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Positive and negative allosteric effects of thiacalix[4]arene-based receptors having urea and crown-ether moieties†

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Heteroditopic receptors (**4**$_{a-e}$) based on a thiacalix[4]arene in the 1,3-*alternate* conformation, which have two urea moieties linking various phenyl groups substituted with either electron-donating or -withdrawing groups at their *m*-, or *p*-positions with a crown-ether moiety at the opposite side of the thiacalix[4]arene cavity, have been synthesized. The two examples with *p*-CH_3– (**4**$_b$) and *p*-NO_2-substituted (**4**$_e$) phenyl groups have been characterized by X-ray crystallography. The binding properties of receptor **4**$_e$ were investigated by means of ^{1}H NMR spectroscopic and absorption titration experiments in $CHCl_3$–DMSO (10 : 1, v/v) solution in the presence of K^+ ions and various anions. Interestingly, it was found that receptor **4**$_e$, which possesses two *p*-nitrophenyl ureido moieties, can complex most efficiently in the urea cavity or the crown-ether moiety; and the plausible allosteric effect of receptor **4**$_e$ was also studied.

Introduction

The use of calix[*n*]arenes[1] as building blocks for receptors capable of the highly selective recognition of cations, anions or neutral molecules has received considerable attention in the field of supramolecular chemistry. Among the various kinds of calix[*n*]arenes available, thiacalix[4]arenes[2,3] are proving to be competent scaffolds and are finding wide use, for example as chemosensors, as well as in catalysis because of their favourable conformational properties, easy functionalization and emerging metal coordination chemistry. Several kinds of systems based on thiacalix[4]arenes are suitable for allosteric regulation[4] of host–guest interactions with metal cations, and these contribute greatly to organic processes in biological systems. Anions also play an important role in biological processes, and are closely related with biological systems such as DNA and enzyme substrates. The development and the investigation of anion selective sensors[5] have attracted considerable interest. However, it is more difficult to accomplish compared with metal cation sensors because anions can possess structures of different shapes,[6] typically spherical (F^-, Cl^-, Br^-, I^-), Y-shaped (AcO^-, $PhCOO^-$) or tetrahedral ($H_2PO_4^-$). In recent years, anion receptors based on calix[*n*]arenes have become an active research topic. Calix[*n*]arene urea derivatives are efficient for anion recognition given the hydrogen-bonding interaction between anions and N–H protons which can occur.

Colorimetric chemosensors[7,8] have also attracted attention due to some desirable features such as easy detection by the naked eye, construction of simple, low-cost devices and so on. Many colorimetric anion receptors containing a variety of chromogenic signaling units such as indole, imidazolium, benzenediimide, 4-nitrophenylazo, diazo and anthraquinone groups have been developed. Furthermore, numerous colorimetric anion sensors utilizing a variety of structural scaffolds, which contain urea groups, have been investigated and proved to be efficient naked-eye detectors for various anions. However, there are a few reports on the development of colorimetric chemosensors based calix[4]arene type scaffolds.[8l,p]

Lhoták[9] and co-workers have reported anion receptors based on either an upper rim substituted calix[4]arene or thiacalix[4]-arene, which contains two *p*-nitrophenyl or *p*-tolyl ureido moieties.[9a–c,h] These anion receptors exhibited effective recognition abilities towards selected anions in common organic solvents. Moreover, Kumar[10] and co-workers reported an anion receptor bearing a calix[4]arene in the 1,3-*alternate* conformation, which contains two *p*-nitrophenyl moieties.[10g] This compound exhibited strong binding and good selectivity for Cl^- ion due to the formation of

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† Electronic supplementary information (ESI) available: Details of the ^{1}H/^{13}C NMR spectra, ^{1}H NMR spectroscopic and UV-vis titration experimental data, the Bensei–Hilderbrand plot and Job's plot. CCDC 1026081 and 1026090. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra15905e

strong hydrogen bonds between the Cl^- ion and N–H protons in common organic solvents. However, investigations concerning the appearance of an allosteric effect in analogues based on the interaction of thiacalix[4]arene and alkali metal cations and anions has not yet been reported.

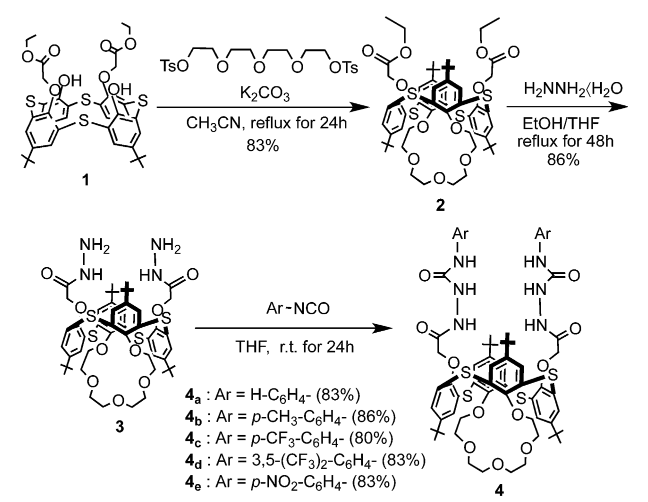
Herein, we have independently designed a heterodimeric system[11] based on a thiacalix[4]arene having two different side arms, *viz* two ureas moieties linking various phenyl groups bearing either electron-donating or -withdrawing groups at their *m*-, or *p*-positions. The calixarene also has a crown ether moiety at the opposite side of the thiacalix[4]arene cavity. We herein put forward the hypothesis (and then demonstrate) that the heterodimeric system, which is controlled by the complexation of the opposing side arms with anions and K^+ ion, exhibits effective positive and negative allosteric effects.

Results and discussions

Synthesis

The *O*-alkylation of *distal*-**1** was carried out with 1.5 equivalents of tetraethyleneglycol ditosylate in the presence of an equivalent of K_2CO_3 according to the reported procedure, and afforded the desired 1,3-*alternate*-**2** in 83% yield.[12] The hydrazinolysis of 1,3-*alternate*-**2** was carried out with a large excess of hydrazine hydrate, and afforded the desired 1,3-*alternate*-**3** in 86% yield. The condensation of 1,3-*alternate*-**3** with 2.2 equivalents of the appropriate isocyanate in THF furnished the receptors $\mathbf{4_{a-e}}$ in good to excellent yields (Scheme 1). In general, the ^1H NMR spectrum of receptors $\mathbf{4_{a-e}}$ in $CDCl_3$–DMSO (10 : 1, v/v) exhibited the characteristics of a 1,3-*alternate* conformation such as two singlets (18H each) for the *tert*-butyl protons, one singlet (4H) for OCH_2CO protons, two singlets (4H each) for aromatic protons and two singlets (2H each) for four urea NH protons.

