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Experimental and computational studies of anion recognition by pyridine-functionalised calixarenes

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Calix[4]arene-based receptors linked to amide and pyridine moieties have been synthesised in four steps from calix[4]arene, and characterised by ¹H and ¹³C NMR spectroscopy. The recognition properties of these receptors towards different anions were evaluated using ¹H NMR and computational studies. The receptors show modest selectivities towards dihydrogen phosphate versus carboxylates.

Keywords: calixarene; anion recognition; receptor; pyridine

1. Introduction

There is a continued interest in the development of anionic receptors in supramolecular chemistry due to the pivotal roles that anions play in many chemical, biological and medicinal processes (1). For example, phosphate ion and its key derivatives play important roles in energy storage and signal transduction in living systems (2). Calixarenes have proven to be versatile scaffolds for the development of anionic receptors due to the ease of functionalisation at their lower or upper rims with linkers decorated with recognition motifs for anions, such as urea, thiourea and amide moieties. These modified calixarenes form a pre-organised core capable of improving the binding and selectivity of anions (3). Calixarenes functionalised with pyridine and pyridinium moieties have been developed (4) and used mainly for the recognition of metal ions (5), and in some cases, neutral species (6). There are, however, only a few examples of pyridine- or pyridinium-functionalised calixarenes that have been used for anion recognition. Calixarene derivatives containing lower rim linkers functionalised with pyridine and pyridinium moieties have been reported by Yilmaz and co-workers. These have been used as extracting agents for dichromate, arsenate and dihydrogen phosphate ions, as well as for transition metals (7). Beer and co-workers (8) have synthesised lower rim calixarene derivatives containing pyridinium-functionalised lower rim linkers that recognise dihydrogen phosphate, chloride, bromide, hydrogen sulphate and show selectivity for dihydrogen phosphate. We report the expedient and efficient syntheses of lower rim distally substituted calix[4]arenes with linkers containing amide moieties and terminate with pyridine moieties. ¹H NMR titration and computational studies

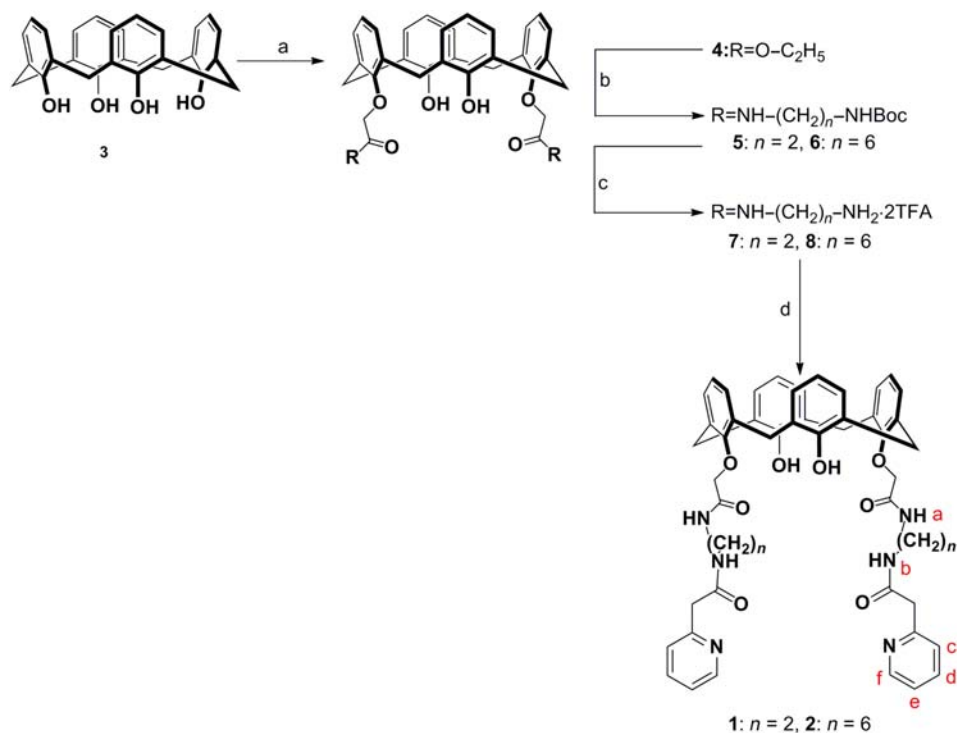
revealed that these calixarenes are novel anion receptors that show modest selectivity for dihydrogen phosphate.

2. Results and discussion

2.1 Synthesis and characterisation of receptors 1 and 2

Target receptors **1** and **2** were synthesised from the commercially available calix[4]arene in four steps (Scheme 1). Calix[4]arene diester **4** was prepared by nucleophilic substitution of calix[4]arene with bromoethyl acetate in the presence of K₂CO₃ in 82% yield, according to the methods described by Reinhoudt and co-workers (9). Treatment of calix[4]arene diester **4** with excess of either *N*-Boc-1,6-hexanediamine or *N*-Boc-ethylenediamine in toluene at 80°C overnight furnished Boc-protected diamines **5** (48%) or **6** (50%). This was done using a modification of a previously reported procedure (10). Deprotection of the Boc-protected diamines **5** and **6** was effected using a 20% solution of TFA in methylene chloride at 0°C for 2 h yielding TFA salts of calix[4]arene diamines **7** (92%)¹ and **8** (97%). Coupling of compounds **7** and **8** with 2-pyridylacetic acid and HATU in the presence of TEA at room temperature for 24 h yielded receptors **1** (50%) and **2** (65%). Conditions for this coupling step were modified from a procedure reported by Echegoyen and co-workers (11) for coupling a calix[6]crown-4-tetraamine with thioctic and 1-pyrenebutyric acids. Structures of receptors **1** and **2** were confirmed using spectroscopic data (¹H NMR, ¹³C NMR and MS). ¹H and ¹³C NMR spectra confirmed that receptors **1** and **2** have C_{2v} symmetry and are locked in the cone conformation. Doublets due to the methylene bridges located at 4.23 and 3.47 ppm for receptor **1**, and 4.19 and 3.50 for receptor **2**, were found in

