1,4-diiodobutane in 28% yield (Scheme 3).

The reaction of **7** with 1,3-diiodopropane gave benzimidazole–benzimidazolium compound **10** and subsequent cyclisation of **10** with a further equivalent of 1,3-diiodopropane afforded receptor **11** in 30% yield after anion exchange with aqueous NH_4PF_6 (Scheme 4).

For comparison purposes a new acyclic tetrapodal imidazolium receptor was also prepared. The synthesis of the tetrapodal resorcinarene cavitand imidazolium receptor **14** involved a simple alkylation reaction of imidazole with tetra(bromomethyl)resorcinarene cavitand[11] **12** followed by reaction with excess 1-bromohexane and anion exchanged to give the pure product in 37% yield (Scheme 5).

All four new tetrakis(imidazolium) macrocycles **3**, **6**, **9**, **11** and tetrapodal cavitand imidazolium receptor **14** were characterised by ^1H, ^{13}C NMR (Fig. 1) spectroscopy, electrospray mass spectrometry and elemental analysis.†

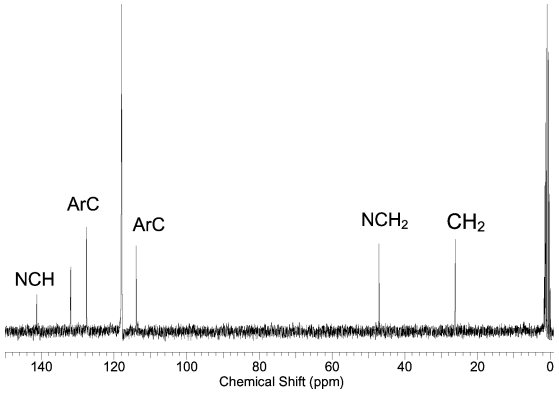
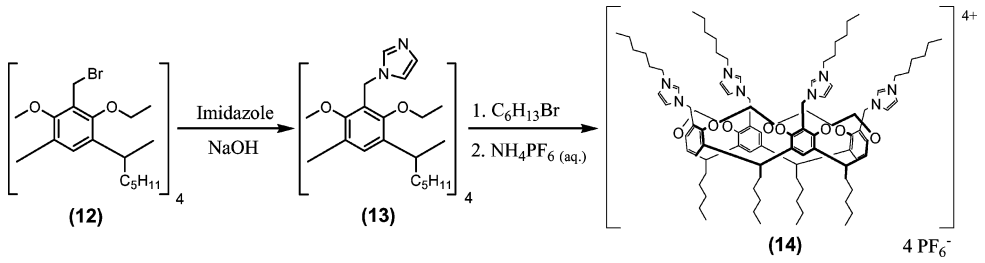


Fig. 1 ^{13}C NMR spectrum or receptor **9** in CD_3CN.



Scheme 5

It is noteworthy that the high field ^{1}H NMR spectra of **6** and **9** reveal a dominant singlet at around 9 ppm for the respective methine $(C–H)^+$ imidazolium proton superimposed upon a much less intense multiplet (Fig. 2 and 3). No evidence of higher oligomers was seen in the electrospray mass spectrum for any of the four macrocycles, only the one plus charged species corresponding to the tetrameric products plus three counter anions with a difference of one mass unit in the respective isotope envelope pattern was observed. This implies the additional multiplet resonances in this methine imidazolium proton region are due to the presence of multiple conformers in solution. Moreover, the ^{1}H NMR spectrum of **6** also displays more than one set of resonances assigned to the aromatic protons of the benzimidazolium moieties (Fig. 2). Resembling the known conformational isomers of calix[4]arenes, in principle these macrocycles may adopt cone, 1,3-alternate, 1,2-alternate and partial cone conformers in solution.[12] Variable temperature ^{1}H NMR spectroscopic experiments up to 100 °C in DMSO-d_6 solution however, resulted in no significant changes in the NMR spectra of the macrocycles.

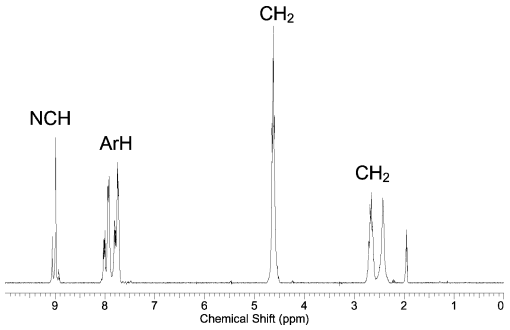


Fig. 2 ^{1}H NMR spectrum of receptor **6** in CD_3CN.

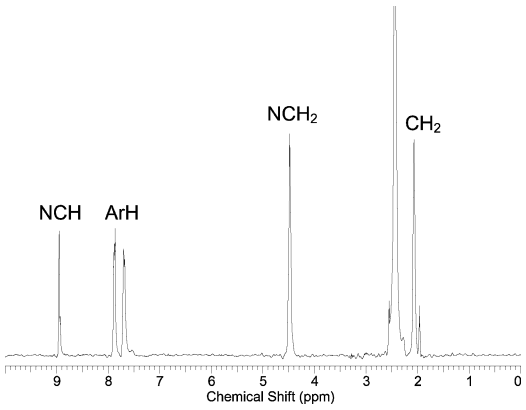


Fig. 3 ^{1}H NMR spectrum of receptor **9** in CD_3CN.

2.2 X-Ray crystal structures

Bis(benzimidazole) precursor compound **4** and receptor **11** were also characterised by single crystal X-ray crystallography. Crystals of **4** suitable for X-ray structural analysis were grown by the slow diffusion of diethyl ether into a chloroform solution of **4**. The crystal system is orthorhombic and the molecule lies on a site with no crystallographic symmetry, but closely approximates to local twofold rotational symmetry (Fig. 4).

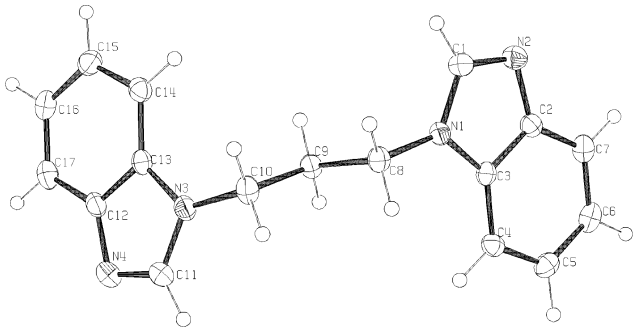


Fig. 4 Thermal ellipsoid plot of the bis(benzimidazole) precursor **4**. Thermal ellipsoids are drawn at the 40% probability level.

