Tuning the strength and selectivity of ion-pair recognition using heteroditopic calix[4]arene-based receptors†‡

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The syntheses, characterisation and ion binding properties of two novel heteroditopic calix[4]arene receptors are reported. These systems were found to demonstrate cooperative binding of certain ion-pairs, with the selectivity depending critically on the structure of the receptors. Furthermore, a macrocyclic effect for ion-pair recognition was observed to operate.

Introduction

The field of ion-pair recognition has attracted much attention in recent years, stimulated by the multiple possible applications of ditopic receptors for salt solubilisation, extraction, and membrane transport,[1] and the opportunity for the fine tuning of their strengths and selectivities of association.[2] In particular, the preparation of receptors capable of the recognition of *contact* ion-pairs is an attractive prospect, as this avoids the otherwise energetically unfavourable separation of the two ions.[3] The design of these receptors normally hinges on the proximal arrangement of known cation and anion binding domains within a given molecular framework. The calix[4]arene structural motif represents an attractive anchor point for such systems, owing to its ease of functionalisation and high degree of preorganisation.[4,5]

Recently, we reported the heteroditopic calix[4]diquinone–isophthalamide receptor **1** (Fig. 1), which was shown to be capable of the cooperative recognition of contact alkali metal and ammonium ion-pairs.[6] Such a recognition process was mediated by placing the calix[4]diquinone[7] cation and isophthalamide[8,9] anion binding sites within the confines of a single macrobicycle. Importantly, the ion pair recognition was shown to occur in a manner consistent with AND logic,[10] whereby the receptor displayed no affinity for either of selected free ions, binding only to the contact ion-pair species. The receptor was not particularly discriminatory between the ion-pairs of different cations, however.

In order to address this issue of cation selectivity, it was decided to alter the nature of the cation binding unit appended to the calix[4]arene motif. Lower-rim ester-substituted calix[4]-arene derivatives have been demonstrated to enforce selectivity for sodium cations,[11] and this unit was consequently used in these studies. Additionally, the impact of the preorganisation of the anion binding site, whether chelating or macrocyclic, was investigated as this should impact significantly on the ion-pair binding affinity.

Taking the above considerations into account, we detail herein the syntheses and binding properties of new heteroditopic calix[4]arene bisester compounds **2** and **3** (Fig. 1), which are shown to demonstrate biased selectivity towards sodium and lithium containing ion pairs, as well as a macrocyclic effect in ion-pair recognition.

Receptor syntheses

The synthesis of receptor **2** was achieved through further reaction of the previously described calix[4]arene bisamine

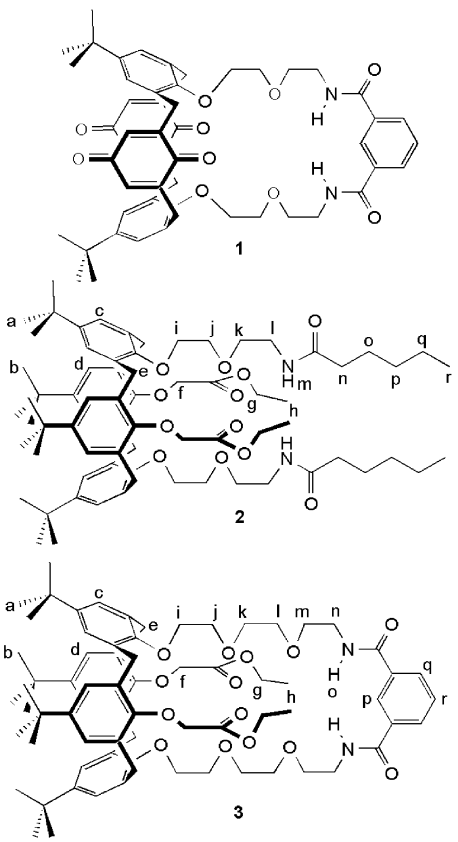

Fig. 1 Calix[4]diquinone receptor **1** and calix[4]arene diester receptors **2** and **3**.

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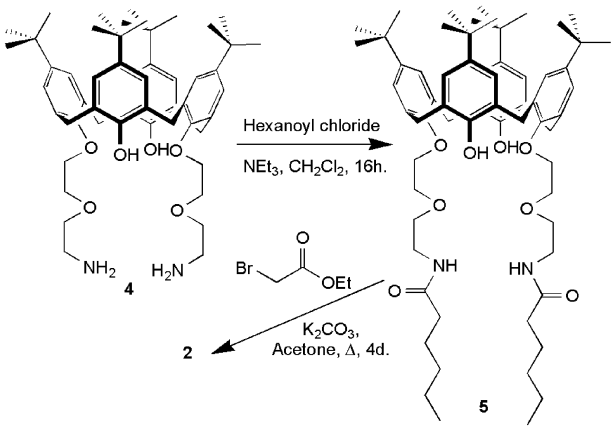
‡ Electronic supplementary information (ESI) available: Synthesis and brief characterisation for previously described compounds, as well as description of titration protocols. See DOI: 10.1039/b615873k



Scheme 1 Synthesis of receptor **2**.