The molecular structures of receptors $\mathbf{4_b}$ and $\mathbf{4_e}$ were also verified by X-ray crystallographic analysis (Fig. 1 and S15 and S16†). Receptors $\mathbf{4_b}$ and $\mathbf{4_e}$ were recrystallized from a mixture of $CHCl_3$–CH_3CN (1 : 1, v/v) by slow evaporation. These results indicate that receptors $\mathbf{4_b}$ and $\mathbf{4_e}$ adopt the 1,3-*alternate*



Scheme 1 Synthesis of receptors 1,3-*alternate*-$\mathbf{4_{a-e}}$.

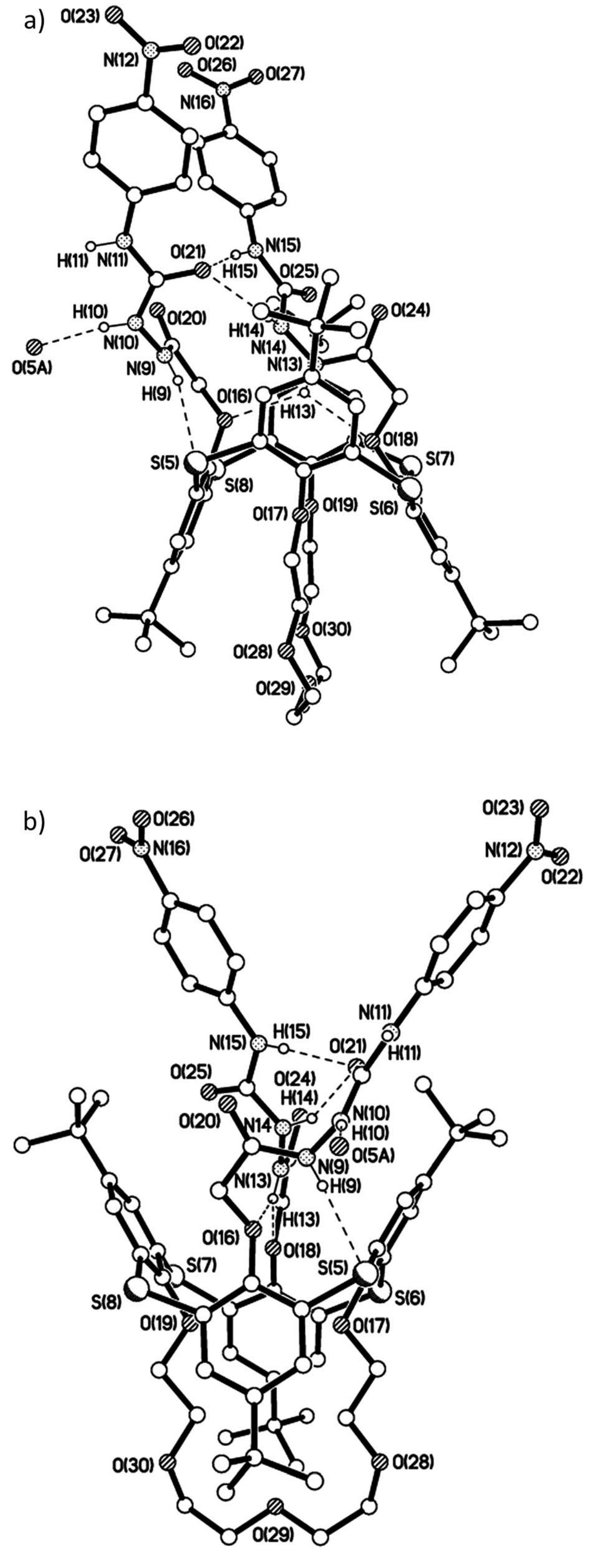


Fig. 1 X-ray crystal structure of receptor $\mathbf{4_e}$. H-bonds shown as dashed lines. One of two similar molecules in the asymmetric unit is shown in two orientations rotated by approx. 90°. H atoms not involved in H-bonding, minor disorder components, and chloroform molecules of crystallization are omitted for clarity.

Table 1 Association constants of receptor 4_{a-e} with Cl^- ions[a,b]

Host	4_a	4_b	4_c	4_d	4_e
R	H	p-CH_3	p-CF_3	3,5-$(CF_3)_2$	p-NO_2
K_a [M^{-1}]	6816 ± 545	3021 ± 242	12 813 ± 1025	6945 ± 625	34 411 ± 2400

[a] Measured in $CDCl_3$–DMSO (10 : 1, v/v) at 298 K by the ^1H NMR titration method using the chemical-shift change of the NH_a proton (Fig. S17–S22); host concentration was 4.0×10^{-3} M. [b] Guests used: Bu_4NCl.

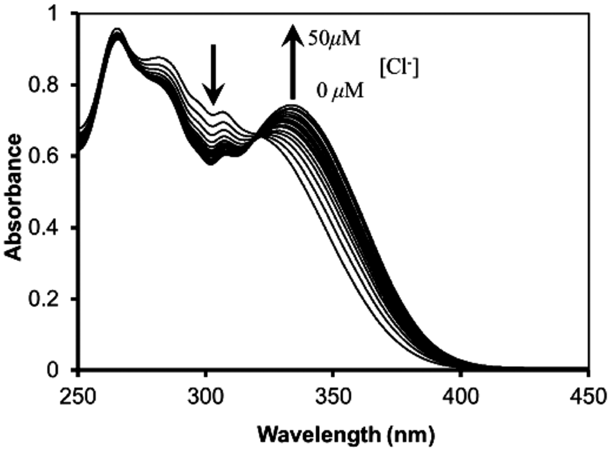


Fig. 2 UV-vis absorption spectra of receptor 4_e (2.5 μM) upon the addition of Bu_4NCl (0–50 μM) in CH_2Cl_2–DMSO (10 : 1, v/v).

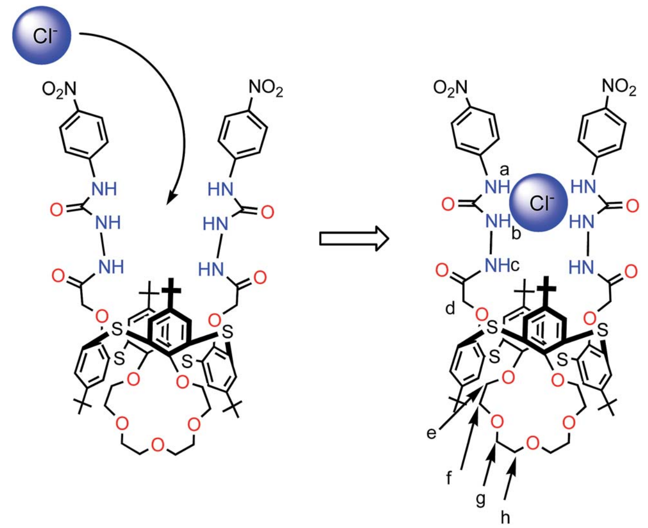


Fig. 3 Binding mode of receptor 4_e upon complexation with Cl^- ions.