Crystals of **11** suitable for X-ray analysis were grown by the slow evaporation of acetonitrile from a solution of receptor **11** in an acetonitrile–water mixture. The crystal system is triclinic and the macrocyclic tetracation is located on a crystallographic centre of inversion (Fig. 5). Two PF_6^- ions (related by the inversion centre) lie partly within the macrocyclic ring where the four benzimidazolium moieties are arranged in a *cis* two up two down 1,2-alternate conformation (Fig. 6).

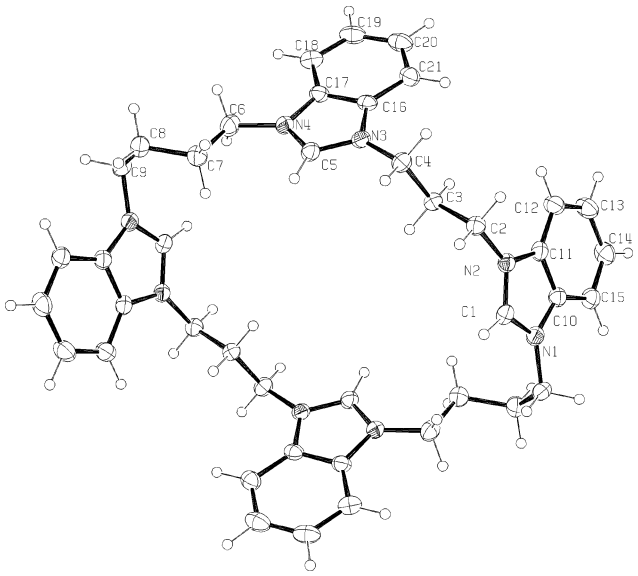


Fig. 5 Thermal ellipsoid plot of the tetrakis(benzimidazolium) receptor **11**. Thermal ellipsoids are drawn at the 50% probability level. The four PF_6^- counter anions and solvent molecules are omitted for clarity.

2.3 Anion binding studies

The complexation of halide and benzoate anions by the macrocyclic receptors **3**, **6**, **9**, **11** and cavitand **14** was investigated by ^{1}H

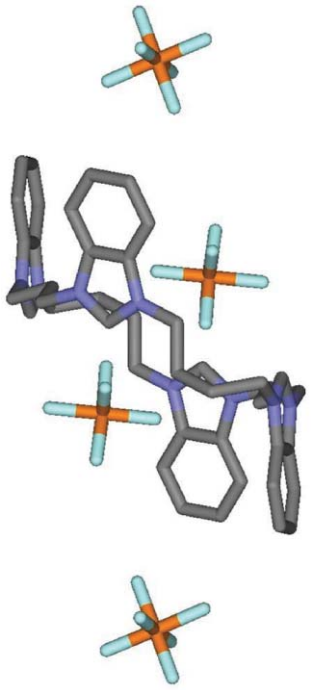


Fig. 6 Stick representation of receptor **11** in a 1,2-alternate conformation with two counter PF_6^- anions lying partially within the macrocyclic cavity.

NMR spectroscopic titration experiments. These anionic guests were chosen for their variety in size, shape and charge density in order to probe the differences in the host–guest binding properties of the receptors. Due to the solubility characteristics of the macrocyclic receptors and their receptor–anion complexes, a highly competitive solvent mixture of acetonitrile-d_3 and water (9 : 1) was used throughout.

In all cases the addition of anions caused significant downfield perturbations of the methine $(C–H)^+$ imidazolium proton resonances of each receptor. Interestingly, with receptor **6** the addition of 1 equivalent of TBA fluoride resulted in the methine proton resonances simplifying to a singlet, which implies that anion complexation results in a single conformer in solution (Fig. 7).

Table 1 Stability constants (K, M^{-1}) for tetrakis(imidazolium) macrocycles with a range of anions[a]

	Receptors				
Anion	**3**	**6**	**9**	**11**	**14**
F^-	[b]	$>10^4$	[c]	$>10^4$	180
Cl^-	[b]	1100	[c]	710	85
Br^-	[b]	1050	[c]	500	90
I^-	370	560	900	470	125
BzO^- [d]	K_1 1800 K_2 470	K_1 1070 K_2 1000	K_1 1700 K_2 940	K_1 2700 K_2 600	[e]

[a] Solvent = $CD_3CN–H_2O$ 9 : 1, temperature = 295 K and errors are ± 10%. [b] Mixed host–guest binding stoichiometry prevented the calculation of a sensible stability constant value. [c] Precipitation occurred during titration. [d] The stoichiometry of receptor–benzoate binding is 1 : 2. K_1 and K_2 are quoted in the table. [e] Minimal changes observed in the chemical shift of the imidazolium proton.

Monitoring the most intense imidazolium methine $(C–H)^+$ proton resonance produced titration curves and Job plots (refer to the electronic supplementary information†) which, after EQNMR,[13] a least squares computer fitting program, analysis of the titration binding isotherms (Fig. 8) gave stability constant values displayed in Table 1.

Receptors **6** and **11** form extremely strong and selective 1 : 1 stoichiometric complexes with fluoride, with estimated stability constant values of $K > 10^4$ M^{-1}. Attempts to repeat the titration experiments with increasing amounts of water unfortunately led to solubility problems. Stoichiometric 1 : 1 complexes were also found with chloride, bromide and iodide anions with a halide selectivity trend of $F^- >> Cl^- \approx Br^- > I^-$ for receptor **6** and $F^- >> Cl^- > Br^- \approx I^-$ for the larger macrocycle **11** (Table 1).