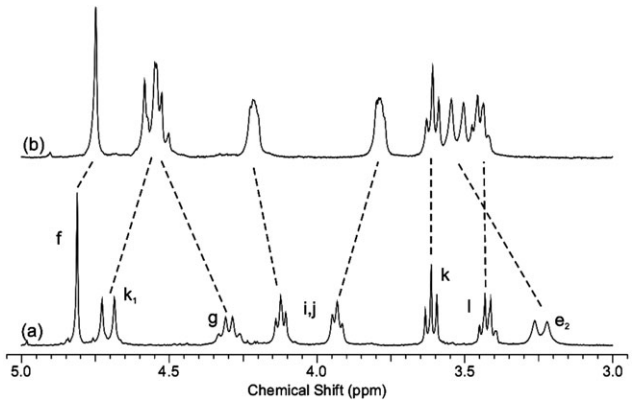


Fig. 2 Perturbations of the aliphatic region of the ^{1}H NMR spectrum of **2** on addition of sodium cation: (a) **2** and, (b) **2** · $NaClO_4$. Solvent: acetone-d_6, 298 K. For proton assignments see Fig. 1.

compound **4** (Scheme 1).[6] Condensation of this bisamine with an excess of hexanoyl chloride and triethylamine in dichloromethane gave the bisamide compound **5** in 84% yield. Heating this species under reflux in acetone with ethyl bromoacetate and potassium carbonate for four days gave the desired receptor **2** in 78% yield.

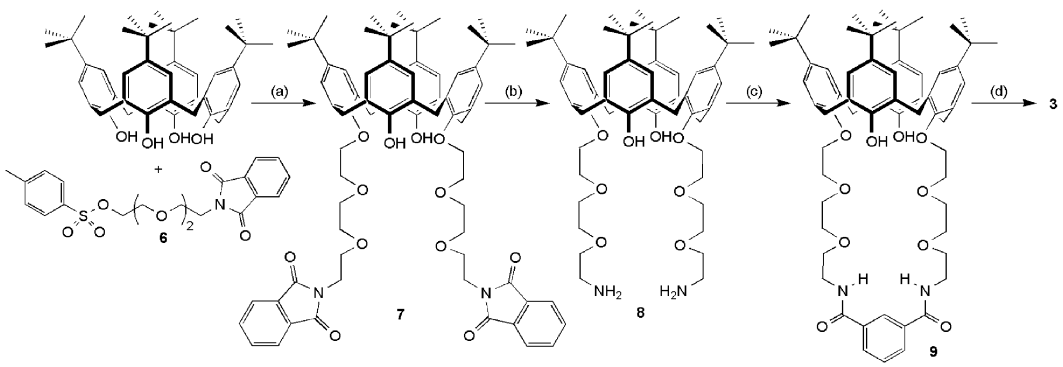
Receptor **3** required a slightly longer preparative route (Scheme 2). The disubstitution of *para-tert*-butylcalix[4]arene with two equivalents of the known compound **6**[12] was accomplished in 60% yield by heating the two components under reflux in acetonitrile for four days, in the presence of potassium carbonate. The reductive cleavage of the phthalimide protecting functionality was then carried out by heating **7** under reflux in ethanol in the presence of excess hydrazine to give the bisamine compound **8** in 95% yield. Under high dilution conditions, condensation of **8** with isophthaloyl dichloride and triethylamine in dichloromethane gave the macrobicyclic species **9** in 69% yield, following silica gel chromatographic purification. Finally, **3** was prepared in 55% yield by heating **9** under reflux in acetonitrile, in the presence of an excess of ethyl bromoacetate and potassium carbonate.

Both new compounds **2** and **3** were characterised by NMR spectroscopy, elemental analysis and electrospray mass spectrometry (see Experimental section).

Ion binding results

Anion and group 1 cation binding properties of the new receptors were studied by ^{1}H NMR spectroscopic methods. The addition of sodium or lithium perchlorate salts to a solution of receptor **2** in acetone-d_6 induced significant changes in the aliphatic region of the spectrum (Fig. 2), indicating an interaction of the components. The stoichiometry of interaction was verified to be 1 : 1, through a Job Plot analysis, and the change in chemical shift of the signal arising from the ethyl ester methylene proton f was monitored as a function of added cation concentration to obtain association constant data using the winEQNMR computer program (Table 1).[13] It may clearly be observed from these data that **2** binds sodium strongly in this solvent, lithium less strongly, and displays no affinity for the larger alkali metal cation potassium, or ammonium. When sodium or lithium perchlorate were added to a 1 : 1 solution of **2** and TBA chloride or bromide salts, however, precipitation was observed, preventing the calculation of association constant data.

