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A Novel Ditopic Receptor and Reversal of Anion Binding Selectivity in the Presence and Absence of Bound Cation

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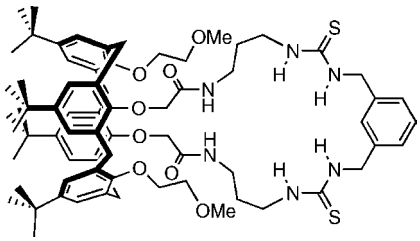
ABSTRACT



A calix[4]arene-derived ditopic receptor 1 has been synthesized. In the absence of Na^+, the receptor binds acetate in preference to diphenyl phosphate (as the tetrabutylammonium salts), but in the presence of Na^+, the selectivity is reversed and the receptor, instead, binds diphenyl phosphate, and not acetate, which preferentially forms a salt ion-pair in free solution.

Anion recognition continues to be a very active and challenging area of research with the possible application of selective ion receptors in biological and environmental systems. Recognition of an anion by neutral receptors can be problematic, however, when there is competition from ion-pairing of the anion with its countercation in solution. A solution to this problem is to prepare ditopic receptors which simultaneously bind both anion and cation, thus producing an overall neutral complex. Several such ditopic receptors have been described and demonstrate that binding of the ion-pair can be stronger than binding either of the cation or anion on their own.[1] Calix[4]arene is one of the most commonly used scaffolds for producing synthetic receptors and has been used to produce ditopic receptors in which the cation and anion binding sites are on opposite rims of the calix[4]arene structure[2] or are together on the same side.[3]

In this paper, we describe the novel cyclic calix[4]arene receptor **1**, featuring both a cation binding site in the form of ether/amide functionality and an anion binding site in the form of a bisthiourea, together on the lower (narrow) rim of the calix[4]arene scaffold. Thioureas are well-known for their anion binding properties, and the *m*-xylyl bisthiourea motif has been previously shown to be a potent binding site for carboxylate and phosphate anions.[4]

Receptor **1** was synthesized from diacid **2**, which was prepared from *p-tert*-butylcalix[4]arene by sequential alky-

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(1) Recent reviews that discuss ion-pair binding: Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, 486. Gale P. A. *Coord. Chem. Rev.* **2003**, *240*, 191. See also Mahoney, J. M.; Beatty, A. M.; Smith B. D. *J. Am. Chem. Soc*. **2001**, *123*, 5847. Deetz, M. J.; Shang, M.; Smith, B. D. *J. Am. Chem. Soc.* **2000**, *122*, 6201 and citations therein.

(2) Scheerder, J.; van Duynhoven, J. P. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **1996**, *35*, 1090. Webber, R. A.; Beer, P. D. *J. Chem. Soc., Dalton Trans.* **2003**, 2249.

(3) Beer, P. D.; Chen, Z.; Gale, P. A.; Heath, J. A.; Knubley, R. J.; Ogden, M. I. *J. Inclusion Phenom.* **1994**, *19*, 343.

(4) Nishizawa, S.; Bühlmann, P.; Iwao, M.; Umezawa, Y. *Tetrahedron Lett*. **1995**, *36*, 6483−6486. Sasaki, S.; Mizuno, M.; Naemura, K.; Tobe, Y. *J. Org. Chem.* **2000**, *65*, 275.

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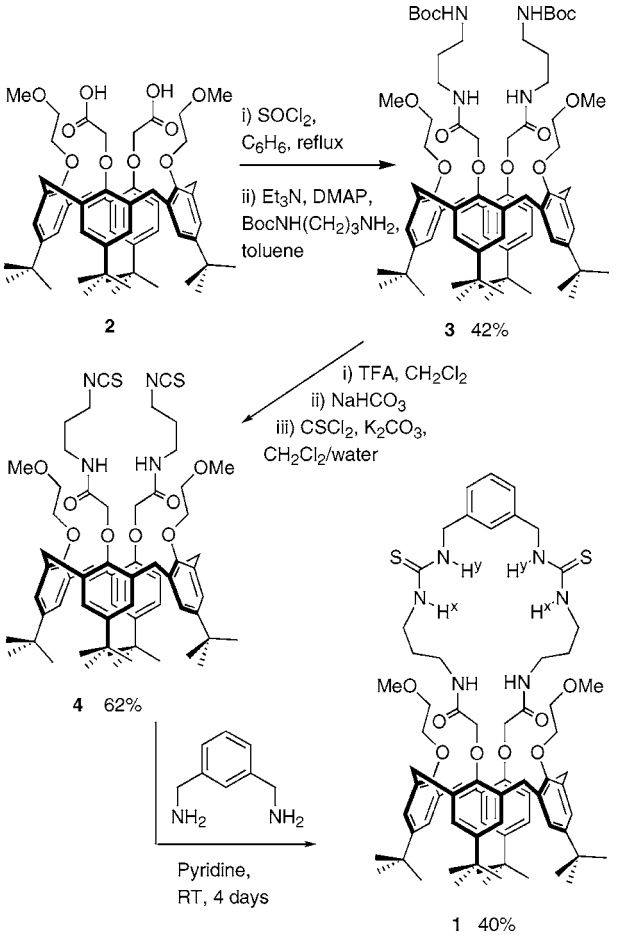
lation with 2-bromoethyl methyl ether and bromomethyl methyl acetate, respectively, using an adapted literature procedure.[5] Diacid **2** was converted to the bisacid chloride and coupled with *N*-Boc-1,3-diaminopropane to give the bisprotected diamine **3** in 42% yield (Scheme 1).