Presumably these stable halide complexes result from the four imidazolium moieties of **6** and **11** binding the halide anionic guest in a cooperative manner forming strong imidazolium $(C–H)^+$-X^- hydrogen bonds. The equilibrium geometry of macrocycle **6** with a bound fluoride anion was calculated using Merck Molecular Force Field (MMFF) using the SPARTAN 04 modelling program[14] and reveals the fluoride anion to be closely bound within the macrocyclic cavity to each of the benzimidazolium moieties (Fig. 9). Similar equilibrium geometries were calculated for both the larger chloride and bromide anions

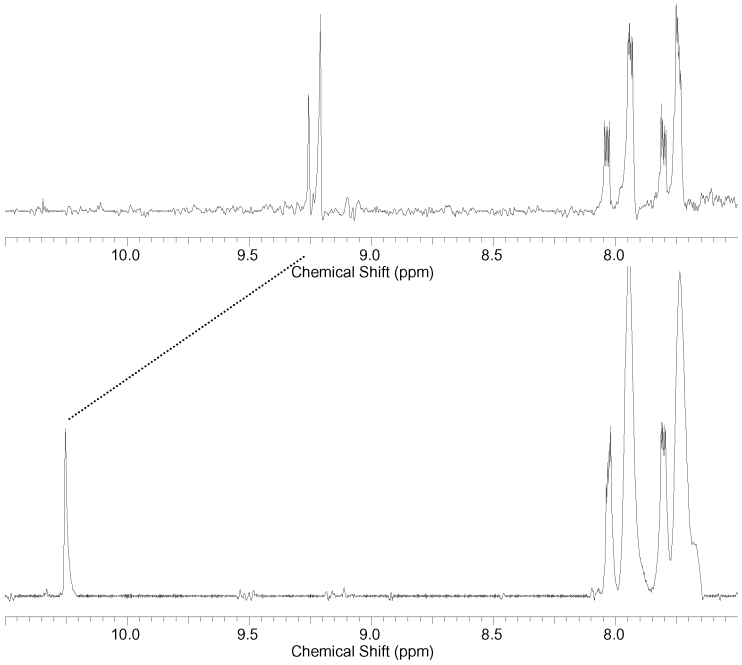


Fig. 7 The aromatic region of the ^1H NMR spectra of receptor **6** upon the addition of 1 equivalent of TBAF to a CD_3CN solution.

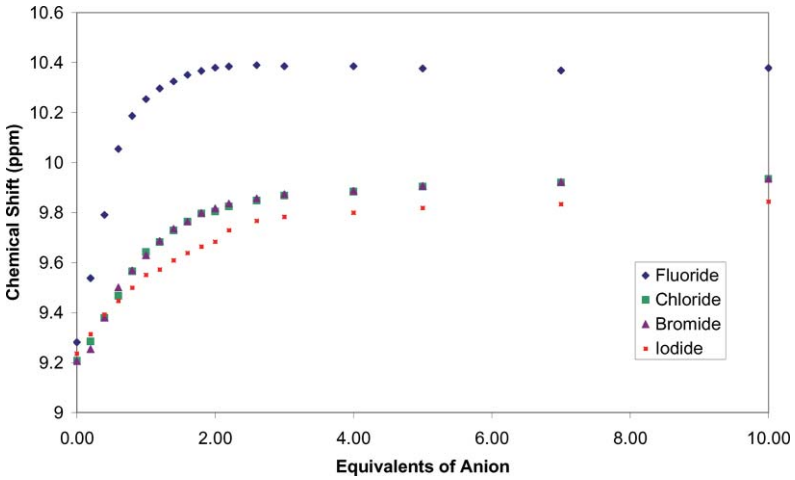


Fig. 8 ^{1}H NMR titration data for the addition of the TBA salt of various halides to a CD_3CN–H_2O (9 : 1) solution of receptor **6**.

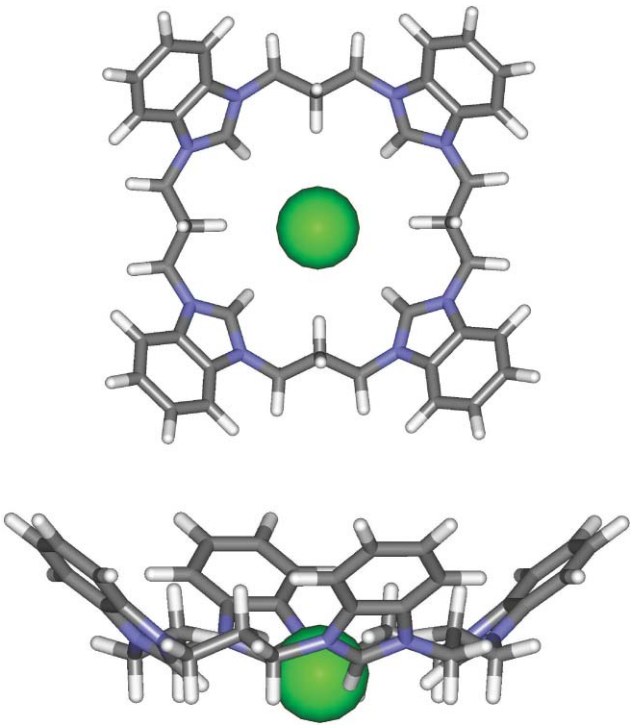


Fig. 9 Molecular mechanics model for the 1 : 1 host–guest binding between receptor **6** and fluoride calculated using SPARTAN 04.

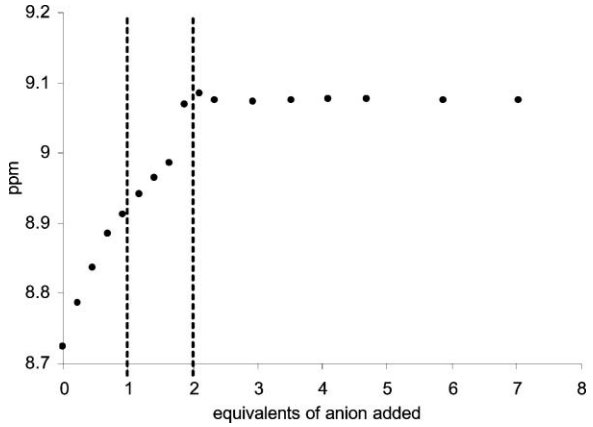


Fig. 10 Titration curve of receptor **3** and TBA Cl monitoring the methine proton in CD_3CN–H_2O 9 : 1.

however, indicating that the pronounced fluoride selectivity exhibited by **6** has little to do with receptor cavity–anion size complementarity. This suggests the more basic character of the fluoride anion dictates the observed selectivity trends with these macrocyclic receptors.