The anion binding properties of **2** were therefore studied in an alternative solvent, acetonitrile-d_3. It was found that the addition of TBA halide salts induced small downfield shifts in the signals arising from the amide protons (m) of the receptor. Importantly, the chemical shift change induced on addition of



Scheme 2 Formation of cyclic receptor **3**. *Reagents and conditions*: (a) **6**, K_2CO_3, CH_3CN, heat, 4 d; (b) $N_2H_4 \cdot H_2O$, EtOH, heat, 16 h; (c) isophthaloyl dichloride, NEt_3, CH_2Cl_2, 16 h; (d) ethyl bromoacetate, K_2CO_3, CH_3CN, heat, 4 d.

Table 1 Cation binding properties of receptor **2**[a]

Cation	Li^{+} [b]	Na^{+} [b]	K^{+} [c]	NH_4^{+} [c]
$\Delta\delta_H$/ppm	0.078	−0.064	−0.002	−0.003
K_{11}/M^{-1}	470	3500	—[d]	—[d]

[a] Solvent: acetone-d_6, 298 K. $\Delta\delta_H$ (ppm) values correspond to the chemical shift change of the ester methylene proton signal (f) induced on addition of one equivalent of cation. Association constant errors <10%. [b] Cation added as perchlorate salt. [c] Cation added as hexafluorophosphate salt. [d] No interaction could be inferred.

Table 2 Anion binding properties of receptor **2**[a]

	2		**2** · $NaClO_4$	
	$\Delta\delta_{NH}$/ppm	K_{11}/M^{-1}	$\Delta\delta_{NH}$/ppm	K_{11}/M^{-1}
TBACl	0.055	<5	0.203	20
TBABr	0.045	10	0.139	20
TBAI	0.003	—[b]	0.016	—[b]

[a] Solvent: CD_3CN, 298 K. $\Delta\delta_{NH}$ (ppm) values correspond to the chemical shift change of the amide proton signal (m) induced on addition of one equivalent of anion. Association constant errors <10%. [b] No interaction could be inferred.

one equivalent of halide anion was larger in the case of **2** · $NaClO_4$ than for **2** alone, suggesting that the bound cation enhances anion recognition. The dependence of the amide proton chemical shift on added anion concentration (Fig. 3) was used to obtain association constant data (Table 2).[13] It can be seen that, although the interaction of **2** with halide anions in this solvent is weak, a definite cooperative enhancement of anion recognition is affected by the presence of sodium cations. No such enhancement was observed for **2** · KPF_6, with the chemical shift changes observed being consistent with first the ion-pair association of potassium and halide anion remote of the receptor, followed by the subsequent binding of the 'free' anion by **2**.

For **3**, as in the case of **2**, it was possible to ascertain the cation binding strength of the bisester cavity by ^{1}H NMR methods, in acetone-d_6. As expected, the addition of lithium and sodium perchlorate induced perturbations in the aliphatic region of the ^{1}H NMR spectrum of the receptor, but was not affected by the addition of potassium, rubidium or ammonium. Job Plot analysis revealed that this had 1 : 1 stoichiometry, and through monitoring the dependence of the chemical shift of the ester CH_2CO f proton on added cation concentration (Fig. 4), it was possible to obtain winEQNMR-derived association constants (Table 3).[13] These confirm that the receptor is selective for sodium and lithium cations. Furthermore, when lithium and sodium perchlorate were added to a 1 : 1 mixture of **3** and TBA bromide, it was found that the cation binding behaviour was influenced. In the case of lithium binding, an enhancement both in the induced chemical shift and resulting association constant was observed, indicating that bromide enhances the affinity of **3** for this cation. For sodium, however, the chemical shift change and association constant obtained were reduced in the presence of bromide, indicating that this anion exerts an anti-cooperative effect on cation binding. This is interesting as sodium enhances the binding of bromide (*vide infra*). It is also notable that addition of sodium or lithium cations to a 1 : 1 solution of **3** and TBA chloride did not reveal any cation binding interaction.