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Scheme 1. Synthesis of calixarene receptors **1** and **2**. (a) $\text{BrCH}_2\text{CO}_2\text{Et}$, K_2CO_3 , CH_3CN , 8 h, 82%; (b) N -Boc-1,6-hexanediamine/ N -Boc-ethylenediamine, toluene, 80°C , 24 h, 48% (**5**), 50% (**6**); (c) TFA/ CH_2Cl_2 , 0°C , 2 h, 92% (**7**), 97% (**8**); (d) 2-pyridylacetic acid, HATU, TEA, RT, 8 h, 50% (**1**), 65% (**2**).

the ^1H NMR spectra. In addition, overlapping signals located at 31.3 ppm for receptor **1**, and at 32 ppm for receptor **2**, were found in the ^{13}C NMR spectra. Signals due to the $[\text{M} + \text{H}]^+$ ions were detected in the mass spectra of these receptors.

2.2 Screening for anions that display recognition properties towards receptors **1** and **2** using computational studies

To screen for anions that will be recognised by our receptors, molecular mechanics calculations were performed using MACROMODEL (12). Based on the recognition properties displayed by distally substituted calixarenes containing ethylene linkers between the amide moieties reported by Balzani and co-workers (13a) and Walsh and co-workers (13b), we chose anions Cl^- , H_2PO_4^- , CH_3CO_2^- and PhCO_2^- for our studies. The HSO_4^- ion was also used as it provided us with an additional example of an anion with tetrahedral geometry. Favourable complexation energy values of the receptor–anion complex were indicative of good binding, and those anions were then tested experimentally. The general procedure for determining the complexation energy of the receptor–anion complex can be described as follows. The lowest energy structure of a receptor (global minimum) was determined by a conformational search using the generalized Born/

surface area (GB/SA) solvation model for CHCl_3 . The complexation energy values of certain receptor–anion complexes were calculated in a gas phase due to the lack of parameters in GB/SA model. Next, the global minima of the receptors complexed with the target anions were calculated. The complexation energy value for each receptor–substrate complex was determined to be the difference in energy between the receptor–anion complex and the sum of the energy values of the receptor and the anion. Complexation energy values that were less than -5 kcal/mol were considered to be indicative of good binding between the anions and the receptors. In gas phase calculations, the threshold value was set to -20 kcal/mol due to the overestimation of complexation energy values in the gas phase.

Based on those values, receptor **1**, with the ethylene linker, was determined to recognise H_2PO_4^- , CH_3CO_2^- , PhCO_2^- and HSO_4^- . Receptor **2**, with the hexylene linker, was determined to recognise H_2PO_4^- and HSO_4^- (see Table 1 of the Supplementary Information, available online).

Calculated structures of receptors with anions gave insight into the binding modes of the anion–receptor complexes. To compare the binding modes of the receptors, we further examined the calculated structures resulting from complexes of receptors **1** and **2** with H_2PO_4^- . To examine the differences in the binding of different anions with a particular receptor, complexes resulting from the binding of receptor **1**

Table 1. Binding constant K (M^{-1})^a of receptors **1** and **2** with anions.

Anions	Receptor 1	Receptor 2
$H_2PO_4^-$	275	31.6
$PhCO_2^-$	14.4	< 10
$CH_3CO_2^-$	114	< 10

^a Measured in DMSO- d_6 at 27°C by the 1H NMR titration method noting the chemical shift change of the NH proton (labelled a in Scheme 1); host concentration was 2.6–4.4 mM. Errors are < 3%.

^b Anions were used as their tetra *n*-butylammonium salts.

with $H_2PO_4^-$ and $CH_3CO_2^-$ were compared. Shown in Figure 1 are the calculated structures of complexes of receptor **1**· $H_2PO_4^-$, receptor **2**· $H_2PO_4^-$ and receptor **1**· $CH_3CO_2^-$ along with their ΔE values (kcal/mol). In all cases, 1:1 anion–receptor binding is predicted. In the case of receptor **1**· $H_2PO_4^-$, calculations reveal that the $H_2PO_4^-$ is locked into place by four hydrogen bond interactions, three of which result from the amide moieties and one from the pyridine moiety. Hydrogen bond distances are N–H···O (average 1.66 Å), O···H–HPO $_4^-$ (1.73 Å) and N_{py}···H–HPO $_4^-$ (1.73 Å). The calculated structure for receptor **2**· $H_2PO_4^-$ also shows four hydrogen bonding interactions, three resulting from the amide moiety and one resulting from the pyridine moiety. Hydrogen bond distances are N–H···O (average 1.62 Å) and N_{py}···H–HPO $_4^-$ (1.81 Å). The calculated structure for **1**· $CH_3CO_2^-$ shows three hydrogen bonding interactions, all from the amide (NH) moieties, with N–H···O distances averaging 1.66 Å.

2.3 NMR studies

2.3.1 Screening

The recognition properties of receptors with anions were further evaluated experimentally using 1H NMR

spectroscopy. In the first step, the results of the computational studies, i.e. selection of anions on the basis of complexation energy values, were tested experimentally. Equivalents (1 and then 5) of anions (as their tetra *n*-butylammonium (TBA) salts) were added to an equivalent of each receptor in DMSO- d_6 and 1H NMR spectra were taken. Complexation-induced shifts (CIS) of the resonances of the receptors were taken as evidence of binding between anions and receptors. Titration studies were subsequently performed with anions ($CH_3CO_2^-$, $H_2PO_4^-$ and $PhCO_2^-$) and receptors as they produced CIS of greater than 0.1 ppm.