It is noteworthy that macrocycle **6** complexes chloride and bromide anions with similar stability (*K ca.* 1100 M^{-1}). A comparison of the receptor stability constant values with iodide reveals that **9** binds this halide guest anion most strongly, which implies a degree of macrocycle size complementarity.

With receptor **3**, a combination of 1 : 1 and 1 : 2 binding stoichiometries were observed with fluoride, chloride and bromide. In a typical titration experiment a steady downfield shift of the imidazolium protons was observed until *ca.* two equivalents whereupon a large perturbation occurred indicative of a change in binding stoichiometry (Fig. 10). Unfortunately, it was not possible to determine stability constant values from such titration isotherm data.

In contrast to macrocycles **6** and **11**, the cavitand receptor **14** only weakly binds halide anions (Table 1) which presumably reflects the tetrapodal receptor's unfavourable cavity size and lack of preorganisation. Indeed, molecular mechanics modelling (SPARTAN 04)[14] of the cavitand receptor showed the upper rim appended imidazolium moieties to be highly flexible resulting in the absence of a preorganised binding site.

With the benzoate anion, a binding stoichiometry of 1 : 2 was obtained for all four macrocyclic receptors. The relative size of the carboxylate anion may be responsible for this result. Benzoate being an essentially planar molecule and larger than the halide anions, cannot fit inside the macrocyclic cavities of the receptors. Similar to the hexafluorophosphate anions shown in the solid state structure of **11** (Fig. 6), benzoate anions are likely to reside only partially within the macrocyclic cavity of the receptors and hence the observation of 1 : 2 receptor–benzoate binding stoichiometry. The stability constant values (K_2) for the binding of the second benzoate are of significant magnitudes (Table 1). This observation suggests the presence of two independent binding sites for benzoate with these macrocyclic systems which also, taking into account the crystal structure of **11**, suggests one benzoate anion may be binding to each side of the receptor. Interestingly, there was no evidence of cavitand receptor **14** binding benzoate in this aqueous–acetonitrile solvent mixture.

3. Conclusions

New (tetrakis)imidazolium macrocyclic receptor systems of various sizes have been prepared *via* sequential alkylation reactions of bis(imidazolium) precursor derivatives. Proton NMR titration investigations revealed the macrocycles to strongly bind halide anions with two macrocycles **6** and **11** exhibiting pronounced selectivity for binding fluoride in a competitive aqueous–acetonitrile (CD_3CN–H_2O 9 : 1) solvent media.

Table 2 Crystal data‡ and refinement details for compounds **4** and **11**

	4	**11**
Chemical formula	$C_{17}H_{16}N_4$	$C_{46}H_{54}F_{24}N_{10}P_4$
Formula weight	276.34	1326.85
Temperature/K	150	150
Wavelength/Å	0.71073	0.71073
Crystal system	Orthorhombic	Triclinic
Space group	*P b c n*	$P\bar{1}$
a/Å	25.1991(4)	9.6741(2)
b/Å	8.6736(2)	12.6292(2)
c/Å	12.6158(2)	13.1081(2)
α (deg)	90	65.7093(10)
β (deg)	90	71.7542(9)
γ (deg)	90	83.9297(7)
Cell volume/Å^3	2757.40(9)	1385.83(4)
Z	8	1
Calculated density/Mg m^{-3}	1.331	1.590
Absorption coefficient/mm^{-1}	0.082	0.262
F_{000}	1168	676
Crystal size/mm	0.20 × 0.20 × 0.40	0.10 × 0.10 × 0.32
Description of crystal	Colourless prism	Colourless prism
Absorption correction	Semi-empirical from equivalent reflections	Semi-empirical from equivalent reflections
Transmission coefficients (min, max)	0.97, 0.98	0.92, 0.97
θ range for data collection (deg)	$5.0 \leq \theta \leq 27.5$	$5.0 \leq \theta \leq 27.5$
Index ranges	$0 \leq h \leq 32, 0 \leq k \leq 11, 0 \leq l \leq 16$	$-11 \leq h \leq 12, -14 \leq k \leq 16, 0 \leq l \leq 16$
Reflections measured	18754	41262
Unique reflections	3564	6294
R_{int}	0.045	0.064
Observed reflections ($I > 3\sigma(I)$)	2021	3552
Refinement method	Full-matrix least-squares on *F*	Full-matrix least-squares on *F*
Parameters refined	190	379
Weighting scheme	Chebychev 3-term polynomial	Chebychev 3-term polynomial
Goodness of fit	1.1219	1.1089
R	0.0337	0.0526
wR	0.0381	0.0611
Residual electron density (min, max)/e Å^{-3}	−0.18, 0.19	−0.49, 0.62

Evidence for a macrocyclic cavity size effect comes from the largest macrocycle **9** forming the strongest complex with iodide.

All four macrocycles complex the benzoate anion with a 1 : 2 receptor–anion binding stoichiometry. A new tetrapodal cavitand imidazolium receptor was also synthesized and proved to be an inferior anion complexing agent which modelling studies attribute to the absence of a preorganised binding site. This highlights the importance of the preorganised cyclic (tetrakis)imidazolium receptor design for anion recognition efficacy.

4. Experimental

4.1 General details

NMR spectra were recorded on Varian utility 300 and 500 MHz spectrometers. Mass spectrometry was carried out on a Micromass LCT electrospray mass spectrometer (ESMS, cone voltage = 20–50 V, desolvation temp. = 80 °C, source temp. = 60 °C). Elemental analysis was performed at the Inorganic Chemistry Laboratory, Oxford. Crystal data (Table 2) was obtained using Mo Kα radiation on an Enraf–Nonius KappaCCD diffractometer.‡ Crystals were mounted on a glass fibre and cooled rapidly to 150 K in a stream of cold nitrogen using an Oxford Cryosystems CRYOSTREAM unit. Intensity data were processed using the DENZO-SMN package.[15] Structures were solved by direct methods using the SIR92 program.[16] Full-matrix least-squares refinement was carried out using the CRYSTALS program suite.[17] Hydrogen atoms were positioned geometrically after each cycle of refinement. A Chebychev polynomial weighting scheme was applied.