Scheme 1. Synthesis of Receptor **1**



The Boc protecting groups were removed using trifluoroacetic acid, and the resulting diamine was reacted with thiophosgene to give bisisothiocyanate **4** in 62% yield. Slow addition of *m*-xylylenediamine to a solution of **4** in pyridine,[6] gave the desired cyclic receptor **1**, which was purified by column chromatography and obtained in 40% yield as a white solid.

Recrystallization from methanol yielded crystals suitable for X-ray crystallography.[7] The crystal structure of **1** (Figure 1) shows that the calixarene adopts a pinched cone conformation with the ethylene glycol substituents suitably disposed to fold in and bind a metal cation at the base of the calixarene and the two thiourea units effectively orientated to provide an anion binding site, as intended.

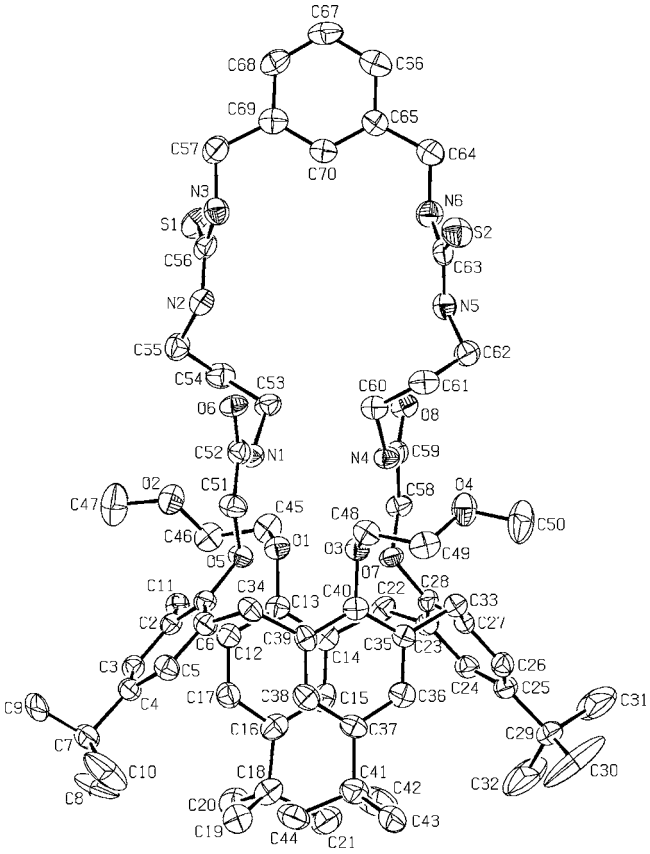


Figure 1. Crystal structure of receptor **1**.

The binding properties of receptor **1** were initially assessed by determining if the receptor led to solubilization of various anions (as the sodium salts) in $CDCl_3$.[8] From these experiments it was rapidly determined that the receptor led to significant solubilization of acetate, phenylphosphinate, and diphenyl phosphate, but no significant solubilization of chloride, bromide, sulfate, nitrate, benzoate, hydrogen phosphate, or dihydrogenphosphate (all as the sodium salts) or of zwitterionic amino acids L-phenylalanine or L-alanine. Binding constants for the three anions acetate, phenylphosphinate, and diphenyl phosphate (as the tetrabutylammonium

(5) Mogck, O.; Parzuchowski, P.; Nissinen, M.; Böhmer, V.; Rokicki, G.; Rissanen, K. *Tetrahedron* **1998**, *54*, 10053.

(6) Santoyo-González, F.; Torres-Pinedo, A. Barria, C. S. *Eur. J. Org. Chem.* **2000**, 3587.