2.3.2 Titration studies

Receptors **1** and **2** (2.6–4.4 mM) were titrated with 0–9 equivalents of anions (as TBA salts) in DMSO- d_6 . A series of spectra resulting from the titration of $H_2PO_4^-$ with receptor **2** is shown in Figure 2.

Downfield shifts are observed for amide resonances at 8.5 and 8.0 ppm (labelled a and b in Scheme 1); an overall $\Delta\delta$ of ~0.3 ppm (over the addition of 9 equivalents) is observed for both NH resonances. This indicates that complexation of $H_2PO_4^-$ by receptor **2** takes place via hydrogen-bonding interactions with the amide proton moieties. We note the disappearance of the signal due to the phenolic hydrogen at 8.32 ppm, and speculate that this is due to either the deprotonation of the phenolic hydrogen or an exchange process that is catalysed in the presence of $H_2PO_4^-$. No significant changes in the position of resonances due to pyridine moieties or the calixarene scaffold were observed. For receptor **1**, similar observations were made with $H_2PO_4^-$ with overall changes of 0.78 and 0.91 ppm in the position of NH resonances at 8.58 and 8.15 ppm (labelled a and b in Scheme 1) upon complexation. The pyridyl hydrogen (labelled c in Scheme 1) shifted

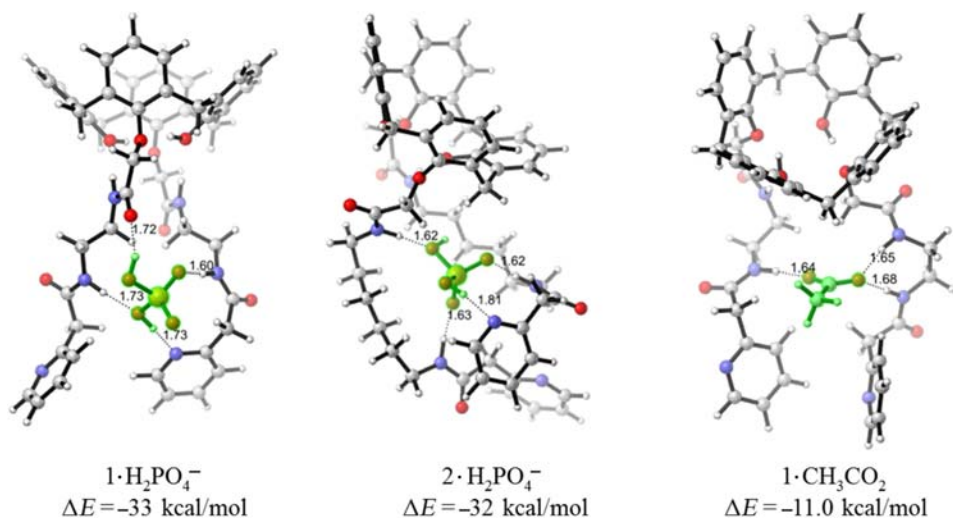


Figure 1. Calculated structures of receptors with $H_2PO_4^-$ and $CH_3CO_2^-$ and their complexation energy values.

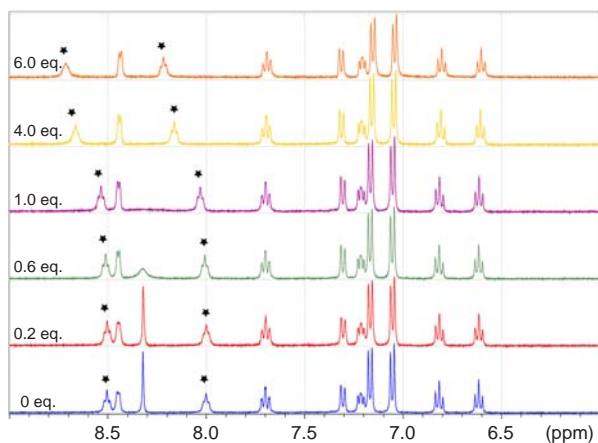


Figure 2. Downfield region of spectra resulting from the titration of H_2PO_4^- (as its TBA salt) into a solution of receptor **2** in $\text{DMSO}-d_6$. Amide resonances are labelled as stars and the phenolic resonance as a square.

slightly downfield (0.1 ppm), indicating that this hydrogen atom is also interacting with H_2PO_4^- via hydrogen bonding (see Figure 2 of the Supplementary Information, available online).

For the carboxylates with receptor **1**, changes averaging 0.2 ppm were observed for the amide protons in the benzoate titration and 0.4 ppm for the acetate titration, but neither the involvement of the pyridyl hydrogen in anion binding nor the disappearance of the phenolic hydrogen was observed (see Figures 5 and 7 of the Supplementary Information, available online).

The experimental results corroborated the computational results in that they showed the pivotal role played by the amide moieties in the recognition of H_2PO_4^- . Note that for receptor **2**, we see evidence of the involvement of both amide resonances, whereas the computational studies predict that only one set of amide resonances will be involved in the binding event. We also do not see any evidence of the involvement of the pyridyl nitrogen in the recognition events; downfield-shifted resonances of the pyridine moieties should have occurred had this been the case. For the carboxylates, the sole involvement of the amide moieties in the complexation of the anion was predicted by the molecular modelling results. The computational results also predict favourable binding between the receptors and HSO_4^- ; however, no CIS were observed in these cases. This indicates that although HSO_4^- had complementary size and shape for the receptor, it was not basic enough to induce complexation. Job's plots (14) of receptors with anions (Supplementary Information, available online) showed that the anion–receptor stoichiometry was 1:1 as predicted by the computational results.

Changes in chemical shifts of the more downfield amide resonance (labelled a in Scheme 1) were then used as a probe to obtain quantitative information of the binding

of receptors with anions. Plots of changes in chemical shifts versus concentration of anion (Figure 3) were analysed using a 1:1 receptor–anion binding model in the nonlinear regression curve-fitting program WinEQNMR2 (15) (Supplementary Information, available online). The binding constants that were obtained are shown in Table 1.