Molecular modelling studies were calculated using Merck Molecular Force Field (MMFF) using the SPARTAN 04 modelling program.[14] The molecular models were constructed in three stages using SPARTAN. The geometry of the benzimidazolium moiety was first refined using the basic molecular mechanics refinement in the program. The macrocyclic receptor was constructed by linking the benzimidazolium moieties and then its geometry was refined. The equilibrium geometry of the macrocyclic receptor was calculated using the Merck Molecular Force Field (MMFF). A variety of anions were then inserted into the model of the receptor and, maximising the number of hydrogen bonds, the equilibrium geometry of the receptor plus anion was calculated using MMFF.

MMFF uses a two stage optimisation routine where atoms are allowed to move large distances followed by small distances. The full developmental details of MMFF can be found in reference 18.

4.2 Syntheses

Imidazole, benzimidazole and the alkylating agents used herein were purchased from Sigma Aldrich whilst 3-aminopropyl imidazole was purchased from Acros Organics and were used without further purification. Tetra(bromomethyl)resorcinarene cavitand **12** was synthesised *via* a literature procedure.[11]

1,3-Bis(imidazole)propane 1. *N*-(3-aminopropyl)imidazole (6.30 g, 0.05 mol) in water (10 mL) was acidified to pH 2 with an aqueous solution of phosphoric acid. Glyoxal (6 mL, 40% aq., 0.05 mol) and formaldehyde (4 mL, 20% aq., 0.05 mol) were added and the reaction mixture was warmed to 95 °C. An aqueous solution of ammonium chloride (2.70 g, 0.05 mol) was added drop wise to the reaction over 1 h. The reaction was heated at 95 °C for a further 15 min and allowed to cool to room temperature before cooling in an ice-water bath. Potassium hydroxide (3.00 g) was dissolved in the cooled reaction mixture and the product was extracted with dichloromethane. The organic phase was washed with water and dried over anhydrous

‡ CCDC reference numbers 283001 and 283002. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b510068b

magnesium sulfate. A pale yellow oil was obtained (0.50 g, 6% yield) after the removal of solvent.

^{1}H NMR ($CDCl_3$, 288 K) δ (ppm) = 7.28 (s, 2H, NCHN), 6.88 (s, 2H, NCHCHN), 6.74 (s, 2H, NCHCHN), 3.74 (t, 6.9 Hz, 4H, N–CH_2–), 2.10 (quintet, 6.9 Hz, 2H, –CH_2–). MS (ESI positive ion, MeOH): *m/z* 177 ($M + H^+$).

Compound 2. 1,3-Bis(imidazole)propane (0.50 g, 2 eq.) and 1,3-diiodopropane (0.42 g, 1 eq.) were dissolved in dioxane (100 mL) and refluxed for 24 h. The reaction mixture was cooled to room temperature and the precipitate collected by filtration. The light brown solid (0.6 g, 66% yield) was washed with diethyl ether and dried *in vacuo.*

^{1}H NMR (d_6-acetone, 288 K) δ (ppm) = 9.05 (s, 2H, NCHN), 8.89 (s, 2H, NCHN), 7.06–7.95 (m, 8H, NCHCHN), 4.33 (m, 12H, N–CH_2–), 2.52 (m, 6H, –CH_2–). MS (ESI positive ion, MeOH): *m/z* 521 $[M - I^-]^+$.

Receptor 3. Compound **2** (0.20 g, 1 eq.) and 1,3-diiodopropane (0.10 g, 1 eq.) were dissolved in DMF (10 mL) and stirred at 50 °C overnight. The solvent was removed under reduced pressure and the residue was redissolved in methanol (5 mL). A saturated aqueous solution of ammonium hexafluorophosphate (5 mL) was added and heated to boiling. The solvent volume was reduced to *ca.* 5 mL and the solution was allowed to cool to room temperature. The precipitate was collected and washed with water and methanol followed by diethyl ether. The white solid (0.20 g, 80% yield) was dried under vacuum.

^{1}H NMR (CD_3CN, 288 K) δ (ppm) = 8.51 (s, 4H, imidazole), 7.46 (s, 8H, imidazole), 4.23 (t, 7.2 Hz, 16H, N–CH_2–), 2.43 (quintet, 7.2 Hz, 8H, –CH_2–). ^{13}C NMR (75 MHz, CD_3CN, 288 K) δ (ppm) = 136.26 (NCHN), 123.24 (NCHCHN), 46.84 (N–CH_2–), 30.22 (CH_2). MS (ESI positive ion, MeOH): *m/z* 363 $[M - 2PF_6^-$. Anal. calcd for $C_{24}H_{36}N_8P_4F_{24}$: C, 28.35; H, 3.54; N, 11.02. Found: C, 28.45; H, 3.51; N, 11.47.

1,3-Bis(benzimidazole)propane 4. Benzimidazole (3.50 g) in THF (50 mL) was added drop wise to a suspension of NaH (60% in mineral oil, 1.20 g) in THF (50 mL) at 0 °C. 1,3-Dibromopropane (3.00 g) was added to the suspension when gas production ceased. The reaction was stirred overnight and filtered. The solvent was removed from the filtrate and redissolved in dichloromethane (100 mL), which was then washed with water (50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo* to give a pale yellow solid (3.50 g, 85% yield).

^{1}H NMR ($CDCl_3$, 288 K) δ (ppm) = 7.84 (m, 4H, NCHN), 7.29 (m, 6H, ArH), 4.17 (t, 6.6 Hz, 4H, N–CH_2–), 2.52 (quintet, 6.6 Hz, 2H, –CH_2–). MS (ESI positive ion, MeOH): *m/z* 277 ($M + H^+$).

Compound 5. 1,3-Bis(benzimidazole)propane **4** (0.50 g, 2 eq.) and 1,3-diiodopropane (0.42 g, 1 eq.) were dissolved in dioxane (100 mL) and refluxed for 24 h. The reaction mixture was cooled to room temperature and the precipitate collected. The light brown solid (0.51 g, 65% yield) was washed with diethyl ether and dried *in vacuo.*

^{1}H NMR (d_6-DMSO, 288 K) δ (ppm) = 9.99 (m, 2H, NCHN), 9.79 (m, 2H, NCHN), 7.18–8.29 (m, 16H, ArH), 4.30–4.73 (m, 12H, N–CH_2–), 2.52 (m, 6H, –CH_2–). MS (ESI positive ion, MeOH): *m/z* 721 $[M - I^-]^+$.

