ChemComm

Anthracene-linked calix[4]pyrroles: fluorescent chemosensors for anions

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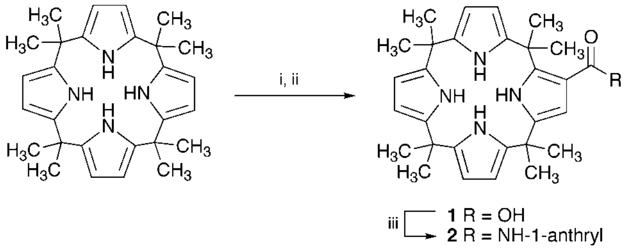
Received (in Cambridge, UK) 24th June 1999, Accepted 27th July 1999

Fluorescent anthracene–calix[4]pyrrole conjugates 2, 4 and 5 have been synthesized; these receptors can detect the presence of anions (*e.g.* F^-, Cl^-, $H_2PO_4^-$) by a significant quenching of their fluorescence.

The selective detection of guest species by redox[1] or photoactive[2] host molecules is a challenging area of supramolecular chemistry that has attracted increasing interest in the last few years. In spite of this, optical sensors for anions are still relatively rare.[3–7] We have recently discovered that calix[4]pyrroles, a class of molecule known for over a century, are effective anion binding agents in solution and in the solid state.[8–10] Our first attempt at using the calixpyrrole moiety as a sensor involved attaching redox active ferrocene moieties to the calixpyrrole skeleton *via* amide linkages and studying perturbations in the ferrocene/ferrocenium redox couple on addition of anionic guests.[11] Substantial changes occurred in the electrochemical properties of these materials but these changes were unpredictable and difficult to rationalize. We therefore decided to investigate whether calix[4]pyrrole, when combined with a fluorescent reporter group, would act as an optical sensor for anions. Here we report the synthesis a series of compounds **2**, **4** and **5** that contain a calix[4]pyrrole anion binding site linked to a fluorescent anthracene moiety.

In order to minimise the distance between the anion binding site and the fluorophore (and also provide a conjugated bond pathway between them), a new calix[4]pyrrole-monoacid precursor **1** was prepared using a modification of the procedure used previously to prepare a homologous calix[4]pyrrole ester derivative.[12] Specifically, *meso*-octamethylcalix[4]pyrrole[13] was dissolved with stirring in dry THF under an argon atmosphere, and the flask cooled to −78 °C. A solution of BuLi in hexanes (4.0 equiv.) was added dropwise to the calix[4]pyrrole solution and, after 30 min, solid CO_2 was added. The reaction was stirred for a further 3 h at −78 °C and then allowed to warm to room temperature. The solvent was removed and the residue was suspended in water. The suspension was filtered to remove unreacted *meso*-octamethylcalix[4]pyrrole and the solution was acidified with perchloric acid, whereupon calix[4]pyrrole acid **1** precipitated out as a white powder. Recrystallisation from acetone–water by slow evaporation produced colourless crystals of the mono-acid **1** in 6.8% yield. The anthracene-linked calix[4]pyrrole **2** was prepared by activation of calix[4]pyrrole acid **1** with DCC and hydroxybenzotriazole hydrate (HOBt) in DMF followed by treatment with commercially available 1-aminoanthracene. Purification by column chromatography afforded compound **2** in 34% yield (Scheme 1).



Scheme 1 *Reagents and conditions*: i, BuLi (4 equiv.), THF; ii, CO_2; iii, 1-aminoanthracene, DCC, HOBt, DMF.

Compound **4** was prepared by coupling calixpyrrole monoacid **3**[12,14] with 1 equiv. of 1-aminoanthracene using the benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) amide coupling reagent (1.1 equiv.) in DMF in the presence of excess Et_3N. After removal of DMF, the calixpyrrole–anthracene conjugate **4** was isolated as a yellow foam by column chromatography in 63% yield. Compound **5** was prepared in an analogous manner by coupling compound **3** with 9-aminomethylanthracene.[15] Compound **5** was isolated by column chromatography as a yellow foam in 51% yield.