Table 1 reveals that receptor **1**, bearing the ethylene linker, recognises carboxylates and dihydrogen phosphate, whereas receptor **2**, bearing the hexylene linker, recognises dihydrogen phosphate. Receptor **1** is moderately selective for H_2PO_4^- with a binding constant (275 M^{-1}) which is a factor of 2.4 greater than CH_3CO_2^- (114 M^{-1}). Among the carboxylates, receptor **1** has a higher binding constant for the more basic carboxylate, acetate ion (114 M^{-1}), a factor of eight times greater than benzoate ion (14.4 M^{-1}). With respect to the dihydrogen phosphate ion, the binding constant for receptor **1** (275 M^{-1}) was 8.5 times greater than the association with receptor **2** (31.6 M^{-1}). We attribute this to the shorter ethylene linker in receptor **1** which allows the amide moieties to be in closer proximity, clearly important for the binding of anions. The binding constants measured here are modest, but this is not surprising considering that DMSO, a good hydrogen bond acceptor solvent, was used for the studies.

We then compared the recognition properties and binding constants of our receptors to those of closely related structures (Figure 4). Receptors **9** and **10**, reported by Beer et al. (8), display 1:1 receptor–anion stoichiometry, recognise Cl^- , AcO^- and H_2PO_4^- and show selectivity for AcO^- . Binding constants that were obtained are greater for **9** than **10** and are attributed to the presence of a Ru(II) metal centre versus the neutral Re compound. Binding constants obtained for **9** and **10** are greater than our receptors for AcO^- and H_2PO_4^- , with the exception of receptor **1**, that shows slightly greater binding than **9** in the case of H_2PO_4^- (275 M^{-1} vs. 240 M^{-1}). Pyridinium-functionalised recep-

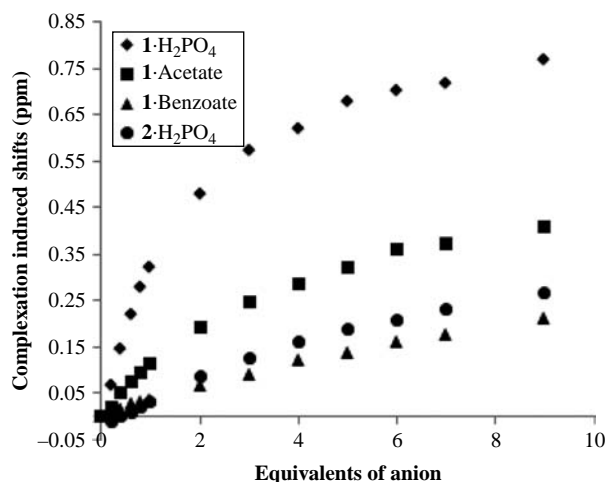


Figure 3. CIS of amide proton resonances versus equivalents of anion.

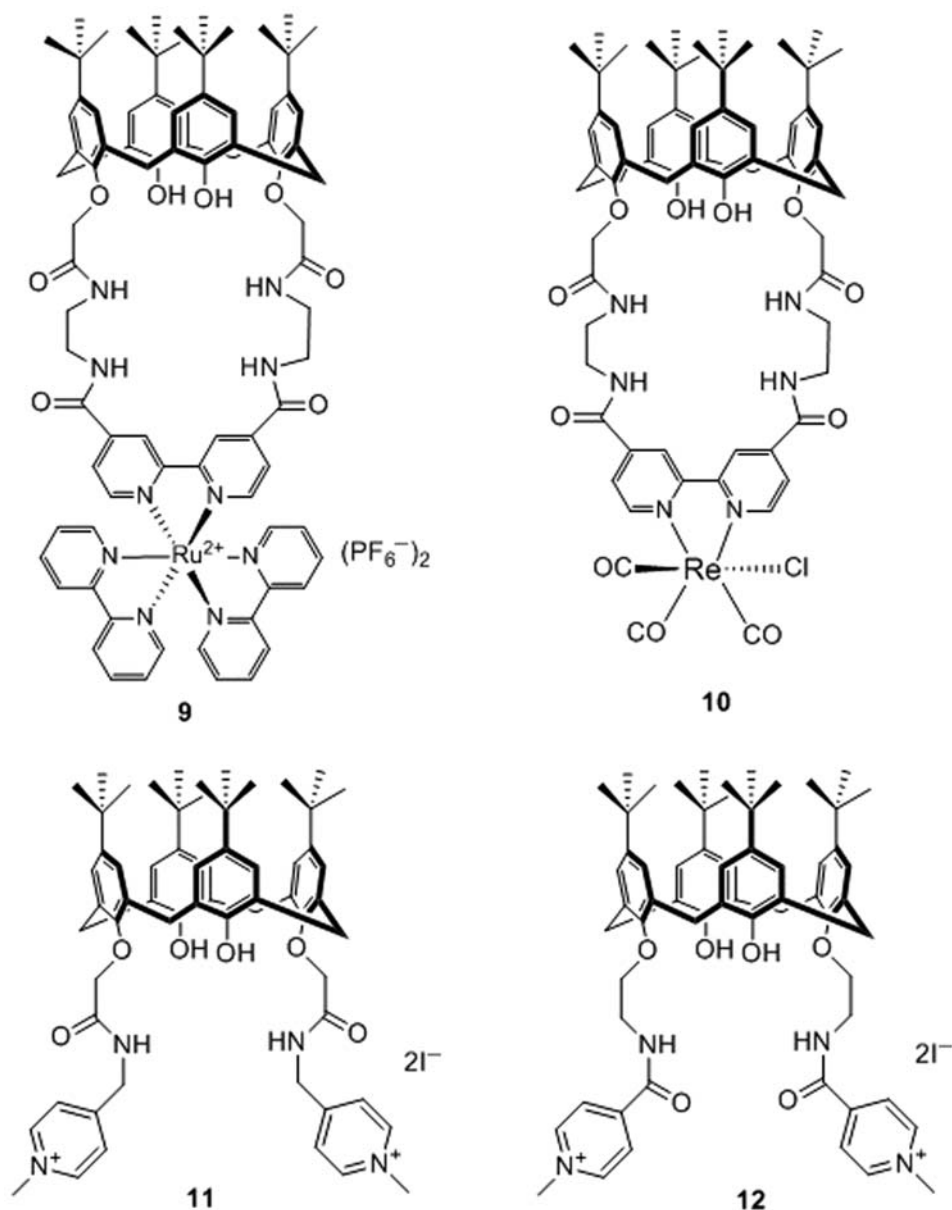


Figure 4. Structures of closely related receptors.