The anion binding properties of receptor **3** were probed in acetone-d_6. The addition of TBA anion salts induced downfield shifts in the amide (o) and isophthalyl (p) protons, revealing a 1 : 1 receptor/anion stoichiometry. Treatment of the concentration dependence of these shifts on added anion salt yielded winEQNMR association constant values (Table 4).[13] These show that **3** binds halide anions in the expected selectivity order of $Cl^- > Br^- > I^-$.[8]

In the presence of one equivalent of cation the binding properties of **3** were considerably modulated. The addition of chloride to **3** · M^+ did not initially lead to any significant changes in the ^{1}H NMR spectrum, but after one equivalent of

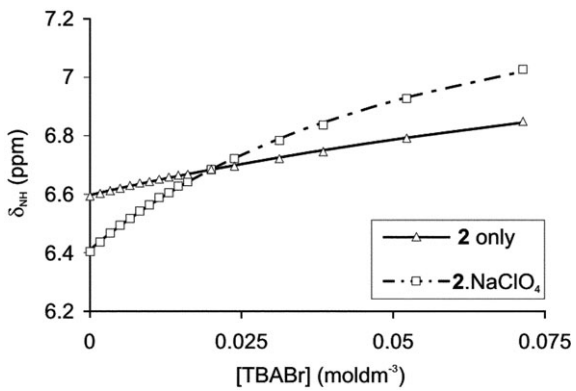


Fig. 3 Dependence of chemical shift of the amide proton signal of **2** on added TBA bromide concentration, in the presence and absence of one equivalent of sodium perchlorate; lines correspond to theoretical 1 : 1 anion binding isotherms. Solvent: acetone-d_6 at 298 K. Endpoint corresponds to ten equivalents of added anion.

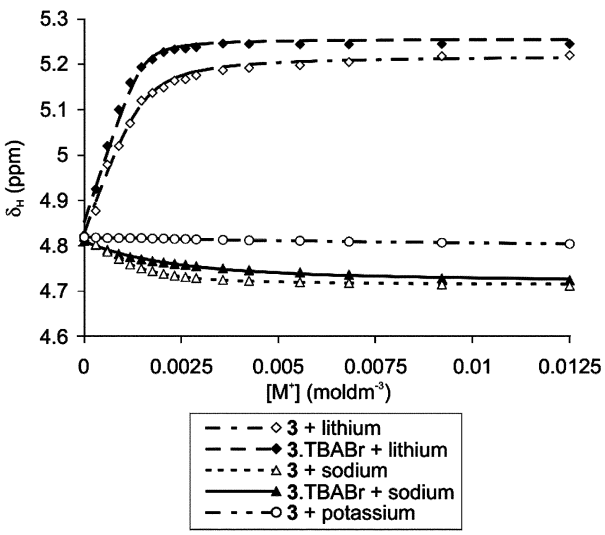


Fig. 4 Dependence of the chemical shift of the ester CH_2CO (f) proton of **3** on added cation concentration, in the presence and absence of one equivalent of TBA bromide guest; lines correspond to theoretical 1 : 1 cation binding isotherms. Solvent: acetone-d_6, 298 K.

Table 3 Cation binding properties of receptor **3**[a]

	3		**3** · TBABr	
	$\Delta\delta_H$/ppm	K_{11}/M^{-1}	$\Delta\delta_H$/ppm	K_{11}/M^{-1}
$LiClO_4$	0.296	2840	0.383	$>10^4$
$NaClO_4$	−0.071	3350	−0.041	740
KPF_6	−0.003	—[b]	−0.007	—[b]
NH_4PF_6	0.004	—[b]	−0.008	—[b]

[a] Solvent: acetone-d_6, 298 K. $\Delta\delta_H$ (ppm) values correspond to the chemical shift change of the ester methylene proton signal (f) induced on addition of one equivalent of cation Association constant errors <10%. [b] No interaction could be inferred.

anion had been added downfield shifts in the amide and isophthalyl protons were observed, consistent with the binding of chloride. This was ascribed to the sequestration of cation by the first equivalent of added anion, followed by unassisted binding of the remainder. Although not accompanied by precipitation in this case, the behaviour is consistent with that observed for receptor **2** in this solvent. Similar behaviour was observed when TBA bromide or iodide were added to 1 : 1 mixtures of **3** and potassium, rubidium or ammonium salts; this is due to ion-pairing rather than sequestration as these cations are not bound by the receptor in the first place.

Conversely, on the addition of TBA bromide and iodide salts to a 1 : 1 mixture of **3** and lithium or sodium cations, significant downfield shifts in the amide and isophthalyl protons o and p were observed (Fig. 5). These were larger than the corresponding changes in chemical shift induced on addition of anion to the free receptors, suggesting an increased strength of interaction. Job Plot analysis indicated a 1 : 1 binding stoichiometry, and by monitoring the dependence of the chemical shift of the amide proton (o) as a function of added anion concentration it was possible to obtain winEQNMR-derived association constant values (Table 4).[13] These anion association constants indicated a cooperative binding effect for lithium and sodium bromide and iodide. Indeed, anion affinity is increased by nearly an order of magnitude.

