

Calix[4]pyrroles: C-rim substitution and tunability of anion binding strength

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Electron-rich and electron-deficient C-rim substituted calix[4]pyrroles 1-4 are synthesised and the anion binding ability of these receptors is found to be dependent upon the C-rim substituents.

Stimulated by how nature utilises anions in numerous biochemically important systems such as chloride channels,¹ proteins² and as polyanions for the storage and transmission of genetic information,³ the molecular recognition of anionic guest species is an area of coordination chemistry attracting increasing interest.⁴⁻⁷ As part of a programme aimed at the synthesis of new easy-to-make anion binding agents, and exploiting our recent discovery that calix[4]pyrroles (*meso*-octaalkylporphyrinogens; first synthesised in 1886 by Baeyer⁸) are effective and selective anion binding agents both in solution and in the solid state,^{9,10} we decided to investigate whether the anion binding ability of these latter materials could be tuned by appending functional groups to the carbon rim (*C*-rim) of the calixpyrrole. Previously, Jacoby *et al.* have investigated modification of the *meso*-octaalkylporphyrinogen skeleton using organometallic methodologies.¹¹ We adopted two strategies for the synthesis of *C*-rim calix[4]pyrroles: firstly, synthesis from 3,4-disubstituted pyrroles and ketones, and secondly, direct modification of the *C*-rim of a pre-synthesised calix[4]pyrrole.

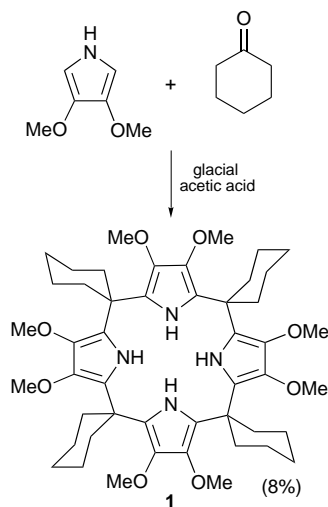
Using the first strategy, 3,4-dimethoxypyrrole¹² was condensed with cyclohexanone in glacial acetic acid. Removal of the acid *in vacuo* and subsequent purification of the residue by column chromatography (silica gel, CH₂Cl₂ eluent) afforded the novel β -octamethoxy-*meso*-tetraspirocyclohexylcalix[4]pyrrole **1** as a white powder in 8% yield (Scheme 1).

Following the second strategy, *meso*-octamethylcalix[4]pyrrole was dissolved with stirring in dry THF under an Ar atmosphere, and the flask cooled to -78 °C. A solution of butyllithium in hexanes (4.0 equiv.) was added dropwise to the calixpyrrole solution and after 30 min, 4.0 equiv. of ethyl bromoacetate were also added. The reaction was stirred for a further 1 h at -78 °C and then allowed to warm to room

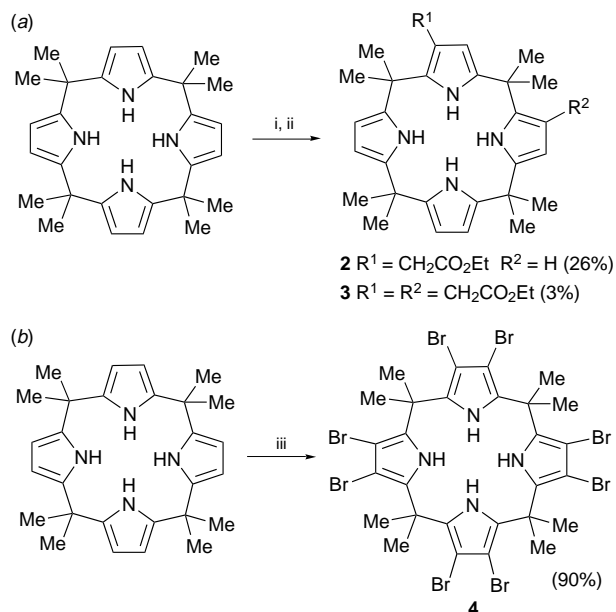
temperature. Purification by column chromatography (silica gel, CH₂Cl₂ eluent) afforded two isolable products. The first proved to be *C*-rim monoester **2** (formed in 26% yield) and the second the diester **3** (3% yield) [Scheme 2(a)]. Surprisingly, ¹H and ¹³C NMR experiments showed that the diester **3** present in the fraction collected was a single isomer. Support for the proposed 1,3-substitution pattern of **3** was obtained from X-ray crystallographic analysis even though the quality of the crystals did not permit a complete refinement.

β -Octabromo-*meso*-octamethylcalix[4]pyrrole **4** was synthesised in 90% yield by reaction of *meso*-octamethylcalix[4]pyrrole with *N*-bromosuccinimide (NBS) in dry THF heated at reflux [Scheme 2(b)]. Single crystals of compound **4** were grown by slow evaporation of a dilute dichloromethane solution of the macrocycle (Fig. 1).[†] The structure reveals that compound **4** exists in a chair-like flattened 1,2-alternate conformation in the solid state (*i.e.* the dihedral angles between pyrrole rings and plane through the calixpyrrole *meso*-carbon atoms are 66.8, 5.8, -66.8 and -5.8°).