tors **11** and **12** were also reported by Beer et al. (13a). They display 2:1 anion–receptor stoichiometry. Proton NMR titration studies revealed that **11** recognises Cl^- , Br^- , H_2PO_4^- and HSO_4^- , whereas **12** recognises Cl^- , Br^- and HSO_4^- . Binding constants for these receptors with anions ranged from 45,225 to $<20\text{ M}^{-2}$ (Table 2).

The binding constants that were obtained were then used to calculate binding free energy values, ΔG_{bind} , for the association with anion and receptors, and these values were compared to the complexation energy values of anion–receptor complexes, ΔE , obtained from the molecular mechanics calculations (Table 3). Generally, ΔE values were an order of magnitude or greater than ΔG_{bind} values. This is attributed to the difference in media

used to perform the calculations and the NMR studies. Calculations were performed in the gas phase or using a solvation model for CHCl_3 (dielectric constant, $\epsilon = 4.81$), while the NMR studies were done in DMSO, (dielectric constant, $\epsilon = 46.7$) and a good hydrogen bond acceptor solvent. The GB/SA parameters for DMSO are not available. The complexation energy values of association calculated by molecular mechanics methods are highly negative, because these values do not include the unfavourable entropy of association which will be associated with a $-T\Delta S$ term of ca. 12 kcal/mol or more for bimolecular association. In addition, the calculations are based upon anion neutral associations, and the effect of the cation may be substantial, as ion-pairing may disfavour

Table 2. Binding constants^a K (M^{-1}) and K (M^{-2}) of receptors **9**–**12** with anions.

Anions	Receptor 9 [K (M^{-1})]	Receptor 10 [K (M^{-1})]	Receptor 11 [K (M^{-2})]	Receptor 12 [K (M^{-2})]
$H_2PO_4^-$	240	185	45,225	–
HSO_4^-	–	–	<20	160
Cl^-	840	435	8350	1150
Br^-	–	–	170	285
AcO^-	4060	760	–	–

^a Measured in DMSO- d_6 at 27°C by the 1H NMR titration method.Table 3. Comparison of calculated (molecular mechanics, gas phase^a) complexation energy values, ΔE , with the experimental binding free energy value (ΔG_{bind}) for anion–receptor complexes (kcal/mol).

Complexes	Calculated ΔE^b	Experimental (ΔG_{bind}) ^c
$1 \cdot H_2PO_4^-$	–33	–3.3
$2 \cdot H_2PO_4^-$	–32	–2.1
$1 \cdot CH_3CO_2^-$	–29	–2.8
$1 \cdot PhCO_2^-$	–38	–1.6

^a Gas phase calculations are listed for the purposes of comparing all the anion–receptor complexes.^b ΔE is the difference between the energy of the anion–receptor complex and the energy of the anion and receptor separately.^c ΔG_{bind} values were estimated from the experimental association constants at 300 K.

association. The molecular mechanics calculations are provided to give some indication of likely structures of receptors and complexes, and to determine if there are likely differences in binding modes of different anions.

2.4 Molecular dynamics simulations

To gain further insight into the binding modes of anions with receptors so as to explain differences in the molecular mechanics calculations and the NMR binding study results, molecular dynamics (MD) simulations were carried out in the gas phase using MACROMODEL. The simulations were run for 50 ps, with a time step of 5 fs. The global minima of the anion–receptor complexes from the molecular mechanics calculations were used as the starting structures for the MD simulations. We examined the distance between the receptors and anions with a simulation time (Figure 5). Starting distances for the simulations were defined as the average distance from the central atom of the anion and the amide hydrogens and, in some cases, the nitrogen atom of the pyridine moieties of the receptors (see Figure 1 of the Supplementary Information, available online). The greatest variations in distances with simulation times were observed for the receptors with Cl^- . For receptor **1**, the distance ranged from 4.28 to 8.54 Å, whereas for receptor **2** the