Initial complexation studies were conducted using ^1H NMR titration techniques. Aliquots of the tetrabutylammonium salts of the putative anionic guests (0.1 mol dm^{-3}) were added to a solution of compound **2**, **4** or **5** (0.01 mol dm^{-3}) in CD_3CN and the shift of the calix[4]pyrrole NH proton noted after each addition. Significant downfield shifts of the pyrrole NH protons were observed upon addition of anions, consistent with the formation of calixpyrrole–anion hydrogen bonds. In the presence of fluoride anions, the NMR spectrum broadened considerably, making a determination of the stability constant impossible by this method. However, analysis of the remaining titration data using the EQNMR[16] computer program revealed that the compounds form 1:1 receptor:anion complexes with chloride, dihydrogen phosphate and bromide anions. The resulting stability constants are shown in Table 1.

Fluorescence quenching experiments were carried out by addition of solutions of anions (tetrabutylammonium fluoride, chloride, bromide, dihydrogenphosphate or hydrogensulfate) to

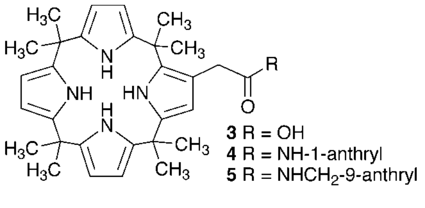


Table 1 Stability constants of compounds **2**, **4** and **5** with various anions in the form of tetrabutylammonium salts determined by ^1H NMR titration in CD_3CN; errors $< 15\%$

	log *K* in CD_3CN		
Anion	2	4	5
F^-	[a]	[a]	[a]
Cl^-	> 4	> 4	> 4
Br^-	3.59	3.00	2.63
$H_2PO_4^-$	> 4[b]	3.50	3.08
HSO_4^-	2.77	[c]	[c]

[a] NH resonance broadened precluding a determination of this value using NMR spectroscopic methods. [b] Stability constant determined by following pyrrole CH resonance. [c] Weak interaction $K < 20$ M^{-1}.

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Table 2 Stability constants for compounds **2**, **4** and **5** with various anions (as tetrabutylammonium salts) in CH_3CN and CH_2Cl_2 as determined from fluorescence quenching analyses at 25 °C. Compound **2** excited at 378 nm, emission λ_{max} at 446 nm, compound **4** excited at 393 nm, emission λ_{max} at 429 nm and compound **5** excited at 387 nm, emission λ_{max} at 418 nm. Errors are estimated to be $< 15\%$

	log *K* in CH_2Cl_2			log *K* in CH_3CN		
Anion	**2**	**4**	**5**	**2**	**4**	**5**
F^-	4.94	4.52	4.49	5.17	4.69	4.69
Cl^-	3.69	2.96	2.79	4.87	3.81	3.71
Br^-	3.01	[a]	[a]	3.98	2.86	[a]
$H_2PO_4^-$	4.20	3.56	[a]	4.96	3.90	[a]

[a] Quenching insufficient to provide an accurate stability constant value.

50 μM solutions of compounds **2**, **4** and **5** in CH_2Cl_2 or CH_3CN. Excitation and λ_{max} (emission) values for the three compounds are given in the footnote to Table 2. Significant fluorescence quenching was observed upon addition of tetrabutylammonium fluoride to compounds **2**, **4** and **5**. For example, the fluorescence spectra of compound **2** obtained as a function of added fluoride anion are shown in Fig. 1.

Quenching was also observed in varying degrees upon addition of other anions to receptors **2**, **4** and **5**. This is illustrated in Fig. 2(*a*) which shows the effects of different anions on the fluorescence of compound **2** in CH_2Cl_2. In this instance it can be seen that, on a per molar basis, the addition of fluoride anion causes the greatest fluorescence quenching, followed by the addition of dihydrogenphosphate and chloride anions. Using these quenching data and standard Scott plot analyses,[17] association constants were calculated for receptors **2**, **4** and **5** interacting with fluoride, chloride, bromide and dihydrogenphosphate anions (Table 2). In general, good agreement was observed between these K_a values and those obtained using NMR analyses. However, several of the flourescence-derived plots exhibited biphasic behaviour. This may be due to aggregation of the anthracene moieties, coordination of the anion to the amide moiety,[11] oligomerisation of dihydrogenphosphate anions[18] or heavy atom effects,[2] and is currently the topic of further investigation.