conformation in the solid state. There are two thiacalixarenes, one water molecule and three chloroform molecules in the asymmetric unit. Interestingly, it was found that two urea groups approach each other and are oriented in parallel due to the existence of dual intramolecular hydrogen bonding (in case of receptor 4_e, for the molecule shown: N(14)–H(14)⋯O(21) 2.37(2); N(15)–H(15)⋯O(21) 2.05(2) Å; for the second molecule: N(2)–H(2)⋯O(10) 2.37, N(3)–H(3)⋯O(10) 1.94(2) Å) (Fig. 1 and S16†). Moreover, the thiacalix[4]-arene-monocrown-5 has a three-dimentional cavity and is large enough to accommodate the metal cation. The association constants (K_a values) between the receptors 4_{a-e} and Cl^- ion were determined by ^1H NMR spectroscopic titration experiments (Table 1). These results suggest that the association constants depend on the electron-donating/withdrawing groups located at the m-, or p-positions. In the presence of the electron-withdrawing groups, such as CF_3 (receptors 4_c and 4_d) and NO_2 (receptor 4_e), the K_a values were greater than that for the unsubstituted receptor (receptor 4_a). In contrast, in the case of receptor 4_b, possessing the electron-donating Me group, there was a general decrease in the K_a value upon complexation with Cl^- ion in comparison with the unsubstituted receptor 4_a. Therefore, the introduction of electron-withdrawing groups at the m-, or p-positions appears to increase the acidity of the urea protons, and hence enhance the anion-binding ability through hydrogen-bonding interactions. The K_a value of receptor 4_e with the electron-withdrawing NO_2 group at the p-position was the best out of all the K_a values measured for receptors 4_{a-e} and Cl^- ion. Interestingly, it was found that the K_a value of receptor 4_c with the electron-withdrawing CF_3 group at the p-position was greater than that of receptor 4_d with the electron-withdrawing CF_3 group at the m-position. This result indicates that electron-withdrawing groups located at the p-position can significantly influence the acidity of the urea protons by conjugating with the phenyl groups. From the above, it is clear that receptor 4_e with the electron-withdrawing NO_2 group at the p-position has the most effective recognition ability toward selected anions. Given this, further complexation studies of receptor 4_e (2.5 μM) exhibits an absorption band at 310 nm in the UV spectrum in the absence of anions. Upon addition of Cl^- ion (0–50 μM) to the solution of receptor 4_e, Fig. 2 reveals a gradual decrease in the absorption of the band at 310 nm with a simultaneous increase in the absorption at 340 nm. Meanwhile, a clear isosbestic point was observed at 322 nm for the receptor 4_e. A Job's plot binding between the receptor 4_e and Cl^- ion reveals a 1 : 1 stoichiometry (Fig. S25†), whilst the association constant (K_a value) for the complexation with Cl^- ion by receptor 4_e was determined to be 34 152 M^{-1} by UV-vis titration experiments in $CHCl_3$–DMSO (10 : 1, v/v) (Fig. S24, S27–S31†). Moreover, the concentration dependence of the ^1H NMR chemical shifts of the ureido protons in receptor 4_e was not observed (Fig. S23†). This result suggests that receptor 4_e has a strong intramolecular hydrogen bond between the two ureas linking the p-nitrophenyl moieties. These results strongly suggested that Cl^- ion recognition by receptor 4_e was *via* a hydrogen-bonding interaction between the Cl^- ion and N–H protons as

Table 2 Association constants of receptor $\mathbf{4_e}$ with various anions[a,b]

Anion	F^-	Cl^-	Br^-	I^-	AcO^-	$PhCO_2^-$	$H_2PO_4^-$
Shape	Spherical	Spherical	Spherical	Spherical	Y-shape	Y-shape	Tetrahedral
K_a [M^{-1}]	128 775 ± 10 302	34 152 ± 2732	7296 ± 584	4540 ± 363	107 298 ± 8584	106 743 ± 8539	108 687 ± 8695

[a] Measured in CH_2Cl_2–DMSO (10 : 1, v/v) at 298 K by UV-vis titration method (Fig. 2, 4, S24 and S27–S31); host concentration was 2.5 μM. [b] Guests used: tetrabutylammonium salt.

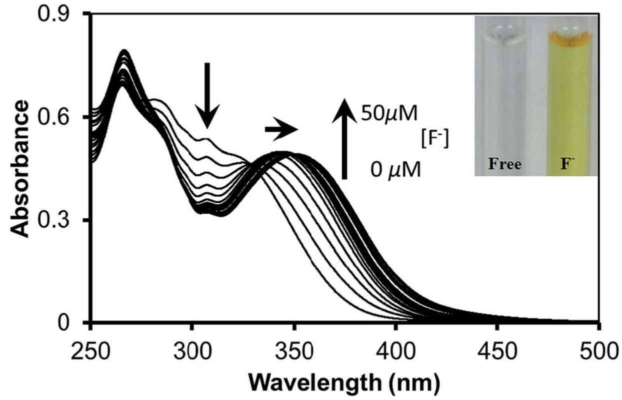


Fig. 4 UV-vis absorption spectra of receptor $\mathbf{4_e}$ (2.5 μM) upon the addition of Bu_4NF (0–50 μM) in CH_2Cl_2–DMSO (10 : 1, v/v).

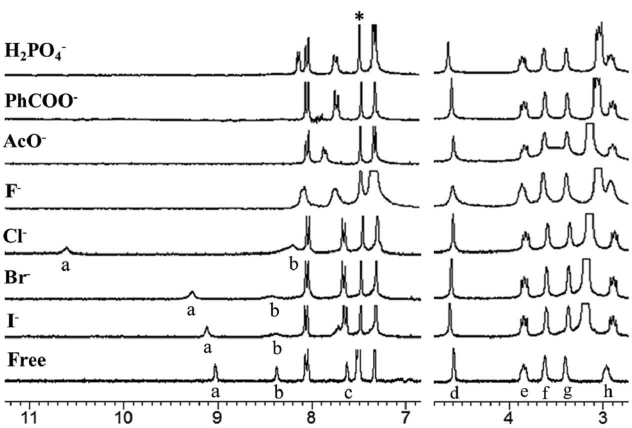


Fig. 5 Partial ^{1}H NMR spectra of receptor $\mathbf{4_e}$/guest ($H/G = 1:1$); free receptor $\mathbf{4_e}$ and in the presence of 1 equiv. of Bu_4NX (X = F, Cl, Br, I, AcO, PhCOO, H_2PO_4). Host concentration was 2.5 μM. Solvent: $CDCl_3$–DMSO (10 : 1, v/v). 300 MHz at 298 K. *Denotes the solvent peak.