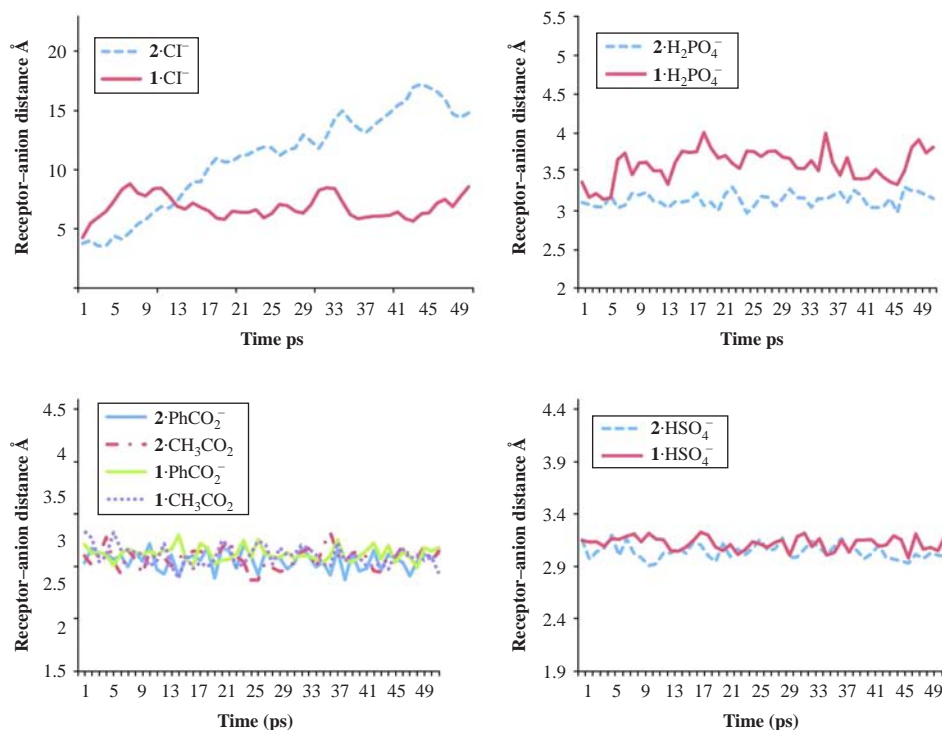


Figure 5. The evolution of anion–receptor distances with time over the course of 50 ps simulations.

distance ranged from 3.78 to 17.2 Å. These large variations (*ca.* 4 Å for receptor **1** and *ca.* 13 Å for receptor **2**) indicate that the associations between Cl^- and the receptors are weak and do not remain intact during the course of the simulation. This is in accord with the lack of binding that was observed between Cl^- and the receptors in the NMR studies. For H_2PO_4^- , distances varied between 3.17 and 4.00 Å for receptor **1** and 3.04 and 3.31 Å for receptor **2**. Small variations in receptor–anion distances with simulation time were also observed for the receptors with the HSO_4^- (0.3 Å) and the carboxylates (0.4 Å for PhCO_2^- and 0.5 Å for CH_3CO_2^-). These small variations account for the binding that is observed in the case of H_2PO_4^- and the carboxylates experimentally, but the MD simulations offer no further insight into the lack of binding between HSO_4^- and the receptors.

3. Conclusion

Novel lower rim distally-substituted calixarenes with linkers containing amide and pyridine moieties have been reported. We felt that the calixarene scaffold was an ideal platform for building our receptors due to the wealth of synthetic procedures that are available for functionalisation of the scaffold. The linkers that are distally-substituted at the lower rim of the calixarene with pyridine and amide moieties offer a degree of preorganisation for anion complexation as shown in this work, as well as the complexation of Ag(I) and Hg(II) salts. These pyridine-functionalised calixarenes can also serve as model complexes for other pyridine-based ligands (bipyridine and terpyridine) that can be used to functionalise receptors. ^1H NMR and computational studies showed that receptor **1**, bearing the ethylene linker, recognises dihydrogen phosphate and carboxylates with moderate selectivity for dihydrogen phosphate. Receptor **2**, bearing the hexylene linker, recognises dihydrogen phosphate. The recognition properties displayed by these receptors are similar to other distally-substituted calixarenes containing ethylene linkers between the amide moieties reported by Balzani and co-workers (*13a*) and Walsh and co-workers (*13b*). Future work will involve evaluating these receptors for ion-pair recognition and modifying these receptors by incorporating a chromophore whose spectroscopic signal can be utilised in the sensing of anions.

4. Experimental

General experimental methods. All reactions were carried out under an Argon atmosphere. All solvents were obtained from a J.C. Meyer solvent dispensing system and used without further purification: flash chromatography was performed using 230–400 mesh SiliaFlash 60[®] silica gel (Silicycle, Inc., Quebec, Canada). ^1H and ^{13}C NMR spectra were recorded with either 300 or 400 MHz spectrometer, and calibrated using residual solvent peaks

as an internal reference. Mass spectra were recorded in ESI mode.

Compound 5. *N*-Boc-ethylenediamine (0.3378 g, 2.1×10^{-3} mol) was added to a solution of calix[4]arene **1** (0.0308 g, 7.25×10^{-5} mol) in toluene (0.6 ml). The reaction mixture was refluxed overnight. The solvent was removed *in vacuo* and then the product was purified by preparative thin-layer chromatography (TLC) (silica, 10% MeOH in CH_2Cl_2). A colourless oil was produced which upon drying or recrystallisation ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ or $\text{CH}_2\text{Cl}_2/\text{hexanes}$) yielded a white solid (0.0285 g, 47.5% yield). ^1H NMR (400 MHz, CDCl_3 , 300 K): δ (in ppm) 8.66 (broad s, 2H, NH), 8.22 (s, 2H, OH), 7.09 (d, $J = 7.5$ Hz, 4H, *m*-ArHOR), 6.99 (d, $J = 7.5$ Hz, 4H, *m*-ArHOH), 6.84 (t, $J = 7.3$ Hz, 2H, *p*-ArHOR), 6.73 (t, $J = 7.3$ Hz, 2H, *p*-ArHOH), 4.63 (s, 4H, ArOCH_2), 4.20 and 3.50 (dd, $J = 13.4$ Hz, 8H, ArCH_2Ar), 3.55–3.34 (m, 8H, $\text{NHCH}_2\text{CH}_2\text{NH}$), 1.35 (s, 18H, $\text{O}-\text{C}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , 300 K): δ (in ppm) 168.9, 156.5, 152.1, 151.3, 133.4, 130.1, 129.5, 128.1, 127.3, 121.3, 79.8, 75.3, 41.2, 39.8, 32.0 and 28.7. HR-ESI-MS, found 825.4020; $\text{C}_{46}\text{H}_{57}\text{N}_4\text{O}_{10}$ ($\text{M} + \text{H}$)⁺, calcd 825.4075.