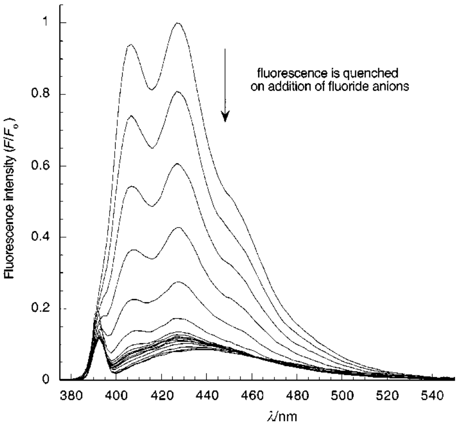

Fig. 1 Fluorescence spectra of calixpyrrole **2** in CH_2Cl_2 (0.05 mM) excited at 378 nm showing the changes induced upon the addition of increasing quantities of tetrabutylammonium fluoride.

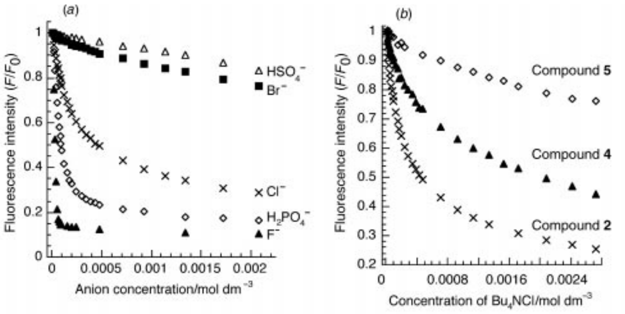

Fig. 2 (*a*) The quenching effect of various anions on compound **2** and (*b*) the fluorescence quenching effect of chloride anions on compounds **2**, **4** and **5**.

Control experiments were carried out with anthracene. At an anthracene concentration of 50 μM in CH_2Cl_2, there was no significant fluorescence quenching observed on addition of fluoride and chloride anions. On the other hand it was found that bromide and iodide acted to quench fluorescence in concentrations between 100 to 1000 mM (presumably due to the heavy atom effect).[2] No significant quenching was observed on addition of dihydrogenphosphate or hydrogensulfate anions to these control anthracene solutions.

A comparison of the quenching caused by chloride at the respective λ_{max} (emission) is shown for each of receptors **2**, **4** and **5** in Fig. 2(*b*). It can be clearly seen that chloride quenches the fluorescence of compound **2** most efficiently and compound **5** least efficiently. This trend may be related to the structure of the receptors and to their affinity for anions. The stability constants of the receptors with chloride follow the trend **2** > **4** > **5** (*cf.* Table 2). Further, the distance between the anthracene fluorophore and the anion-binding site increases in the order **2** < **4** < **5**. Finally, compound **2** has a conjugated bond pathway linking the fluorophore and anion-binding site of the calixpyrrole providing an electronic communication pathway between them, whereas compounds **4** and **5** do not. It might therefore be expected that fluorescence quenching is most efficient in compound **2** and least efficient in compound **5**.

In summary, a series of calixpyrrole–anthracene conjugate compounds have been synthesized that possess conjugated (compound **2**) and unconjugated bond pathways of different lengths (compounds **4** and **5**) between the calix[4]pyrrole anion binding site and the anthracene reporter group. The fluorescence of these receptors is quenched significantly in the presence of certain anionic guests. Compounds **2**, **4** and **5** thus represent prototypical calix[4]pyrrole based-fluorescent anion sensing agents.

This work was supported by the National Institutes of Health (Grant GM58907 to J. L. S.), the Texas Advanced Research Program (Grant No.3658 to J. L. S.) and by a Royal Society University Research Fellowship to P. A. G.

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Communication 9/05054J