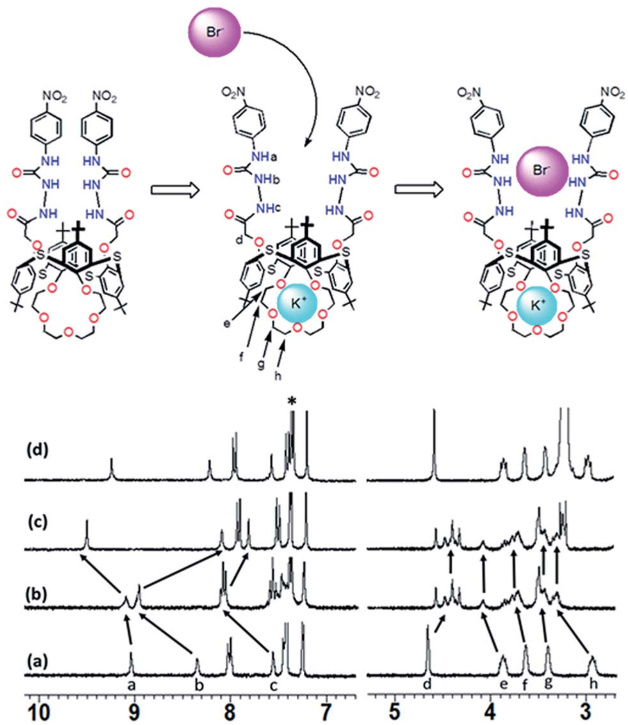


Fig. 6 Proposed positive allosteric behaviour of receptor $\mathbf{4_e}$ with Br^- and K^+ ions. Partial ^{1}H NMR spectra of $\mathbf{4_e}$/guest ($H/G = 1:1$); (a) free $\mathbf{4_e}$; (b) $\mathbf{4_e}\supset KSO_3CF_3$; (c) $Bu_4NBr\subset[\mathbf{4e}\supset K^+]$; (d) $\mathbf{4_e}\supset Bu_4NBr$. Solvent: $CDCl_3$–DMSO (10 : 1, v/v). 300 MHz at 298 K. *Denotes the solvent peak.

shown in Fig. 3. Similarly, the UV-vis titration experiments of receptor $\mathbf{4_e}$ with other various anions besides Cl^- ion were carried out, and the K_a values are summarized in Table 2. As a result, it was found that receptor $\mathbf{4_e}$ exhibited high selectivity towards F^- ion amongst all of the anions tested, and was capable of complexing with all of the anions tested, irrespective of their shape. Interestingly, the color of the receptor $\mathbf{4_e}$ solution changed from colorless to dark yellow upon addition of F^- ion (5 equivalents), and this could be easily observed by the naked eye. Upon the addition of F^- ions (0–50 μM) to the solution of the receptor $\mathbf{4_e}$, the absorption peak at 342 nm gradually moved to a longer wavelength, finally reaching a maximum value at 360 nm (Fig. 4 and S26†). This result suggests that the quinoid structure was formed by the deprotonation of urea NH groups in the *p*-nitrophenyl ureido moiety. Moreover, the addition of F^-, AcO^-, $PhCOO^-$ or $H_2PO_4^-$ (1 equivalent) to solutions of receptor $\mathbf{4_e}$ in $CHCl_3$–DMSO (10 : 1, v/v) during the ^{1}H NMR titration experiments resulted in the disappearance of the urea proton signals, NH_a and NH_b (Fig. 5). These results indicate that strong interactions between these anions and the urea NH groups in the receptor $\mathbf{4_e}$ occur and that the kinetics of these anion exchanges is on the NMR time scale. On the other hand, ^{1}H NMR spectroscopic and UV-vis titration experiments of receptor $\mathbf{4_e}$ with K^+ ion at the crown-ether moiety were also carried out (Fig. S32 and S33†). When only K^+ ion (1 equivalent) were added, not only the downfield shift of the crown-ether bridge protons was observed, but also all the NH protons in ^{1}H NMR titration experiments (Fig. 6b and 7b). It was found that a Job's plot binding between

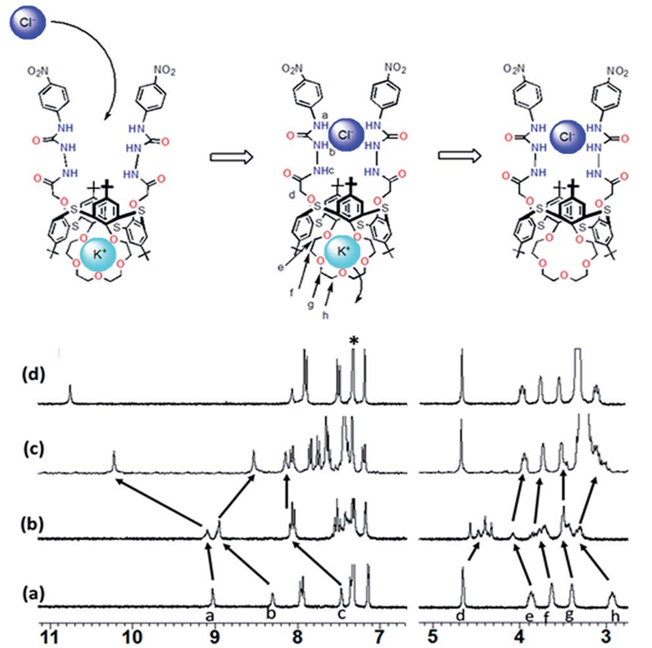


Fig. 7 Proposed negative allosteric behaviour of 4_e with Cl^- and K^+ ions. Partial ^1H NMR spectra of 4_e/guest ($H/G = 1:1$); (a) free 4_e; (b) $4_e \supset KSO_3CF_3$; (c) $Bu_4NCl \subset [4_e \supset K^+]$; (d) $4_e \supset Bu_4NCl$. Solvent: $CDCl_3$–DMSO (10 : 1, v/v). 300 MHz at 298 K. *Denotes the solvent peak.

receptor $\mathbf{4_e}$ and K^+ ion exhibited a 1 : 1 stoichiometry and that the K_a value for the complexation with K^+ ion was determined to be 28 536 (±1998) M^{-1} by UV-vis titration experiments in CH_2Cl_2–DMSO (10 : 1, v/v) (Fig. S34 and S35†). These results suggest that the crown-5 ring of receptor $\mathbf{4_e}$ binds K^+ ion. To seek more detailed information about the presence of an effective positive or negative allosteric effect between receptor $\mathbf{4_e}\cdot K^+$ and Br^- or Cl^- ions, ^1H NMR spectroscopic and UV-vis titration experiments in $CHCl_3$–DMSO (10 : 1, v/v) (Fig. S36†) were carried. Fig. 6 reveals that when Br^- ion were added to the solution of $[\mathbf{4_e} \supset KSO_3CF_3]$ (Fig. 6c), the addition induces a downfield shift of 0.42 ppm ($\delta = 9.09$ to 9.51 ppm) for the NH_a protons, and upfield shifts of 0.85 ppm ($\delta = 8.95$ to 8.10 ppm) for the NH_b protons and of 0.29 ppm ($\delta = 8.10$ to 7.81 ppm) for the NH_c protons, while the chemical shifts for the crown-ether bridge protons did not change. These results suggested the formation of a heteroditopic dinuclear complex of the type $Br^- \subset [\mathbf{4_e} \supset K^+]$ (Fig. 6c), and we propose a positive allosteric effect of receptor $\mathbf{4_e}$ towards Br^- ions in the presence of K^+ ion by an ion-pair electrostatic interaction and a conformational change of the flexible thiacalix[4]arene cavity as shown in Fig. 6. On the other hand, Fig. 7 shows that when Cl^- ions were added to the solution of $[\mathbf{4_e} \supset KSO_3CF_3]$ (Fig. 7c), this addition induces a downfield shift of 1.11 ppm ($\delta = 9.09$ to 10.2 ppm) for the NH_a protons and 0.04 ppm ($\delta = 8.10$ to 8.14 ppm) for the NH_c protons, and an upfield shift of 0.37 ppm ($\delta = 8.95$ to 8.58 ppm) for the NH_b protons, together with upfield shifts for the crown-ether bridge protons. Interestingly, when Cl^- ions were added to the solution of $[\mathbf{4_e} \supset KSO_3CF_3]$ (Fig. 7c), the chemical shifts for the crown-ether bridge protons most closely matched the chemical shifts for the free crown-ether bridge protons (Fig. 7c and d). These results suggested that the two urea groups in two *p*-nitrophenyl ureido moieties of receptor $\mathbf{4_e}\cdot K^+$ bind the Cl^- ion by an ion-pair electrostatic interaction and a conformational change of the flexible thiacalix[4]arene cavity. This induces the decomplexation of the K^+ ion from the crown-5 ring of receptor $\mathbf{4_e}$ because the Cl^- ion has a smaller ionic radius and therefore an increase in basicity in comparison with the Br^- ion, and a negative allosteric effect of receptor $\mathbf{4_e}$ to Cl^- ion in the presence of K^+ ion as shown in Fig. 7 is proposed.