(7) Crystallographic data: $C_{72}H_{104}N_6O_{10}S_2$, orthorhombic, space group $Pna2_1$, a = 23.8484(9) Å, b = 20.3212(6) Å, c = 15.0907(4) Å, U = 7313.4(4) Å^3, D_c = 1.160 Mg m^{-3}, Z = 4, T = 120(2) K, colourless rod, 0.26 × 0.08 × 0.06 mm^3. Data collection was carried out using a Bruker-Nonius KappaCCD area detector and SHELXS-97 and SHELXL-97 programs were used for structure solution and refinement. 25269 reflections collected, 11 335 independent [R(int) = 0.0646], giving R_1 = 0.0530 for observed unique reflections [$F^2 > 2s(F^2)$] and wR_2 = 0.1389 for all data. The maximum and minimal residual electron densities on the final difference Fourier map were 0.358 and −0.227 eÅ^{-3}, respectively. The asymmetric unit contains two molecules of water and one tertiary butyl group exhibits some disorder. Supplementary data have been deposited with the CCDC in CIF format with the deposition number CCDC224706.

(8) The sodium salt of the requisite anion was suspended in a solution of receptor **1** in $CDCl_3$ and stirred vigorously. The resulting solution was filtered, and the ^{1}H NMR spectrum was recorded. The degree of solubilisation of the salt was determined by integration of signals for receptor and anion. For inorganic anions (which do not have signals in the ^{1}H NMR spectrum), lack of solubilization was adjudged by the fact that the spectrum for the receptor after stirring with the sodium salt was unaltered relative to the spectrum of the receptor on its own.

salts) with receptor **1**, in CD_3CN, were then determined using NMR titration experiments. Addition of aliquots of the anions led to significant downfield shifts of the thiourea NH signals (>1 ppm) and amide NH signals (0.3−0.7 ppm) indicative of hydrogen bond formation and suggesting that the amide proton is significantly involved in the anion binding.

The binding constants were calculated by analyzing the titration data using the NMRTit_HG computer program[9] and are summarized in Table 1. A 1:1 binding stoichiometry with all three anions was confirmed with Job plots.[10]

Table 1. Binding Constants for Receptor **1** with Anions in the Absence of, and in the Presence of, Na^+ (in CD_3CN)

		binding constants (M^{-1})	
receptor	anions	without Na^+	with Na^+
1	$CH_3CO_2^-$	11 000	
1	$PPh(H)(O)O^-$	24 000	
1	$Ph_2PO_4^-$	1800	2200

The receptor binds the tetrahedral anion phenylphosphinate more strongly than the Y-shaped acetate anion. Diphenyl phosphate, however, is bound significantly less strongly. This is in contrast to results from Umezawa and from Tobe[4] who reported that simple receptors featuring a *m*-xylyl bisthiourea motif bound phosphates significantly more strongly than acetate. In the present case, the weaker binding of diphenyl phosphate compared to acetate may not be simply due to the size of the guest ie. to steric factors (since phenylphosphinate is bound strongly), but might be attributable to electronic repulsion between the phenoxy groups of the anion and the ether oxygens in the receptor.

Binding of the three alkali metal cations Li^+, Na^+, and K^+ in CD_3CN was also investigated using NMR titration experiments. Addition of aliquots of the perchlorate salts[11] to a solution of receptor **1** led to the appearance of a new set of signals in the ^1H NMR spectrum for the bound receptor and a decrease in intensity for the signals from the unbound receptor. The NH signals of the receptor-metal complex were generally rather broad and were not significantly shifted compared to the free receptor, but new signals for several CH's were clearly identifiable, most notably for signals for the calix-ArCH_2Ar which appeared 0.2 ppm further downfield for the metal-bound receptor. Binding of the alkali metal cations by receptor **1** is a slow exchange process on the NMR time scale and binding constants were calculated using the method described by Macomber[12] (Table 2). The receptor clearly binds Na^+ more strongly than the two other cations.

Table 2. Binding Constants for **1** with Alkali Metal Cations (in CD_3CN)

	binding constant (M^{-1})		
receptor	Li^+	Na^+	K^+
1	760	5500	970

Binding studies with the two anions, acetate and diphenyl phosphate, and receptor **1** were then carried out in the presence of Na^+. One equivalent of $NaClO_4$ was added to the sample of receptor in CD_3CN, giving ~90% saturation of the receptor, and minimizing the amount of free Na^+ cation in the solution.

With receptor **1**·Na^+ complex, addition of acetate did not lead to any significant shifts for the NH signals until >1 equiv of anion had been added, at which point significant downfield shifts were noted, similar to those observed on addition of the anion to free receptor, and consistent with 1:1 binding (Figure 2).