Compound 6. *N*-Boc-1,6-hexanediamine (0.4724 g, 2.2×10^{-3} mol) was added to a solution of calix[4]arene **1** (0.0296 g, 5.0×10^{-5} mol) in toluene (0.6 ml). The reaction mixture was refluxed overnight. The solvent was removed *in vacuo* and then the product was purified by column chromatography (silica, 10% MeOH in CH_2Cl_2) and then isolated further by preparative TLC. A colourless oil was produced which upon drying or recrystallisation ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ or $\text{CH}_2\text{Cl}_2/\text{hexanes}$) yielded a white solid (0.0236 g, 50.4% yield). ^1H NMR (400 MHz, CDCl_3 , 300 K): δ (in ppm) 8.80 (t, $J = 5.4$ Hz, 2H, NH), 8.10 (s, 2H, OH), 7.11 (d, $J = 7.5$ Hz, 4H, *m*-ArHOR), 6.90 (d, $J = 7.6$ Hz, 4H, *m*-ArHOH), 6.86 (t, $J = 7.4$ Hz, 2H, *p*-ArHOR) and 6.78 (t, $J = 7.5$ Hz, 2H, *p*-ArHOH), 4.60 (s, 4H, ArOCH_2), 4.13 and 3.52 (dd, $J = 13.4$ Hz, 8H, ArCH_2Ar), 3.42–1.266 (m, 12H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$), 1.43 (s, 18H, $\text{O}-\text{C}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3 , 300 K): δ (in ppm) 168.2, 156.4, 152.3, 151.1, 133.1, 130.2, 129.6, 127.8, 127.3, 121.2, 79.3, 75.4, 40.8, 39.8, 32.0, 30.1, 29.5, 28.8, 27.2 and 26.9. HR-ESI-MS, found 954.5596; $\text{C}_{58}\text{H}_{67}\text{N}_6\text{O}_{10}$ ($\text{M} + \text{NH}_4$)⁺, calcd 954.5592.

Compound 7.2TFA. Compound **5** (0.0898 g, 1.09×10^{-4} mol) was added to a round-bottomed flask, and 5 ml of a 20% TFA/ CH_2Cl_2 solution was added to the flask and the reaction was stirred at 0°C until TLC showed that the reaction was complete (~ 1 –2 h). TFA was removed using the following procedure. $\text{N}_2(\text{g})$ was blown into the flask until all the solvent was removed. CH_2Cl_2 was added, the solution was briefly stirred and the solvent was removed by blowing $\text{N}_2(\text{g})$ into the flask. This was repeated three more times. The resulting cream-coloured solid was dried on the vacuum line overnight. Yield: 0.0849 g, 91.5%. ^1H NMR (400 MHz, $\text{MeOH}-d_4$, 300 K): δ (in ppm), 7.15

(d, $J = 7.5$ Hz, 4H, *m*-ArHOR), 6.98 (d, $J = 7.6$ Hz, 4H, *m*-ArHOH), 6.80 (t, $J = 7.6$ Hz, 2H, *p*-ArHOR), 6.72 (t, $J = 7.5$ Hz, 2H, *p*-ArHOH), 4.64 (s, 4H, ArOCH₂), 4.26 and 3.51 (dd, $J = 13.3$ Hz, 4H, ArCH₂Ar), 3.79 (t, $J = 5.9$ Hz, 2H, NHCH₂CH₂NH₂), 3.23 (t, $J = 5.7$ Hz, 2H, NHCH₂CH₂NH₂); ¹³C NMR (75 MHz, MeOH-*d*₄, 300 K): δ (in ppm) 170.9, 152.4, 151.6, 133.5, 129.5, 129.0, 128.1, 126.1, 120.3, 74.1, 40.0, 37.0 and 31.1; MS (ESI): calcd. For [M]⁺ $m/z = 624.29$, found [M + H]⁺ $m/z = 625.2$ and [M + Na]⁺ = 647.2. HR-ESI-MS, found 625.3010; C₃₆H₄₀N₄O₆ (M + H)⁺ calcd 625.3026.

Compound 8.2TFA. Compound **6** (0.1198 g, 1.28×10^{-4} mol) was added to a round-bottomed flask, and 5 ml of a 20% TFA/CH₂Cl₂ solution was added to the flask and the reaction was stirred at 0°C until TLC showed that the reaction was complete (~1–2 h). TFA was removed using the following procedure. N₂(g) was blown into the flask until all the solvent was removed. CH₂Cl₂ was added, the solution was briefly stirred and the solvent was removed by blowing N₂(g) into the flask. This was repeated three times. The resulting cream-coloured solid was dried on the vacuum line overnight. Yield: 0.1196 g, 96.9%. ¹H NMR (400 MHz, MeOH-*d*₄, 300 K): δ (in ppm) 9.05 (broad singlet, 2H, NH), 7.20 (d, $J = 7.7$ Hz, 4H, *m*-ArHOR), 7.04 (d, $J = 7.5$ Hz, 4H, *m*-ArHOH), 6.86 (t, $J = 7.3$ Hz, 2H, *p*-ArHOR), 6.77 (t, $J = 7.7$ Hz, 2H, *p*-ArHOH), 4.68 (s, 4H, ArOCH₂), 4.20 and 3.59 (dd, $J = 13.5$ Hz, 4H, ArCH₂Ar), 3.44–1.38 (m, 12H, NHCH₂CH₂CH₂CH₂CH₂CH₂NH); ¹³C NMR (75 MHz, MeOH-*d*₄, 300 K): δ (in ppm) 169.5, 152.1, 151.1, 133.4, 129.8, 129.4, 127.9, 126.6, 120.8, 74.4, 39.5, 39.4, 31.3, 29.2, 27.4, 26.6 and 26.2; MS (ESI): calcd. For [M]⁺ $m/z = 736.4$, found [M + H]⁺ $m/z = 737.3$ and [M + Na]⁺ = 759.4. HR-ESI-MS, found 737.4279; C₄₄H₅₇N₄O₆ (M + H)⁺, calcd 737.4278.