Conclusion

In summary, a new family of heteroditopic receptors ($\mathbf{4_{a-e}}$) based on a thiacalix[4]arene in the 1,3-*alternate* conformation, which has two ureas moieties bearing various phenyl groups substituted with either electron-donating or -withdrawing groups at their *m*-, or *p*-positions, as well as a crown-ether moiety at the opposite side of thiacalix[4]arene cavity, has been synthesized. By using ^1H NMR spectroscopic and UV-vis titration experiments, receptor $\mathbf{4_e}$ possessing an electron-withdrawing NO_2 group at the *p*-position has the most effective recognition ability towards the selected anions. The binding of K^+ ions and various anions at the crown-5 ring moiety and the two urea NH groups in two *p*-nitrophenyl ureido moieties, respectively, was investigated. The results indicated the complexation mode, and it was found that receptor $\mathbf{4_e}$ was able to bind all of the anions tested, irrespective of their shape. Receptor $\mathbf{4_e}$ exhibited highest selectivity towards F^- ion amongst all of the anions tested and indicated that this receptor might be a promising candidate as a colorimetric chemosensor. The appearance of positive and negative allosteric effects in receptor $\mathbf{4_e}$ was also investigated by ^1H NMR and UV-vis titration experiments. Interestingly, the formation of a heteroditopic dinuclear complex of receptor $\mathbf{4_e}$ with Br^- and K^+ ions by a positive allosteric effect could be observed. On the other hand, the fact that two urea NH groups in two *p*-nitrophenyl ureido moieties of receptor $\mathbf{4_e}\cdot K^+$ bind the Cl^- ion, which then induces the decomplexation of the K^+ ion from the crown-5 ring, is indicative of a negative allosteric effect.

Experimental section

General

All melting points were determined with Yanagimoto MP-S1. ^1H-NMR spectra were determined at 300 MHz with a Nippon Denshi JEOL FT-300 NMR spectrometer with $SiMe_4$ as an internal reference; *J*-values are given in Hz. UV spectra were measured by a Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at an ionization energy of 70 eV using a direct inlet system through GLC. Elemental analyses were performed by Yanaco MT-5.

Materials

Unless otherwise stated, all other reagents used were purchased from commercial sources and used without further purification.

Compounds **1**[13] and **2**[12] were prepared following the reported procedures.

Synthesis of compound 3

Compound **2** (1.0 g, 0.95 mmol) was put into a round-bottom flask and ethanol (120 mL), THF (120 mL) and hydrazine hydrate (14 mL, large excess) were added and refluxed for 48 h. After cooling, the solvents and excess hydrazine were removed under reduced pressure to give the crude product as a white solid. The residue was triturated sequentially with water and methanol and the product collected by filtration. Compound **3** was obtained 0.84 g (86%) as a white solid. M.p. 216–218 °C. IR: ν_{max} (KBr)/cm^{-1}: 3421, 2961, 1670, 1438, 1263, 1091, 1019 and 801. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (18H, s, *t*Bu × 2), 1.37 (18H, s, *t*Bu × 2), 3.00 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 3.39 (4H, br, OCH_2 × 2), 3.48 (4H, br, NH_2 × 2), 3.60 (4H, broad s, OCH_2 × 2), 3.96 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 4.55 (4H, s, OCH_2CO × 2), 7.35 (4H, s, Ar-*H* × 2), 7.41 (4H, s, Ar-*H* × 2) and 7.54 (2H, s, N*H* × 2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.5$ (CH_3), 33.5 ($C(CH_3)_3$), 64.9 (OCH_2), 67.4 (OCH_2), 69.2 (OCH_2), 70.5 (OCH_2), 72.6 (OCH_2), 126.2 (ArC), 126.4 (ArC), 126.5 (ArC), 126.7 (ArC), 146.5 (ArC), 146.7 (ArC), 153.6 (ArC), 155.4 (ArC) and 167.6 (CO) ppm. FABMS: *m*/*z*: 1023.38 (M^+). $C_{52}H_{70}N_4O_9S_4$ (1023.39): calcd C 61.03, H 6.89, N 5.47. Found: C 61.33, H 6.79, N 5.57.

Synthesis of receptor 4_a

To compound **3** (150 mg, 0.147 mmol) in THF (10 mL), was added phenyl isocyanate (38 mg, 0.320 mmol) and the mixture was stirred for at room temperature for 24 h under argon. The resulting precipitate was collected by filtration, washed with hexane to give receptor $\mathbf{4_a}$ as a white solid. Recrystallization from $CHCl_3$–CH_3CN (4 : 1) gave receptor $\mathbf{4_a}$ (154 mg, 83%) as white solid. M.p. 202–205 °C. IR: ν_{max} (KBr)/cm^{-1}: 3270, 2956, 1674, 1547, 1442, 1263, 1221, 1153, 1091, 799 and 751. ^{1}H NMR (300 MHz, $CDCl_3$–DMSO, 10 : 1): $\delta = 1.25$ (18H, s, *t*Bu × 2), 1.39 (18H, s, *t*Bu × 2), 2.97 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.63 (4H, s, OCH_2 × 2), 3.85 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 4.59 (4H, s, OCH_2CO × 2), 6.95 (2H, t, $J = 7.3$ Hz, phenyl-*H* × 2), 7.15 (4H, t, $J = 7.6$ Hz, phenyl-*H* × 4), 7.31 (4H, d, $J = 7.7$ Hz, phenyl-*H* × 2), 7.35 (4H, s, Ar-*H* × 4), 7.48 (4H, s, Ar-*H* × 4), 7.57 (2H, s, N*H* × 2), 8.10 (2H, s, N*H* × 2), 8.32 (2H, s, N*H* × 2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$–DMSO, 10 : 1): $\delta = 29.9$ (CH_3), 30.4 (CH_3), 33.5 ($C(CH_3)_3$), 33.5 ($C(CH_3)_3$), 64.9 (OCH_2), 67.5 (OCH_2), 69.0 (OCH_2), 70.6 (OCH_2), 72.6 (OCH_2), 118.4 (ArC), 120.4 (ArC), 121.8 (ArC), 125.6 (ArC), 126.1 (ArC), 126.3 (ArC), 127.1 (ArC), 127.5 (ArC), 128.0 (ArC), 128.2 (ArC), 137.3 (ArC), 146.4 (ArC), 147.5 (ArC), 153.7 (ArC), 154.0 (CO), 154.6 (ArC) and 167.5 (CO) ppm. FABMS: *m*/*z*: 1261.43 (M^+). $C_{66}H_{80}N_6O_{11}S_4$ (1260.48): calcd C 62.83, H 6.39, N 6.66. Found: C 62.59, H 6.23, N 6.45.