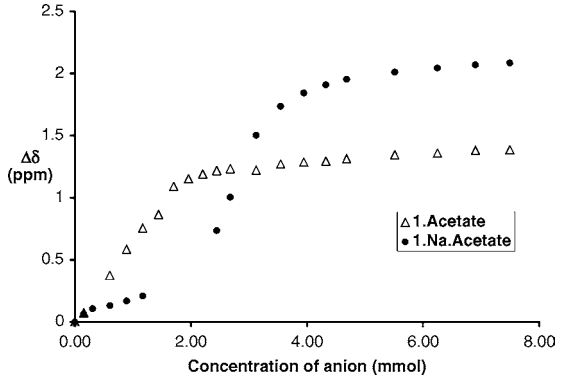


Figure 2. Titration binding curves for receptor **1** (1.87 mM in CD_3CN) with acetate (Δ) and receptor **1**·Na^+ complex (1.87 mM in CD_3CN) with acetate (●) following the thiourea NH^x signal. Some data points for the latter titration could not be determined due to overlap with other signals.

These data clearly indicates that addition of the first equivalent of anion leads to sequestering of the cation from the receptor to form a more stable ion-pair in solution, and anion binding by the receptor is effectively inhibited by this process. Smith et al.[13] have described a related effect in which binding of anions by a simple neutral host was inhibited in the presence of metal cations in solution as a result of preferential salt ion-pairing. In their case, they were able to reverse the inhibition by using a ditopic receptor able to simultaneously bind the metal cation and anion.

(9) Bisson, A. P.; Hunter, C. A.; Morales, J. C.; Young, K. *Chem. Eur. J.* **1998**, *4*, 845. Errors in the calculated association constants were estimated, based on quality of fit of the experimental data with the theoretical curve, and experimental errors in carrying out the experiment, as <10%. Association constants are therefore reported to 2 s.f. Detailed binding data and titration curves are provided in the Supplementary Information.

(10) (a) Connors, K. A. *Binding Constants, The Measurement of Molecular Complex Stability*; Wiley: New York, 1987; p 24. (b) Job, A. *Ann. Chim.* **1928**, *9*, 113.

(11) CAUTION: perchlorate salts are potentially explosive.

(12) Macomber, R. S. *J. Chem. Educ.* **1992**, *69*, 375. Errors in the calculated association constants were estimated, based on experimental errors in carrying out the experiment, as <10%. Association constants are therefore reported to 2 s.f.

(13) Shukla, R.; Kida, T.; Smith, B. D. *Org. Lett.* **2000**, *2*, 3099. See also: Camiolo, S.; Coles, S. J.; Gale, P. A.; Hursthouse, M. B.; Tizzard, G. J. *Supramol. Chem.* **2003**, *15*, 231.

Addition of diphenyl phosphate to receptor **1**·Na^+ complex, however, gave titration data consistent with 1:1 binding (confirmed by a Job plot[10]) and $K_{assoc} = 2200\ M^{-1}$ (Table 1), slightly larger than the binding constant for diphenyl phosphate with free receptor **1**. Binding of diphenyl phosphate with receptor **1**·Na^+ complex, however, leads to a significant downfield shift of the thiourea proton NH^x (>1.2 ppm) but a negligible shift of the other thiourea proton NH^y, suggesting that in the **1**·Na^+·diphenyl phosphate complex interaction with thiourea proton NH^y may be negligible. This may be compensated for by electrostatic interactions between the phenoxy groups with the bound Na^+.

Thus, receptor **1**, in the absence of a bound Na^+ cation, shows an unexpected selectivity for acetate anion over diphenyl phosphate, which might be attributed to electrostatic repulsion between the phenoxy groups of the latter and the ether oxygens in the receptor. In the presence of Na^+ cation, the phenoxy groups may interact favorably with the bound cation, leading to the observed strong binding of the ion-pair, whereas the ion-pairs sodium acetate and sodium phenylphosphinate are not bound by the same receptor.[14]

Acknowledgment. This work was supported by the Thailand Research Fund (PHD/00190/2541). G.T. is a Ph.D. student supported by the Royal Golden Jubilee Program.

Supporting Information Available: Detailed binding data from NMR titration experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Calixarene-derived receptors which change conformation on binding a metal cation and thereby allow anion binding have been described: Murakami, H.; Shinkai, S. *Tetrahedron Lett.* **1993**, *34*, 4237. Murakami, H.; Shinkai, S. *Chem. Commun.* **1993**, 1533.