Discussion

The anion, cation and ion-pair binding observations outlined above demonstrate that both of these ditopic receptors will

Table 4 Anion binding properties of receptor **3**[a]

	TBACl		TBABr		TBAI	
	$\Delta\delta_{NH}$/ ppm	K_{11}/ M^{-1}	$\Delta\delta_{NH}$/ ppm	K_{11}/ M^{-1}	$\Delta\delta_{NH}$/ ppm	K_{11}/ M^{-1}
3	1.135	1550	0.406	250	0.044	45
3 · $LiClO_4$	0.037	—[b]	0.975	2320	0.205	420
3 · $NaClO_4$	0.022	—[b]	0.936	2150	0.150	290
3 · KPF_6	0.007	—[b]	0.192	—[b]	0.032	—[b]

[a] Solvent: acetone-d_6, 298 K. $\Delta\delta_{NH}$ (ppm) values correspond to the chemical shift change of the amide proton signal (o) induced on addition of one equivalent of anion. Association constant errors <10%. [b] No association constant could be determined due to ion-pairing phenomena on addition of first equivalent of TBA anion salt.

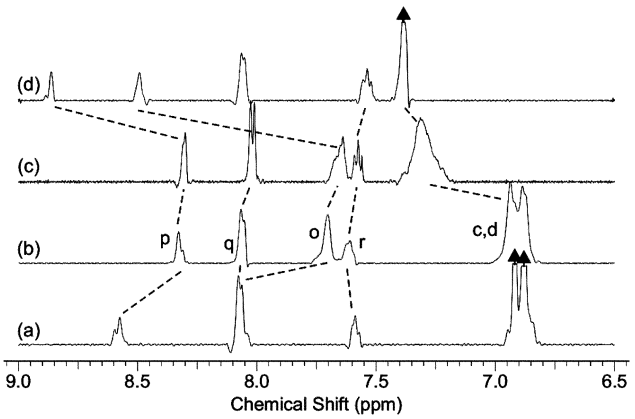


Fig. 5 Perturbations in the aromatic region of the ^{1}H NMR spectrum of **3** on the addition of one equivalent of (a) TBABr, (b) nothing, (c) $NaClO_4$ and (d) NaBr. Solvent: acetone-d_6, 298 K.

bind ion pairs in a cooperative fashion, given the correct conditions. This can be lent credence by a consideration of the results as a function of the potential equilibria that may occur in solution, summarised in Fig. 6.[14] For the case of 'pure' anion binding, it is normally assumed that when the counter-cation is non-coordinating (such as TBA), K_{ip}, K_2 and K_3 are negligible; thus any measurable changes in spectra of the receptor consistent with binding are defined by K_1. The same applies to cation binding in the presence of a non-coordinating anion (K_3).

When both cation and anion are coordinating it is no longer possible to neglect the other equilibria in Fig. 6. Therefore, on addition of for example halide anion to a 1 : 1 mixture of ditopic receptor and metal salt of a non-coordinating anion, the behaviour observed depends on all four of these processes. If the system is an appropriately designed ditopic receptor, then the observed anion association constant, K_{obs}(anion), which is itself a conflation of K_1 and K_2, will be larger than that observed when the counter-cation is non-coordinating, demonstrating that the receptor behaves in a cooperative manner. If the system is not ideally suited to the binding of an ion-pair (K_2), then the competing equilibrium defined by K_{ip} will result in a K_{obs} reduced in comparison to that observed in the absence of a coordinating counter-cation. Should K_{ip} be the dominant contributor, then the changes observed will be consistent primarily with sequestration of the metal cation, followed by binding of the free anion defined by K_1. Needless to say, the solvent is highly influential on which situation dominates.

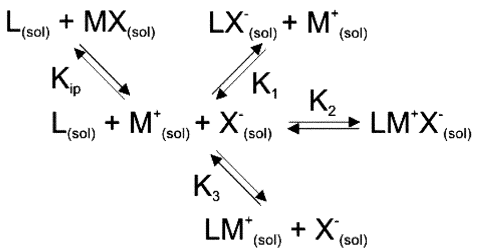


Fig. 6 Summary of potential solution equilibria on binding ion-pair species.

All three of these potential behaviours are observed in the binding properties of **2** and **3**. For **2**, a modest cooperative interaction can be inferred in acetonitrile-d_3 solution from the halide binding properties in the presence and absence of sodium cations, but the association constants observed were very small. Investigations in the less polar solvent acetone-d_6 were not possible due to precipitation problems.

Receptor **3** demonstrated somewhat different binding properties towards ion pairs. For chloride-containing species, anti-cooperative behaviour consistent with strong ion-pairing was observed, as in the case of **2** in acetone-d_6; this was ascribed to ion-sequestration phenomena. For the association of bromide and iodide, however, a definite cooperative effect was seen, indicating a significant contribution of K_2 to the observed anion binding constant. This cooperativity extended to the binding of lithium, but interestingly sodium binding was found to be inhibited by the presence of bromide ion. This latter phenomenon is not easy to rationalise. For the larger alkali metal cation potassium, and ammonium, the behaviour of **3** was decidedly anti-cooperative in nature, such that the presence of these cations inhibited anion binding completely. This is because the receptor does not bind these cations (K_3 tends to zero).