Analyses of the solution phase anion binding properties of calix[4]pyrroles **1**, **2** and **4** were made using ¹H NMR spectroscopic titrations carried out in CD₂Cl₂. Data analysis and stability constant determinations were then made using the EQNMR computer program fitting the binding profiles to a 1 : 1 calixpyrrole-anion solution complex model.¹³ The results are summarised in Table 1. Compound **1** has lower stability constants with fluoride and chloride than *meso*-tetraspirocyclohexylcalix[4]pyrrole.⁹ This may be due to the electron-donating ability of the eight *C*-rim methoxy groups causing a decrease in the acidity of the pyrrole NH protons and hence reducing anion binding ability. Likewise compound **2** shows lower stability constants for the complexation of fluoride, chloride and dihydrogen phosphate anions than does *meso*-



Scheme 1



Scheme 2 Reagents: i, BuLi (4 equiv.), THF; ii, BrCH₂CO₂Et (4 equiv.); iii, NBS, THF

octamethylcalix[4]pyrrole.⁹ In this case the reduction in anion binding strength (with the respect to *meso*-octamethylcalix[4]pyrrole) may be due to unfavourable interactions between the bound anion and the lone pair electrons on the oxygen atoms of the *C*-rim ester group.

In contradistinction to receptors **1** and **2**, compound **4** exhibits higher stability constants for the binding of fluoride, chloride and dihydrogen phosphate anions than does *meso*-octamethylcalix[4]pyrrole under the same conditions. This may be due to the electron-withdrawing nature of the eight *C*-rim bromine atoms increasing the acidity of the pyrrole NH protons and thus enhancing anion binding ability.

In summary, we have shown that the anion binding ability of the calix[4]pyrroles can be tuned by appending different groups to the carbon or *C*-rim of the calixpyrrole. Receptors with an increased anion binding ability such as **4** may have potential uses as anion sequestering agents (*e.g.* in removal of phosphate pollutants from aqueous environments) while those with

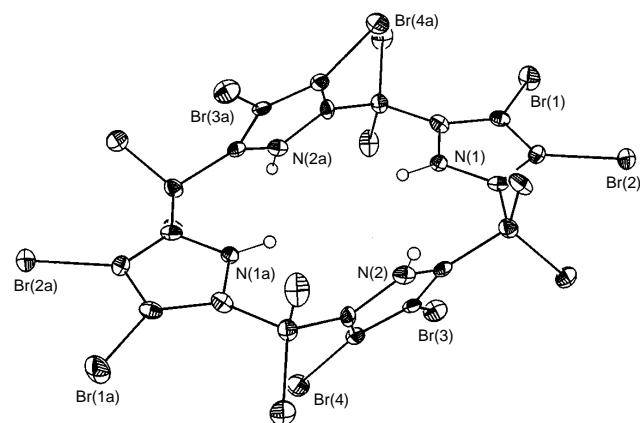


Fig. 1 View of $C_{28}H_{28}N_4Br_8$ **4** showing the flattened 1,2-alternate conformation. Thermal ellipsoids are scaled to the 30% probability level.

Table 1 Stability constants for compounds **1**, **2** and **4** with anionic substrates^a in CD_2Cl_2 at 298 K

Anion	Stability constant/dm ³ mol ⁻¹		
	1	2	4
Fluoride	$1.7 (\pm 0.2) \times 10^2$	$1.1 (\pm 0.2) \times 10^3$	$2.7 (\pm 0.4) \times 10^{4b}$
Chloride	< 10	47 (± 1)	$4.3 (\pm 0.6) \times 10^3$
Dihydrogen-phosphate	— ^c	< 10	$6.5 (\pm 0.4) \times 10^2$

^a Anions were added as 0.03 M CD_2Cl_2 solutions of their tetrabutylammonium salts to 3 mM solutions of the receptor in CD_2Cl_2 with concentration changes being accounted for by EQNMR (ref. 13). In determining the stability constants, the possible effects of ion pairing (if any) were ignored. ^b Estimated value. The NH proton resonance broadened considerably during the titration, forcing the frequency of the resonance to be noted manually. This value should, therefore, be treated with caution. ^c Not determined.

decreased anion binding ability (compounds **1** and **2**) could prove useful as HPLC column media since in this latter application low affinity constants and fast complexation–decomplexation rates generally lead to efficient separation of substrates.¹⁴ In any event the fact that compounds **2** and **3** come ‘prefunctionalised’ with ester groups should facilitate the attachment of other substituents, making it easier to use the calix[4]pyrroles in a range of applications.

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Footnotes

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† *Crystal data* for $C_{28}H_{28}N_4Br_8$: Large, colourless prisms were grown by slow evaporation from CH_2Cl_2 . Crystals were monoclinic, $P2_1/n$, $Z = 2$, $a = 10.819(4)$, $b = 12.042(4)$, $c = 12.746(4)$ Å, $\beta = 99.01(2)^\circ$, $V = 1640.1(10)$ Å³, $D_c = 2.15$ g cm⁻³, $\mu = 98.07$ cm⁻¹, $F(000) = 1008$. A total of 7416 reflections were measured, 3763 unique [$R_{int}(F^2) = 0.091$] on a Siemens P3 diffractometer using graphite monochromatised Mo-K α radiation ($\lambda = 0.71073$ Å) at $-75^\circ C$. The structure was refined on F^2 using SHELXTL/PC (ver. 5.03, Siemens Analytical X-ray Instruments, Madison, WI, USA) to an $R_w = 0.131$, with a conventional $R = 0.0575$ (2231 reflections with $F_0 > 4[\sigma(F_0)]$), and a goodness-of-fit = 1.105 for 182 refined parameters. The molecule lies on a crystallographic inversion centre at 0,0,0. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/395.

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