Receptor 1. Compound **7** (11.2 mg, 1.31×10^{-5} mol) was added to a round-bottomed flask with 1 ml DMF, and the resulting solution was stirred under inert atmosphere. HATU (39.1 mg, 1.03×10^{-4} mol), 2-pyridyl acetic acid (18 mg, 1.03×10^{-4} mol) and TEA (46 μ l, 3.28×10^{-4} mol) were added to a second round-bottomed flask along with 1 ml DMF. The resulting solution was stirred under inert atmosphere for 5 min. The contents of this round-bottomed flask were added to the calixarene solution, and the resulting reaction mixture was stirred under Ar until TLC analysis showed reaction completion (8–24 h). The product, a colourless oil, was isolated by removing DMF *in vacuo* and dissolving the residue in the minimum amount of CH₂Cl₂ and performing preparative TLC (10% MeOH, CH₂Cl₂). Yield (5.6 mg, 49.5%). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K): δ (in ppm) 8.58 (t, $J = 5.9$ Hz, 2H, NH), 8.43 (d, $J = 4.9$ Hz, 2H, py-*H*), 8.36 (s, 2H, ArOH), 8.14 (t, $J = 5.1$ Hz, 2H, NH), 7.66 (t, $J = 8.4$ Hz, 2H, py-*H*), 7.20 (m, 4H, py-*H*), 7.17 (d, $J = 7.7$ Hz, 4H, *m*-ArHOR), 7.07 (d, $J = 7.7$ Hz, 4H, *m*-ArHOH), 6.81 (t, $J = 7.7$ Hz, 2H, *p*-ArHOR), 6.61 (t,

$J = 7.6$ Hz, 2H, *p*-ArHOH), 4.52 (s, 4H, ArOCH₂), 4.23 and 3.47 (dd, $J = 13$ Hz, 8H, ArCH₂Ar), 3.41 (s, 4H pyCH₂CONH), 3.43–3.28 (m, 8H, NHCH₂CH₂NH). ¹³C NMR (75 MHz, CH₃OH-*d*₄, 300 K): δ (in ppm) 170.4, 168.7, 154.5, 151.2, 150.2, 147.6, 136.4, 132.5, 128.4, 128.0, 126.7, 125.0, 123.4, 121.3, 119.3, 73.2, 43.0, 38.1, 37.4, 30.0 and 28.6. HR-ESI-MS, found 863.3789; C₅₀H₅₁N₆O₈ (M + H)⁺, calcd 863.3768.

Receptor 2. Compound **8** (9.0 mg, 9.33×10^{-6} mol) was added to a round-bottomed flask with 1 ml DMF, and the resulting solution was stirred under inert atmosphere. HATU (28 mg, 7.3×10^{-5} mol), 2-pyridyl acetic acid (12.5 mg, 7.18×10^{-5} mol) and TEA (32.5 μ l, 2.33×10^{-4} mol) were added to a second round-bottomed flask along with 1 ml DMF. The resulting solution was stirred under inert atmosphere for 5 min. The contents of this round-bottomed flask were added to the calixarene solution, and the resulting reaction mixture was stirred under inert atmosphere until TLC analysis showed reaction completion (8–24 h). The product, a yellow oil, was isolated by removing the DMF *in vacuo* and dissolving the residue in the minimum amount of CH₂Cl₂ and performing preparative TLC (10% MeOH, CH₂Cl₂). Yield: 6 mg, 65.9%. ¹H NMR (400 MHz, DMSO-*d*₆, 300 K): δ (in ppm) 8.51 (t, $J = 5.4$ Hz, 2H, NH), 8.45 (d, $J = 4.0$ Hz, 2H, py-*H*), 8.32 (s, 2H, ArOH), 8.00 (t, $J = 5.6$ Hz, 2H, NH), 7.70 (t, $J = 7.9$ Hz, 2H, py-*H*), 7.30 (d, $J = 7.9$ Hz, 2H, py-*H*), 7.21 (t, $J = 6.0$ Hz, 2H, py-*H*), 7.17 (d, $J = 7.6$ Hz, 4H, *m*-ArHOR), 7.06 (d, $J = 7.7$ Hz, 4H, *m*-ArHOH), 6.82 (t, $J = 7.7$ Hz, 2H, *p*-ArHOR), 6.62 (t, $J = 7.7$ Hz, 2H, *p*-ArHOH), 4.53 (s, 4H, ArOCH₂), 4.19 and 3.50 (dd, $J = 13$ Hz, 8H, ArCH₂Ar), 3.57 (s, 4H pyCH₂-CONH) (buried under solvent residual peak), 3.30 (m, 4H, NHCH₂CH₂CH₂CH₂CH₂CH₂NH), 3.00 (m, 4H, NHCH₂-H₂CH₂CH₂CH₂CH₂CH₂NH), 1.52 (m, 4H, NHCH₂CH₂-H₂CH₂CH₂CH₂CH₂CH₂NH), 1.27 (m, 12H, NHCH₂CH₂CH₂CH₂CH₂CH₂NH); ¹³C NMR (75 MHz, DMSO-*d*₆, 300 K): δ (in ppm) 171.0, 169.5, 156.0, 152.2, 151.2, 148.8, 137.7, 133.4, 129.7, 129.3, 127.9, 126.5, 124.5, 122.6, 120.7, 74.5, 44.7, 39.4, 31.3, 29.8, 29.3, 29.1, 26.8 and 26.7. HR-ESI-MS, found 975.5021; C₅₈H₆₇N₆O₈ (M + H)⁺, calcd 975.5020.

Supplemental material

Supplemental material is available online. DOI: 10.1080/10610278.2013.794946

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Note

- Compound **7** (not as the TFA salt) has been previously synthesised (see Ref. (10)).

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