Receptor 6. Compound **5** (0.50 g, 1 eq.) and 1,3-diiodopropane (0.18 g, 1 eq.) were dissolved in DMF (10 mL) and stirred at 50 °C overnight. The solvent was removed under vacuum and the residue was redissolved in methanol (5 mL). A saturated solution of ammonium hexafluorophosphate (5 mL) was added and heated to boiling. The solvent volume was reduced to *ca.* 10 mL and the solution was allowed to cool to room temperature. The precipitate was collected and washed with water and methanol followed by diethyl ether. The white solid (0.19 g, 31% yield) was dried under vacuum.

^{1}H NMR (CD_3CN, 288 K) δ (ppm) = 8.97 (m, 4H, NCHN), 8.01 (m, 2H, ArCH), 7.93 (m, 6H, ArCH), 7.79 (m, 2H, ArCH), 7.74 (m, 6H, ArCH), 4.62 (t, 7.2 Hz, 16H, N–CH_2-), 2.65 (quintet, 7.2 Hz, 8H, –CH_2–). ^{13}C NMR (75 MHz, CD_3CN, 288 K) δ (ppm) = 141.50 (NCHN), 131.97 (ArC), 128.02 (ArCH), 113.92 (ArCH), 44.8 (–NCH_2–), 28.8 (CH_2). MS (ESI positive ion, MeCN): *m/z* 1071 $[M - PF_6^-]^+$. Anal. calcd for $C_{40}H_{44}N_8P_4F_{24}.H_2O$: C, 38.88; H, 3.73; N, 9.08. Found: C, 38.84; H, 3.84; N, 9.06.

1,4-Bis(benzimidazole)butane 7. The procedure for the preparation of **7** was analogous to the synthesis of compound **4** using 1,4-di-bromobutane (3.30 g) was used instead of 1,3-dibromopropane. The product was isolated as a white solid (2.73 g, 66% yield).

^{1}H NMR ($CDCl_3$, 288 K) δ (ppm) = 7.79 (m, 4H, NCHN), 7.29 (m, 6H, ArH), 4.12 (m, 4H, N–CH_2–), 1.88 (m, 4H, –CH_2–). MS (ESI positive ion, MeOH): *m/z* 291 ($M + H^+$).

Compound 8. 1,3-Bis(benzimidazole)butane **5** (1.00 g, 2 eq.) and 1,3-diiodobutane (0.53 g, 1 eq.) were dissolved in dioxane (100 mL) and heated under reflux for 24 h. The reaction mixture was cooled to room temperature and the precipitate collected. The light brown solid (1.00 g, 46% yield) was washed with diethyl ether and dried *in vacuo.*

^{1}H NMR (d_6-DMSO, 288 K) δ (ppm) = 9.85 (m, 2H, NCHN), 9.79 (m, 2H, NCHN), 7.18–8.29 (m, 16H, ArH), 4.55 (m, 8H, N–CH_2–), 4.31 (m, 4H, N–CH_2–), 2.02 (m, 8H, –CH_2–), 1.88 (m, 4H, –CH_2–). MS (ESI positive ion, MeOH): *m/z* 763 $(M - I^-)^+$, 318 (M^{2+}).

Receptor 9. Compound **8** (0.50 g, 1 eq.) and 1,3-diiodobutane (0.18 g, 1 eq.) were dissolved in DMF (10 mL) and stirred at 50 °C overnight. The solvent was removed under reduced pressure and the residue was redissolved in methanol (5 mL). A saturated solution of ammonium hexafluorophosphate (5 mL) was added and heated to boiling. The solvent volume was reduced to *ca.* 5 mL and the solution was allowed to cool to room temperature. The precipitate was collected and washed with water and methanol followed by diethyl ether. The white solid (0.20 g, 30% yield) was dried under vacuum.

^{1}H NMR (CD_3CN, 288 K) δ (ppm) = 8.95 (bs, 4H, NCHN), 7.86 (m, 8H, ArH), 7.69 (m, 8H, ArH), 4.47 (br, 16H, N–CH_2–), 2.06 (br, 16H, –CH_2–). ^{13}C NMR (75 MHz, CD_3CN, 288 K) δ (ppm) = 141.25 (NCHN), 131.95 (ArC), 127.59 (ArCH), 113.94 (ArCH), 47.09 (N–CH_2–), 26.15 (–CH_2–). MS (ESI positive ion, MeCN): *m/z* 1127 $[M - PF_6^-]^+$. Anal. calcd for $C_{44}H_{52}N_8P_4F_{24}$: C, 41.52; H, 4.12; N, 8.80. Found: C, 41.60; H, 4.10; N, 8.85.

Compound 10. 1,3-Bis(benzimidazole)butane **5** (1.00 g, 2 eq.) and 1,3-diiodopropane (0.53 g, 1 eq.) were dissolved in dioxane (100 mL) and refluxed for 24 h. The reaction mixture was cooled to room temperature and the precipitate collected by filtration. The light brown solid (1.00 g, 46% yield) was washed with diethyl ether and dried *in vacuo.*

^{1}H NMR (d_6-DMSO, 288 K) δ (ppm) = 8.05 (s, 2H, NCHN), 8.00 (s, 2H, NCHN), 7.14–7.82 (m, 16H, ArH), 4.14–4.60 (m, 12H, N–CH_2–), 1.88 (br, 2H, –CH_2–), 1.75 (br, 8H, –CH_2–). MS (ESI positive ion, MeOH): *m/z* 749 $(M - I^-)^+$.

Receptor 11. Compound **10** (0.50 g, 1 eq.) and 1,3-diiodopropane (0.18 g, 1 eq.) were dissolved in DMF (10 mL) and stirred at 50 °C overnight. The solvent was removed under vacuum and the pale yellow solid washed with diethyl ether. The solid was subsequently dissolved in the minimum amount of methanol before the addition of a saturated aqueous solution of NH_4PF_6 (5 mL). The white solid (0.21 g, 94% yield) was collected by filtration and was dried under vacuum.