Synthesis of receptor 4_b

To compound **3** (150 mg, 0.147 mmol) in THF (10 mL), was added *p*-tolyl isocyanate (43 mg, 0.320 mmol) and the mixture was stirred for at room temperature for 24 h under argon. The resulting precipitate was collected by filtration, washed with EtOH to give receptor $\mathbf{4_b}$ as a white solid. Recrystallization from $CHCl_3$–CH_3CN (2 : 1) gave receptor $\mathbf{4_b}$ (163 mg, 86%) as white solid. M.p. 205–207 °C. IR: ν_{max} (KBr)/cm^{-1}: 3283, 2955, 1678, 1547, 1444, 1266, 1207, 1151, 1089, 999 and 815. ^{1}H NMR (300 MHz, $CDCl_3$–DMSO, 10 : 1): $\delta = 1.27$ (18H, s, *t*Bu × 2), 1.39 (18H, s, *t*Bu × 2), 2.28 (6H, s, CH_3 × 2), 2.97 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.63 (4H, s, OCH_2 × 2), 3.85 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 4.58 (4H, s, OCH_2CO × 2), 6.96 (4H, d, $J = 7.7$ Hz, phenyl-*H* × 4), 7.16 (4H, d, $J = 7.7$ Hz, phenyl-*H* × 4), 7.35 (4H, s, Ar-*H* × 4), 7.48 (4H, s, Ar-*H* × 4), 7.51 (2H, s, N*H* × 2), 8.10 (2H, s, N*H* × 2), 8.22 (2H, s, N*H* × 2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$–DMSO, 10 : 1): $\delta = 20.7$ (CH_3), 30.9 (CH_3), 31.4 (CH_3), 34.4 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 65.9 (OCH_2), 68.6 (OCH_2), 70.0 (OCH_2), 71.6 (OCH_2), 73.6 (OCH_2), 119.4 (ArC), 126.6 (ArC), 127.0 (ArC), 127.3 (ArC), 128.2 (ArC), 129.0 (ArC), 129.5 (ArC), 131.9 (ArC), 135.7 (ArC), 136.1 (ArC), 147.4 (ArC), 148.5 (ArC), 154.4 (ArC), 154.8 (ArC), 155.1 (CO), 155.5 (ArC) and 168.5 (CO) ppm. FABMS: *m*/*z*: 1289.46 (M^+). $C_{68}H_{84}N_6O_{11}S_4$ (1289.69): calcd C 63.33, H 6.56, N 6.52. Found: C 62.56, H 6.56, N 6.25.

Synthesis of receptor 4_c

To compound **3** (150 mg, 0.147 mmol) in THF (10 mL), was added *p*-trifluoromethylphenyl isocyanate (59 mg, 0.320 mmol) and the mixture was stirred for at room temperature for 24 h under argon. The resulting precipitate was collected by filtration, washed with EtOH to give receptor $\mathbf{4_c}$ as a white solid. Recrystallization from $CHCl_3$–CH_3CN (1 : 1) gave receptor $\mathbf{4_c}$ (164 mg, 80%) as white solid. M.p. 207–210 °C. IR: ν_{max} (KBr)/cm^{-1}: 3283, 2959, 1687, 1548, 1445, 1266, 1158, 1091, 1068 and 840. ^{1}H NMR (300 MHz, $CDCl_3$–DMSO, 10 : 1): $\delta = 1.27$ (18H, s, *t*Bu × 2), 1.40 (18H, s, *t*Bu × 2), 2.97 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.63 (4H, s, OCH_2 × 2), 3.85 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 4.61 (4H, s, OCH_2CO × 2), 7.36 (4H, s, Ar-*H* × 4), 7.39–7.42 (8H, m, phenyl-*H* × 8), 7.49 (4H, s, Ar-*H* × 4), 7.56 (2H, s, N*H* × 2), 8.29 (2H, s, N*H* × 2), 8.69 (2H, s, N*H* × 2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$–DMSO, 10 : 1): $\delta = 30.9$ (CH_3), 31.3 (CH_3), 34.4 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 66.1 (OCH_2), 68.5 (OCH_2), 69.9 (OCH_2), 71.6 (OCH_2), 73.5 (OCH_2), 118.1 (ArC), 122.9 (ArC), 123.9 (CF_3), 124.2 (CF_3), 125.6 (ArC), 125.8 (ArC), 125.9 (ArC), 126.4 (ArC), 126.9 (ArC), 127.0 (ArC), 128.2 (ArC), 147.4 (ArC), 148.4 (ArC), 154.6 (ArC), 154.8 (CO), 155.5 (ArC) and 167.5 (CO) ppm. FABMS: *m*/*z*: 1397.44 (M^+). $C_{68}H_{78}F_6N_6O_{11}S_4$ (1397.63): calcd C 58.44, H 5.63, N 6.01. Found: C 58.62, H 5.53, N 6.13.

Synthesis of receptor 4_d

To compound **3** (150 mg, 0.147 mmol) in THF (10 mL), was added 3,5-bis(trifluoromethyl)phenyl isocyanate (82 mg, 0.320 mmol) and the mixture was stirred for at room temperature for 24 h under argon. The resulting precipitate was collected by filtration, washed with EtOH to give receptor $\mathbf{4_d}$ as a white solid. Recrystallization from $CHCl_3$–CH_3CN (1 : 1) gave receptor $\mathbf{4_d}$ (187 mg, 83%) as white solid. M.p. 208–210 °C. IR: ν_{max} (KBr)/cm^{-1}: 3315, 2963, 1677, 1577, 1443, 1215, 1136, 1092, 1019 and 880. ^{1}H NMR (300 MHz, $CDCl_3$–DMSO, 10 : 1): $\delta = 1.32$