As a result, receptor **3** provides an example of a system wherein the ion-pair cooperativity is highly selective for certain salts, namely the bromide and iodide salts of sodium and lithium, while displaying little or no affinity for other ion pairs. Such a selectivity may be very useful in the design of molecular devices, and suggests a use for ditopic receptors in the fine-tuning of ion-recognition processes. Furthermore, although impossible to compare directly the binding properties of the two receptors detailed here due to the different solvents used to measure their anion association constants, it is nonetheless evident that **3**, wherein the anion and cation binding sites may be considered as being enclosed within the same macrocycle motif, behaves as a superior binder for ion-pairs, being less prone to solvent ion-pairing or precipitation effects. This suggests a macrocyclic effect for ion-pair recognition, which is in turn consistent with the binding of both ions as a single unit, or a contact ion pair.

Conclusions

The two new receptors **2** and **3** demonstrate that the strength and selectivity of ion-pair recognition may be tuned by the appropriate design of cation and anion binding sites within a given motif. In particular, the inclusion of these two sites within a macrocycle appears to support a contact ion-pair recognition process which maximises the electrostatic forces between cation and anion within the receptor · MX complex, and therefore the cooperativity of interaction.

Experimental

Materials and instrumentation

All commercial grade chemicals were used without further purification. TBA anion salts, as well as hexafluorophosphate and perchlorate cation salts were stored prior to use under vacuum in a desiccator containing phosphorus pentaoxide and self-indicating silica. Elemental analyses were carried out by the service at the Inorganic Chemistry Laboratory, University of Oxford. Mass spectra were obtained on a Micromass LCT (ESMS) instrument. NMR spectra were recorded on a Varian Mercury 300, Oxford Instruments Venus 300, or Varian Unity Plus 500 spectrometer, with the solvent as serving as the lock and internal reference. Coupling constants (J values) quoted below are in Hertz.

Syntheses

Receptor 2. A solution of compound **5** (0.43 g, 0.42 mmol), anhydrous K_2CO_3 (0.29 g, 2.1 mmol) and ethyl 2-bromoacetate (0.28 mL, 2.52 mmol) was heated under reflux in acetone (10 mL) for 4 days, under a nitrogen atmosphere. The reaction mixture was then allowed to cool to room temperature, filtered, and the precipitate washed with copious CH_2Cl_2. The combined filtrate was subsequently concentrated *in vacuo*, and the resulting off-white crude product purified by silica gel chromatography (CH_2Cl_2–MeOH 95 : 5 v/v) to give **2** as a white solid (0.40 g, 78%) (Found: C, 70.5; H, 8.6; N, 2.2. $C_{72}H_{106}N_2O_{12} \cdot \frac{1}{2}CH_2Cl_2$ requires: C, 70.6; H, 8.7; N, 2.3%); δ_H (300 MHz; $CDCl_3$) 0.87 (6H, t, ^3J = 6.7, H_r), 1.04 (18H, s, $H_{a/b}$), 1.05 (18H, s, $H_{a/b}$), 1.27 (14H, m, H_h, H_p and H_q), 1.61 (4H, m, H_o), 2.14 (4H, t, ^3J = 7.6, H_n), 3.15 (4H, d, ^2J = 12.9, $H_{e,out}$), 3.44 (4H, t, ^3J = 4.7, H_k), 3.56 (4H, t, ^3J = 4.7, H_l), 3.92 (4H, t, ^3J = 5.3, H_j), 4.20 (8H, m, H_i and H_g), 4.59 (4H, d, ^2J = 12.9, $H_{e,in}$), 4.68 (4H, s, H_f), 6.29 (2H, br, H_m), 6.75 (4H, s, $H_{c/d}$), 6.79 (4H, s, $H_{c/d}$); δ_C (75.5 MHz; $CDCl_3$) 13.97, 14.23, 22.43, 25.45, 31.33, 31.41, 31.49, 31.51, 33.85, 36.61, 39.33, 60.62, 69.84, 70.46, 71.30, 72.99, 76.63, 125.12, 125.33, 133.23, 133.67, 138.19, 145.24, 152.49, 153.58, 170.37, 173.33; m/z (ES+): 1191.78 ($M + H^+$), 1213.76 ($M + Na^+$).