^{1}H NMR (CD_3CN, 288 K) δ (ppm) = 8.86–8.94 (m, 4H, NCHN), 7.90 (m, 8H, ArH), 7.71 (m, 8H, ArH), 4.45–4.62 (br m, 16H, N–CH_2–), 2.66 (br m, 4H, propyl CH_2), 2.09 (br, 8H, butyl

CH_2). ^{13}C NMR (75 MHz, CD_3CN, 288 K) δ (ppm) = 149.72 (NCHN), 132.00, 131.90 (ArC), 127.73, 127.84 (ArCH), 114.02, 113.80 (ArCH), 47.15 (N–CH_2–), 44.70 (N–CH_2–), 28.63, 26.07 (–CH_2–); MS (ESI positive ion, MeCN): m/z 1099 [M − PF_6^-]$^+$. Anal. calcd for $C_{42}H_{48}N_8P_4F_{24}$: C, 40.91; H, 3.97; N, 9.18. Found: C, 40.53; H, 3.89; N, 9.00.

Tetra(bromomethyl)resorcinarene cavitand 12. Tetramethylresorcinarene cavitand[11] (7.00 g, 8.02 mmol) and a catalytic amount of AIBN were dissolved in 1,2-dichloroethane (150 mL). NBS (7.00 g, 38.99 mmol) was added portionwise to the solution which was then stirred at 80 °C under N_2 for 3 h. Additional NBS (1.00 g) and AIBN (catalytic amount) were added at this stage. The orange solution was then stirred at room temperature for a further 18 h, after which time the solvent was removed under reduced pressure. The resulting solid was stirred in EtOH (150 mL) for 2 h and the resulting precipitate filtered off. This solid was dissolved in CH_2Cl_2 (20 mL) and layered with EtOH (50 mL) in order to induce crystallisation. The resulting cream crystals were collected and dried *in vacuo* (8.05 g, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.11 (s, 4H, ArH), 6.01 (d, J = 6.6 Hz, 4H, OCH_2 [H_{outer}]), 4.75 (t, J = 7.8 Hz, 4H, ArCH), 4.53 (d, J = 6.9 Hz, 4H, OCH_2 [H_{inner}]), 4.40 (s, 8H, CH_2Br), 2.17 (m, 8H, ArCHCH_2), 1.33 (m, 24H, CH_2), 0.89 (t, J = 6.9 Hz, 12H, CH_3). Anal. calcd for $C_{56}H_{68}Br_4O_8 \cdot \frac{1}{2}H_2O$: C, 56.16; H, 5.81; Found: C, 56.06; H, 5.68.

Tetra(imidazolylmethyl)resorcinarene cavitand 13. Tetra(bromomethyl)resorcinarene cavitand **12** (0.10 g, 0.10 mmol) in THF (10 mL) was added dropwise to a suspension of imidazole (25 mg, 0.40 mmol) and NaOH (0.05 g) in THF (50 mL). The mixture was heated under reflux overnight, then the solvent was removed *in vacuo*. The resulting residue was redissolved in CH_2Cl_2 (50 mL) and washed with water (2 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and a pale yellow powder (0.10 g, yield 96%) was obtained after solvent removal.

^{1}H NMR (300 MHz, $CDCl_3$, 288 K) δ (ppm) = 7.38 (s, 4H, NCHN), 7.16 (s, 4H, ArH), 6.99 (s, 4H, NCHCHN), 6.87 (s, 4H, NCHCHN), 5.90 (d, J = 6.6 Hz, 4H, OCH_2 [H_{outer}]), 4.85 (s, 8H, N–CH_2), 4.70 (t, J = 7.8 Hz, 4H, ArCH), 4.08 (d, J = 6.9 Hz, 4H, OCH_2 [H_{inner}]), 2.16 (m, 8H, ArCHCH_2), 1.34 (m, 24H, CH_2), 0.88 (t, J = 6.9 Hz, 12H, CH_3). MS (ESI positive ion, MeCN): m/z 1137 [M + H$^+$].

Tetrakisimidazolium resorcinarene cavitand 14. Tetra(imidazolylmethyl)resorcinarene cavitand **13** (0.10 g, 0.10 mmol) and 1-bromohexane (5 mL, excess) in toluene (10 mL) were heated under reflux for 3 d. The solvent was removed under vacuum and the residue redissolved in MeOH (10 mL). Saturated NH_4PF_6 (aq., 5 mL) was added to the solution and the resulting precipitate was collected by filtration. A pale yellow powder (0.51 g, yield 37%) was obtained on drying *in vacuo.*

^{1}H NMR (300 MHz, CD_3CN, 288 K) δ(ppm) = 8.53 (s, 4H, NCHN), 7.54 (s, 4H, ArH), 7.38 (s, 8H, NCHCHN), 6.23 (d, J = 6.6 Hz, 4H, OCH_2 [H_{outer}]), 5.13 (s, 8H, N–CH_2), 4.68 (t, J = 7.8 Hz, 4H, ArCH), 4.55 (d, J = 6.9 Hz, 4H, OCH_2 [H_{inner}]), 4.13 (t, J = 6.9 Hz, 8H, hexyl CH_2), 2.16 (m, 8H, ArCHCH_2), 1.82 (m, 8H, hexyl CH_2), 1.38 (m, 24H, CH_2), 3.15 (m, 24H, hexyl CH_2), 0.89 (m, 24H, CH_3). ^{13}C NMR (75 MHz, CD_3CN, 288 K) δ (ppm) = 153.2, 139.0, 135.5, 123.5, 122.6, 122.4, 121.0, 99.7, 49.7, 42.9, 37.5, 31.8, 30.7, 29.4, 27.2, 25.3, 22.3, 22.1, 13.4 and 13.2 ppm. MS (ESI positive ion, MeCN): m/z 883 [M − 2PF_6^-]$^{2+}$, 1912 [M − PF_6^-]$^+$.

4.3 ^{1}H NMR titration protocol

^{1}H NMR spectroscopic titration experiments were carried out at *ca.* 293 K on a 500 MHz Varian Utility Spectrometer. Data were analysed using the computer fitting program EQNMR©. For further details on the workings of the EQNMR computer program please refer to Professor M. J. Hynes.[13] To calculate stability constants the binding stoichiometry must be known and the rate of exchange between the complexed and the free receptor must be rapid on the NMR timescale. Therefore the signal is a weighted average of the signals of the two species.