(18H, s, *t*Bu × 2), 1.39 (18H, s, *t*Bu × 2), 3.01 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.64 (4H, s, OCH_2 × 2), 3.89 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 4.63 (4H, s, OCH_2CO × 2), 7.28 (2H, s, phenyl-*H* × 2), 7.38 (4H, s, Ar-*H* × 4), 7.42 (4H, s, phenyl-*H* × 4), 7.49 (4H, s, Ar-*H* × 4), 7.82 (2H, s, N*H* × 2), 8.49 (2H, s, N*H* × 2), 9.05 (2H, s, N*H* × 2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$–DMSO, 10 : 1): $\delta = 30.8$ (CH_3), 31.2 (CH_3), 34.3 ($C(CH_3)_3$), 34.4 ($C(CH_3)_3$), 65.8 (OCH_2), 67.9 (OCH_2), 69.7 (OCH_2), 71.4 (OCH_2), 73.4 (OCH_2), 115.3 (ArC), 117.7 (ArC), 121.6 (ArC), 124.3 (CF_3), 126.1 (ArC), 126.7 (ArC), 127.0 (ArC), 127.9 (ArC), 131.7 (ArC), 140.4 (ArC), 147.4 (ArC), 148.4 (ArC), 154.1 (ArC), 154.5 (ArC), 155.4 (CO), 155.5 (ArC) and 167.4 (CO) ppm. FABMS: *m*/*z*: 1533.48 (M^+). $C_{70}H_{76}F_{12}N_6O_{11}S_4$ (1533.63): calcd C 54.82, H 4.99, N 5.48. Found: C 54.63, H 5.05, N 5.35.

Synthesis of receptor 4_e

To compound **3** (150 mg, 0.147 mmol) in THF (10 mL), was added *p*-nitrophenyl isocyanate (53 mg, 0.320 mmol) and the mixture was stirred for at room temperature for 24 h under argon. The resulting precipitate was collected by filtration, washed with EtOH to give receptor $\mathbf{4_e}$ as a pale yellow solid. Recrystallization from $CHCl_3$–CH_3CN (3 : 1) gave receptor $\mathbf{4_e}$ (165 mg, 83%) as pale yellow solid. M.p. 212–215 °C. IR: ν_{max} (KBr)/cm^{-1}: 3257, 2957, 1682, 1555, 1512, 1445, 1415, 1266, 1150, 1091 and 850. ^{1}H NMR (300 MHz, $CDCl_3$–DMSO, 10 : 1): $\delta = 1.27$ (18H, s, *t*Bu × 2), 1.39 (18H, s, *t*Bu × 2), 2.97 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.63 (4H, s, OCH_2 × 2), 3.85 (4H, t, $J = 9.1$ Hz, OCH_2 × 2), 4.58 (4H, s, OCH_2CO × 2) 7.40 (4H, s, Ar-*H* × 4), 8.57 (4H, s, Ar-*H* × 4), 7.58 (4H, d, $J = 9.3$ Hz, phenyl-*H* × 4), 7.66 (2H, s, N*H* × 2), 8.06 (4H, d, $J = 9.3$ Hz, phenyl-*H* × 4), 8.40 (2H, s, N*H* × 2), 9.08 (2H, s, N*H* × 2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$–DMSO, 10 : 1): $\delta = 30.9$ (CH_3), 31.3 (CH_3), 34.4 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 66.2 (OCH_2), 69.0 (OCH_2), 69.9 (OCH_2), 71.7 (OCH_2), 73.6 (OCH_2), 118.1 (ArC), 124.9 (ArC), 126.2 (ArC), 127.1 (ArC), 127.7 (ArC), 128.0 (ArC), 128.4 (ArC), 142.6 (ArC), 144.5 (ArC), 147.5 (ArC), 147.3 (ArC), 147.9 (ArC), 148.2 (ArC), 154.0 (ArC), 154.2 (CO), 155.7 (ArC) and 168.5 (CO) ppm. FABMS: *m*/*z*: 1351.57 (M^+). $C_{66}H_{78}N_8O_{15}S_4$ (1351.63): calcd C 58.65, H 5.82, N 8.29. Found: C 58.81, H 5.75, N 8.12.

Determination of the association constants

The association constants were determined by using ^{1}H NMR spectroscopic titration experiments in a constant concentration of host receptor (4.0×10^{-3} M) and varying the guest concentration (0–8.0×10^{-3} M). The ^{1}H NMR chemical shift of the urea protons (NH) signal was used as a probe. The association constant (K_a) for the complexes of receptor $\mathbf{4_{a-e}}$ were calculated by nonlinear curve-fitting analysis of the observed chemical shifts of the NH protons according to the literature procedure.[14]

^{1}H NMR titration experiments

A solution of Bu_4NX (X = F, Cl, Br, I, AcO, PhCOO, H_2PO_4) in CD_3CN (4.0×10^{-3} M) was added to a $CDCl_3$ solution of receptor $\mathbf{4_{a-e}}$ in the absence or presence of KSO_3CF_3 in an NMR tube. ^{1}H NMR spectra were recorded after addition of the reactants and the temperature of the NMR probe was kept constant at 27 °C. The ^{1}H NMR spectroscopic data of representative complexes are given below:

Receptor $\mathbf{4_a \supset Cl^-}$. ^{1}H NMR (300 MHz, $CHCl_3$–DMSO–CH_3CN, 10 : 1 : 1, v/v): $\delta = 2.97$ (4H, br, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.63 (4H, br, OCH_2 × 2), 3.85 (4H, br, OCH_2 × 2), 4.59 (4H, s, OCH_2O × 2), 7.89 (2H, br, NH_c × 2), 8.10 (2H, br, NH_b × 2) and 8.95 (2H, br, NH_a × 2) ppm.

Receptor $\mathbf{4_b \supset Cl^-}$. ^{1}H NMR (300 MHz, $CHCl_3$–DMSO–CH_3CN, 10 : 1 : 1, v/v): $\delta = 2.97$ (4H, br, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.63 (4H, br, OCH_2 × 2), 3.85 (4H, br, OCH_2 × 2), 4.68 (4H, s, OCH_2O × 2), 7.80 (2H, br, NH_c × 2), 8.09 (2H, br, NH_b × 2) and 8.63 (2H, br, NH_a × 2) ppm.

Receptor $\mathbf{4_c \supset Cl^-}$. ^{1}H NMR (300 MHz, $CHCl_3$–DMSO–CH_3CN, 10 : 1 : 1, v/v): $\delta = 2.97$ (4H, br, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.63 (4H, br, OCH_2 × 2), 3.85 (4H, br, OCH_2 × 2), 4.68 (4H, s, OCH_2O × 2), 8.01 (2H, br, NH_c × 2), 8.20 (2H, br, NH_b × 2) and 9.58 (2H, br, NH_a × 2) ppm.

Receptor $\mathbf{4_d \supset Cl^-}$. ^{1}H NMR (300 MHz, $CHCl_3$–DMSO–CH_3CN, 10 : 1 : 1, v/v): $\delta = 3.01$ (4H, br, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.64 (4H, br, OCH_2 × 2), 3.89 (4H, br, OCH_2 × 2), 4.63 (4H, s, OCH_2O × 2), 7.94 (2H, br, NH_c × 2), 8.33 (2H, br, NH_b × 2) and 9.70 (2H, br, NH_a × 2) ppm.