Receptor 3. Compound **9** (0.20 g, 0.19 mmol), ethyl 2-bromoacetate (0.09 g, 0.5 mmol) and K_2CO_3 (0.06 g, 0.5 mmol) were suspended in CH_3CN (10 mL), and the mixture heated under reflux under a nitrogen atmosphere for 18 h. The reaction mixture was allowed to cool, then filtered. The precipitate was washed with copious CH_2Cl_2, and the combined filtrate was reduced *in vacuo*. The resulting crude product was purified by silica gel chromatography ($CHCl_3$–MeOH 90 : 10) to give the white solid **3** (0.12 g, 55%) (Found: C, 66.0; H, 7.5; N, 1.9. $C_{72}H_{96}N_2O_{14} \cdot CHCl_3$ requires: C, 65.8; H, 7.3; N, 2.1%); δ_H (300 MHz, $CDCl_3$) 0.90 (18H, s, $H_{a/b}$), 1.09 (18H, s, $H_{a/b}$), 1.15 (6H, t, ^3J = 7.5, H_h), 3.06 (4H, d, ^2J = 12.9, $H_{e,out}$), 3.58 (16H, m, H_k, H_l, H_m and H_n), 4.02 (12H, m, H_i, H_j and H_g), 4.43 (4H, d, ^2J = 12.9, $H_{e,in}$), 4.58 (4H, s, H_f), 6.59 (4H, s), 6.81 (4H, s, $H_{c/d}$), 7.47 (3H, m, H_o and H_r), 8.02 (2H, d, ^3J = 7.9, H_q), 8.13 (1H, s, H_p); δ_C (75.5 MHz; $CDCl_3$) 14.12, 30.99, 31.23, 31.49, 31.63, 33.75, 40.04, 60.77, 70.16, 70.28, 70.52, 72.44, 124.08, 125.11, 125.24, 125.38, 131.17, 131.23, 132.73, 134.06, 134.17, 134.47, 143.47, 145.06, 166.90, 189.44, 192.31. m/z (ES+) 1235.63 ($M + Na^+$).

Calixarene bishexylamide 5. A solution of compound **4** (0.5 g, 0.61 mmol), and NEt_3 (0.34 mL, 2.43 mmol) in dry CH_2Cl_2 (50 mL) was cooled to 0 °C, then a solution of hexanoyl

chloride (0.26 mL, 1.83 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise, under a nitrogen atmosphere. Once addition was complete, the reaction mixture was allowed to warm to room temperature, and stirred for a further 16 h under an atmosphere of nitrogen. The reaction mixture was then washed consecutively with 1 M $HCl_{(aq)}$ (2 × 100 mL), 1 M $NaOH_{(aq)}$ (2 × 100 mL), H_2O (100 mL) and saturated $NaCl_{(aq)}$ (100 mL). The organic phase was subsequently dried over $MgSO_4$, filtered, and the solution concentrated *in vacuo* to afford compound **5** as a white solid (0.52 g, 84%); δ_H (300 MHz, $CDCl_3$) 0.83 (6H, t, ^3J = 7.1, CH_2CH_3), 1.10 (18H, s, *t*-Bu), 1.17 (8H, m, $CH_2CH_2CH_3$), 1.22 (18H, s, *t*-Bu), 1.43 (4H, m, $NCOCH_2CH_2$), 1.84 (4H, t, ^3J = 7.0, $NCOCH_2$), 3.33 (4H, d, ^2J = 12.9, $ArCH_{in}H_{out}Ar$), 3.60 (4H, t, ^3J = 4.1, CH_2CH_2N), 3.73 (4H, m, CH_2N), 3.99 (4H, m, CH_2CH_2OAr), 4.20 (4H, m, CH_2OAr), 4.38 (4H, d, ^2J = 12.9, $ArCH_{in}H_{out}Ar$), 6.97 (4H, s, Ar*H*), 7.01 (4H, s, Ar*H*), 7.24 (2H, br, N*H*), 8.38 (2H, s, O*H*); δ_C (75.5 MHz; $CDCl_3$) 14.01, 22.44, 25.51, 31.15, 31.28, 31.53, 31.97, 33.85, 34.12, 36.09, 39.53, 69.80, 70.09, 75.14, 76.22, 125.39, 125.88, 128.41, 133.31, 142.64, 147.51, 149.20, 149.80, 173.97; *m*/*z* (ES+): 1019.71 ($M + H^+$), 1041.68 ($M + Na^+$).