The procedure for ^{1}H NMR titrations was as follows: 1.5 × 10^{-6} moles of host was dissolved in 500 μL of 9 : 1 CD_3CN–H_2O (so as to avoid deuterium exchange). 3 × 10^{-5} moles of TBA anion salt was dissolved in 400 μL of the same solvent corresponding to one equivalent having a volume of 20 μL. A proton NMR of the host was recorded and subsequently aliquots of the anion solution were added to the host (11 × 0.2 eq., 2 × 0.4 eq., 2 × 1 eq., 1 × 2 eq. and 1 × 3 eq.). After each addition of anion, another ^{1}H NMR was recorded.

Acknowledgements

We gratefully acknowledge the EPSRC for studentships (W.W.H.W and M.S.V.).

References

1 (*a*) R. Martínez-Máñez and F. Sancenón, *Chem. Rev.*, 2003, **103**, 4419; P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed.*, 2001, **40**(3), 486; P. A. Gale, *Coord. Chem. Rev.*, 2003, **240**, 191; F. P. Schmidtchen and M. Berger, *Chem. Rev.*, 1997, **97**, 1609; P. D. Beer and D. K. Smith, *Prog. Inorg. Chem.*, 1997, **46**, 1; J. L. Atwood, K. T. Holman and J. W. Steed, *Chem. Commun.*, 1996, 1401; *Supramolecular Chemistry of Anions*, ed. A. Bianchi, K. Bowman-James and E. García-Espãna, New York, Chichester, Wiley-VCH, 1997; (*b*) P. D. Beer, *Acc. Chem. Res.*, 1998, **31**, 71; A. P. de Silva, H. Q. N. Guarantee, T. Gunnlaugsson, A. J. Huxley, C. P. McCoy, J. T. Rademacher and T. R. Rice, *Chem. Rev.*, 1997, **97**, 1515.

2 (*a*) C. R. Bondy, P. A. Gale and S. J. Loeb, *J. Am. Chem. Soc.*, 2004, **126**, 5030; (*b*) K. Choi and A. D. Hamilton, *Coord. Chem. Rev.*, 2003, **240**, 101; (*c*) J. L. Sessler, S. Camiolo and P. A. Gale, *Coord. Chem. Rev.*, 2003, **240**, 17; (*d*) F. P. Schmidtchen, *Org. Lett.*, 2002, **4**, 431.

3 (*a*) K. Kavallieratos, C. M. Bertao and R. H. Crabtree, *J. Org. Chem.*, 1999, **64**, 1675; (*b*) T. R. Kelly and M. H. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 7072; (*c*) P. A. Gale, J. L. Sessler, V. Kral and V. Lynch, *J. Am. Chem. Soc.*, 1996, **118**, 5140.

4 (*a*) S. Ramos, E. Alcalde, G. Doddi, P. Mencarelli and L. Perez-Garcia, *J. Org. Chem.*, 2002, **67**, 8463; (*b*) M. S. Vickers, K. Martindale and P. D. Beer, *J. Mater. Chem.*, 2005, **15**, 2784.

5 (*a*) S. K. Kim, N. J. Singh, S. J. Kim, H. G. Kim, J. K. Kim, J. W. Lee, K. S. Kim and J. Yoon, *Org. Lett.*, 2003, **12**, 2083; (*b*) J. Yoon, S. K. Kim, N. J. Singh, J. W. Lee, Y. J. Yang, K. Chellappan and K. S. Kim, *J. Org. Chem.*, 2004, **69**, 581; (*c*) J. Y. Kwon, N. J. Singh, H. N. Kim, S. K. Kim, K. S. Kim and J. Yoon, *J. Am. Chem. Soc.*, 2004, **126**, 8892.

6 (*a*) S. Yun, H. Ihm, H. G. Kim, C. W. Lee, B. Indrajit, K. S. Oh, Y. J. Gong, J. W. Lee, J. Yoon, H. C. Lee and K. S. Kim, *J. Org. Chem.*, 2003, **68**, 2467; (*b*) H. Ihm, S. Yun, H. G. Kim, J. K. Kim and K. S. Kim, *Org. Lett.*, 2002, **4**, 2897; (*c*) K. Sato, S. Arai and T. Yamagishi, *Tetrahedron Lett.*, 1999, **40**, 5219; (*d*) W. W. H. Wong, D. E. Phipps and P. D. Beer, *Polyhedron*, 2004, **23**, 2821.

7 Two examples of tetrakis(imidazolium) macrocycles can be found in the literature: (*a*) K. Chellappan, N. J. Singh, I.-C. Hwang, J. W. Lee and K. S. Kim, *Angew. Chem., Int. Ed.*, 2005, **44**, 2899; (*b*) K. Sato, T. Onitake, S. Arai and T. Yamagishi, *Heterocycles*, 2003, **60**(4), 779.

8 P. A. Gale, P. Anzenbacher Jr. and J. L. Sessler, *Coord. Chem. Rev.*, 2001, **222**, 57–102.

9 A. A. Gridnev and I. M. Mihaltseva, *Synth. Commun.*, 1994, **24**, 1547.

10 E. Alcalde, S. Ramos and L. Perez-Garcia, *Org. Lett.*, 1999, **1**, 1035; R. Vilar, *Angew. Chem., Int. Ed.*, 2003, **42**, 1460.

11 H. Boerrigter, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.*, 1997, **62**, 7148.

12 C. D. Gutsche, *Calixarenes*, 1989; T. Harada, J. M. Rudzinski, E. Osawa and S. Shinkai, *J. Chem. Soc., Perkin Trans. 2*, 1992, 2109.

13 M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311.

14 Wavefunction Inc., 2004, *SPARTAN 04 program for PC*.

15 Z. Otwinowski, W. Minor, *Processing of X-Ray Diffraction Data Collected in Oscillation Mode (Methods Enzymol.)*, ed C. W. Carter and R. M. Sweet, Academic Press, 1997, p. 276.

16 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Ploidori and M. Camalli, *J. Appl. Crystallogr.*, 1994, **27**, 435.

17 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge, R. I. Cooper, *CRYSTALS issue 11*, Chemical Crystallography Laboratory, Oxford, UK, 2001.

18 T. A. Halgren, *J. Comput. Chem.*, 1996, **17**, 616.