Receptor $\mathbf{4_e \supset Cl^-}$. ^{1}H NMR (300 MHz, $CHCl_3$–DMSO–CH_3CN, 10 : 1 : 1, v/v): $\delta = 2.97$ (4H, br, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.63 (4H, br, OCH_2 × 2), 3.85 (4H, br, OCH_2 × 2), 4.60 (4H, s, OCH_2O × 2), 8.10 (2H, br, NH_c × 2), 8.18 (2H, br, NH_b × 2) and 10.8 (2H, br, NH_a × 2) ppm.

Receptor $\mathbf{4_e \supset K^+}$. ^{1}H NMR (300 MHz, $CHCl_3$–DMSO–CH_3CN, 10 : 1 : 1, v/v): $\delta = 3.11$ (4H, br, OCH_2 × 2), 3.36–3.58 (4H, m, OCH_2 × 2), 3.64–3.90 (4H, m, OCH_2 × 2), 4.08 (4H, br, OCH_2 × 2), 4.30–4.61 (4H, m, OCH_2O × 2), 8.10 (2H, s, NH_c × 2), 8.95 (2H, broad s, NH_b × 2) and 9.09 (2H, broad s, NH_a × 2) ppm.

$\mathbf{Cl^- \subset}$[receptor $\mathbf{4_e \supset K^+}$]. ^{1}H NMR (300 MHz, $CHCl_3$–DMSO–CH_3CN, 10 : 1 : 1, v/v): $\delta = 2.97$ (4H, br, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.63 (4H, br, OCH_2 × 2), 3.85 (4H, br, OCH_2 × 2), 4.60 (4H, s, OCH_2O × 2), 8.14 (2H, br, NH_c × 2), 8.58 (2H, br, NH_b × 2) and 10.2 (2H, br, NH_a × 2) ppm.

Receptor $\mathbf{4_e \supset Br^-}$. ^{1}H NMR (300 MHz, $CHCl_3$–DMSO–CH_3CN, 10 : 1 : 1, v/v): $\delta = 2.97$ (4H, br, OCH_2 × 2), 3.40 (4H, br, OCH_2 × 2), 3.63 (4H, br, OCH_2 × 2), 3.85 (4H, br, OCH_2 × 2), 4.60 (4H, s, OCH_2O × 2), 7.52 (2H, br, NH_c × 2), 8.25 (2H, br, NH_b × 2) and 9.27 (2H, br, NH_a × 2).

$\mathbf{Br^- \subset}$[receptor $\mathbf{4_e \supset K^+}$]. ^{1}H NMR (300 MHz, $CHCl_3$–DMSO–CH_3CN, 10 : 1 : 1, v/v): $\delta = 3.11$ (4H, br, OCH_2 × 2), 3.36–3.58 (4H, m, OCH_2 × 2), 3.64–3.90 (4H, m, OCH_2 × 2), 4.08 (4H, br, OCH_2 × 2), 4.30–4.61 (4H, m, OCH_2O × 2), 7.81 (2H, br, NH_c × 2), 8.10 (2H, br, NH_b × 2) and 9.51 (2H, br, NH_a × 2).

Crystallographic analysis of receptors 4_b and 4_e

Crystal data for $\mathbf{4_b}$. $C_{68}H_{84}N_6O_{11}S_4 \cdot ½(H_2O) \cdot 1½(CHCl_3)$, $M_r = 1477.71$. Monoclinic, $P2_1/n$; $a = 18.8935$ (13), $b = 23.9302$ (16), $c = 33.589$ (2) Å; $\beta = 91.5063$ (12)°; $V = 15\,181.2$ (17) Å^3; $Z = 8$; $D_x = 1.293$ Mg m^{-3}; $F(000) = 6224$; $T = 210(2)$ K; μ (Mo-K$_\alpha$) = 0.34 mm^{-1}; $\lambda = 0.71073$ Å, crystal size 0.71 × 0.54 × 0.32 mm^3. Crystals were colorless blocks. Diffraction data were measured on a Bruker APEX 2 CCD diffractometer equipped with graphite monochromated $Mo_{K\alpha}$ radiation by thin-slice ω-scans.[15] 134 900 measured reflections, 31 218 independent reflections ($R_{int} = 0.049$) to $\theta_{max} = 26.5°$; 19 539 reflections with $I > 2\sigma(I)$. The structure was determined by direct methods using the SHELXS program and refined by the full-matrix least-squares method, on F^2, in SHELXL-2013/14.[16,17] The non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms on C were included in idealized positions and their U_{iso} values were set to ride on the U_{eq} values of the parent atoms. H atoms on N were freely refined. At the conclusion of the refinement, $wR_2 = 0.173$ (all data) and $R_1 = 0.056$ (observed data), 1903 parameters, $\Delta\rangle_{max} = 0.56$ eÅ^{-3}; 465 restraints, $\Delta\rangle_{min} = -0.43$ eÅ^{-3}. The platon squeeze procedure was used to model two of the three unique $CHCl_3$ molecules due to severe disorder.[18] Two-fold disorder was modelled in some *t*Bu groups, in parts of one of the crown ether chains and the other $CHCl_3$ molecule. H atoms on water molecule O(23) could not be located in difference maps, so were not included in the model.†

Crystal data for 4$_e$. $C_{66}H_{78}N_8O_{15}S_4\cdot½(CHCl_3)\cdot3(MeCN)$, $M_r = 1534.44$. Monoclinic, $P2_1/c$; $a = 17.7980$ (10), $b = 26.7870$ (16), $c = 32.552$ (2) Å; $\beta = 96.384$ (4)°; $V = 15 423.1$ (16) Å^3; $Z = 8$; $D_x = 1.322$ Mg m^{-3}; $F(000) = 6472$; $T = 100$ (2) K; μ (Mo-Kα) = 0.31 mm^{-1}; $\lambda = 0.7749$ Å, crystal size 0.25 × 0.25 × 0.02 mm^3. Crystals were colorless plates. Diffraction data were measured on a Bruker APEX 2 CCD diffractometer at station 11.3.1 of the ALS using synchrotron radiation by thin-slice ω-scans.[15] 155 885 measured reflections, 50 956 independent reflections ($R_{int} = 0.052$) to $\theta_{max} = 34.8°$; 35 702 reflections with $I > 2\sigma(I)$. Structure solution with SHELXT and refinement as above.[16,17] Hydrogen atoms on C and some N atoms were included in idealized positions and their U_{iso} values were set to ride on the U_{eq} values of the parent atoms. H atoms on the remaining N atoms were freely refined. At the conclusion of the refinement, $wR_2 = 0.294$ (all data) and $R_1 = 0.086$ (observed data), 2055 parameters, $\Delta\rangle_{max} = 2.44$ eÅ^{-3}; 656 restraints, $\Delta\rangle_{min} = -1.86$ eÅ^{-3}. The platon squeeze procedure was used to model four of the six unique MeCN molecules due to severe disorder.[18] Two-fold disorder was modelled in some *t*Bu groups and in parts of one the crown ether chains and one HN-*p*-$C_6H_4NO_2$ group.†

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