Calixarene diphthalimide 7. *para-Tert*-butylcalix[4]arene (4.70 g, 7.24 mmol) and K_2CO_3 (2.10 g, 15.2 mmol) were suspended in dry CH_3CN (200 mL), and stirred under a nitrogen atmosphere for 30 min. Compound **6** (7.85 g, 18.1 mmol) was then added, and the resulting mixture was heated under reflux under a nitrogen atmosphere for 4 days. After this time, the suspension was allowed to cool, and the solvent carefully removed *in vacuo* to give a sticky solid material which was triturated with 1 M $HCl_{(aq)}$ (200 mL). The resulting suspension was extracted with CH_2Cl_2 (3 × 100 mL), and the organic extracts combined, washed with H_2O (2 × 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel chromatography ($CHCl_3$–acetone 95 : 5) gave the white solid **7** (4.97 g, 60%); δ_H (300 MHz, $CDCl_3$) 0.93 (18H, s, *t*-Bu), 1.26 (18H, s, *t*-Bu), 3.24 (4H, d, ^2J = 13.2, $ArCH_{in}H_{out}Ar$), 3.72 (12H, m, $ArOCH_2CH_2OCH_2CH_2O$), 3.85 (4H, t, ^3J = 6.6, $ArOCH_2$), 3.89 (4H, t, ^3J = 4.6, CH_2CH_2N), 4.07 (4H, t, ^3J = 4.6, CH_2N), 4.31 (4H, d, ^2J = 13.2, $ArCH_{in}H_{out}Ar$), 6.75 (4H, s, calixAr*H*), 7.07 (4H, s, calixAr*H*), 7.18 (2H, s, O*H*), 7.67 (2H, dd, ^3J = 5.5, ^4J = 3.0, Phth*H*), 7.80 (2H, dd, ^3J = 5.5, ^4J = 3.0, Phth*H*); *m*/*z* (ES+): 1193.61 ($M + Na^+$).

Calixarene bisamine 8. Compound **7** (3.40 g, 2.9 mmol) was suspended in EtOH (70 mL), and hydrazine monohydrate (3 mL, excess) added. This suspension was then heated under reflux for 18 h, during which time the white suspension was seen to dissolve. The reaction mixture was then allowed to cool to room temperature, then added to H_2O (200 mL) to give a white suspension which was extracted with EtOAc (3 × 50 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, then concentrated *in vacuo* to give the white solid **8** (2.51 g, 95%); δ_H (300 MHz, $CDCl_3$) 0.78 (18H, s, *t*-Bu), 1.23 (18H, s, *t*-Bu), 3.06 (4H, m, CH_2NH_2), 3.24 (4H, d, ^2J = 13.1, $ArCH_{in}H_{out}Ar$), 3.76 (12H, m, $OCH_2CH_2OCH_2CH_2N$), 3.85 (4H, m, $ArOCH_2CH_2$), 4.12 (4H, m, $ArOCH_2$), 4.26 (4H, d, ^2J = 13.1, $ArCH_{in}H_{out}Ar$), 6.58 (s, 4H, Ar*H*), 7.02 (4H, s, Ar*H*); *m*/*z* (ES+): 911.61 ($M + H^+$), 937.58 ($M + Na^+$).

Calixarene macrobicycle 9. Separate solutions of **8** (1.0 g, 1.1 mmol) in dry CH_2Cl_2 (100 mL) and isophthaloyl chloride (0.22 g, 1.1 mmol) in dry CH_2Cl_2 (100 mL) were added dropwise, simultaneously, to a stirred solution of NEt_3 (1 mL, excess) in dry CH_2Cl_2 (800 mL) over the period of 1 h. The reaction mixture was then left to stir for 18 h before being reduced *in vacuo* to approximately 150 mL in volume. This solution was washed with 1 M $HCl_{(aq)}$ (150 mL), H_2O (100 mL), 1 M $NaOH_{(aq)}$ (100 mL) and saturated $NaCl_{(aq)}$ (100 mL), then dried over $MgSO_4$ and reduced *in vacuo*. Purification by silica gel chromatography (EtOAc–acetone 95 : 5) gave the white solid **9** (0.79 g, 69%) (Found: C, 71.6; H, 7.9; N, 2.5. $C_{64}H_{84}N_2O_{10} \cdot 2H_2O$ requires: C, 71.4; H, 8.2; N, 2.6%); δ_H (300 MHz; $CDCl_3$) 0.89 (18H, s, *t*-Bu), 1.30 (18H, s, *t*-Bu), 3.25 (4H, d, ^2J = 13.1, $ArCH_{in}H_{out}Ar$), 3.69 (20H, m, $CH_2OCH_2CH_2OCH_2CH_2N$), 4.03 (4H, m, $ArOCH_2$), 4.28 (4H, d, ^2J = 13.1, $ArCH_{in}H_{out}Ar$), 6.70 (4H, s, calixAr*H*), 7.05 (4H, s, calixAr*H*), 7.58 (1H, t, ^3J = 7.6, Ar*H*), 7.69 (2H, br, N*H*), 8.11 (2H, d, ^3J = 7.6, Ar*H*), 8.39 (1H, s, Ar*H*). *m*/*z* (ES+): 1041.63 ($M + H^+$), 1063.60 ($M + Na^+$).

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