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Pentapyrrolic calix[4]pyrrole†

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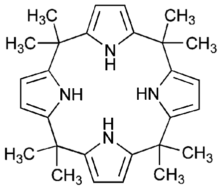
A new calix[4]pyrrole has been synthesised that contains a 3,4,5-trisbromopyrrole appended to a *meso*-position which shows enhanced anion affinity as compared to the parent *meso*-octamethylcalix[4]pyrrole macrocycle.

The discovery by Sessler and co-workers[1] that *meso*-octamethylcalix[4]pyrrole **1** (a macrocycle first reported by Baeyer in 1886)[2] is an effective and selective anion receptor has led to a number of strategies to modulate and enhance the affinity or selectivity of this class of anion receptor. These have included the synthesis of expanded analogues,[3] the attachment of electron withdrawing groups to enhance the acidity of the pyrrole NH protons and hence the strength of the hydrogen bonds formed to a putative anionic guest,[4] the synthesis of extended cavity systems,[5] strapped calix[4]pyrrole[6] and calixpyrroles with pendant arms.[7] We recently reported the synthesis of a mono-ferrocene functionalised calix[4]pyrrole.[8] In this receptor the cyclopentadienyl ring of the ferrocene was directly attached to the *meso*-position of calix[4]pyrrole. Upon addition of anions, significant downfield shifts of one of the cyclopentadienyl protons was observed, suggesting that this proton was involved in hydrogen bonding to the anionic guest. We therefore set out to synthesise calix[4]pyrrole **2** which contains a pyrrole ring such that the pyrrole NH group would be capable of forming a hydrogen bond to a bound anionic guest, with the aim of enhancing the anion affinity of the receptor as compared to the parent macrocycle **1**.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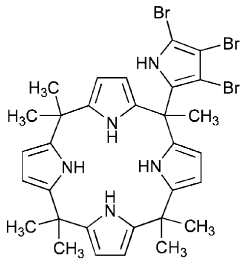
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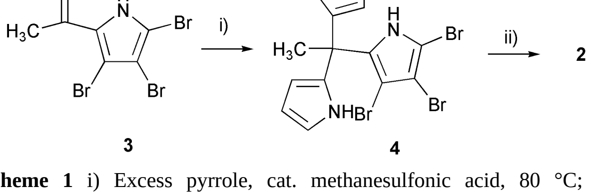
In order to synthesise a calix[4]pyrrole with a single pyrrole pendant arm, a statistical condensation was employed[9] (Scheme 1). 2-Acetyl-3,4,5-tribromopyrrole[10] **3** was chosen as a starting material as the 5-position of the pyrrole is blocked by a bromine substituent allowing for a controlled condensation reaction with pyrrole to form the trispyrrolylmethane **4**. In addition the bromine substituents serve to increase the acidity of the pyrrole NH[4] group so enhancing any putative NH···anion hydrogen bonding interactions. Pyrrole was used as solvent in large excess and the reaction catalysed by a small quanity of methanesulfonic acid. An analytically pure sample of compound was obtained by column chromatography on silica gel eluting with dichloromethane. The compound crystallised from chloroform as colourless needles suitable for X-ray crystallographic analysis.‡ The structure (shown in Fig. 1) reveals NH···Br interactions in the solid state which link the trispyrrolic fragments in a zig-zag fashion.



Scheme 1 i) Excess pyrrole, cat. methanesulfonic acid, 80 °C; ii) dimethyldipyrromethane, acetone, cat. methanesulfonic acid, methanol, RT. See ESI† for more details.

The pentapyrrolic calix[4]pyrrole **2** was synthesised by methanesulfonic acid catalysed condensation of compound **4** with dimethyldipyrromethane[11] and acetone and purified by column chromatography on silica eluted with dichloromethane affording the macrocycle in 14% overall yield (Scheme 1).

There has been some debate recently over the effectiveness of NMR titrations to determine stability constants of calix[4]pyrroles with anions.[6,12] In these studies we elected to use identical conditions to those used to originally determine the stability constants of anions with compound **1**. We therefore hoped to generate an internally self-consistent data set which would allow comparison between the two calixpyrroles.

Therefore ^{1}H NMR titrations were conducted with compound **2** in deuteriated dichloromethane solution[13] and the data compared with those obtained previously with compound **1** (Table 1). Upon addition of fluoride to the solution of compound **2**, all the NH protons broadened and hence the stability constant with this anion was not determined.

Compound **2** has three different NH proton resonances—the pendant pyrrole NH (**a**) and two inequivalent NH resonances from the calixpyrrole (**b** (upfield calixpyrrole NH) and **c**(downfield calixpyrrole NH)). There is generally very good agreement between the stability constant values determined for each NH proton in the system.

The data show an enhancement in the anion complexation affinity of **2** as compared to the parent macrocycle **1**. As can be seen from Table 1, compound **2** has a considerably higher affinity for benzoate and acetate than the parent calix[4]pyrrole **1** whilst binding the other anionic guest species with moderately higher affinities. The ^{1}H NMR titration curves of compounds **1** and **2** with benzoate are shown in Fig. 2.

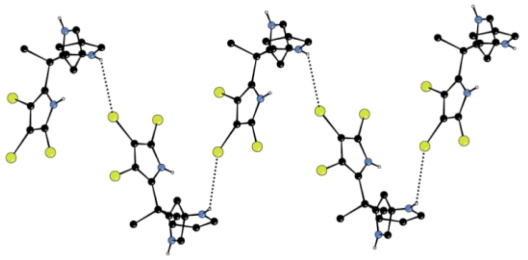


Fig. 1 The X-ray crystal structure of **4** showing NH···Br interactions.

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† Electronic supplementary information (ESI) available: NMR titration plots; experimental section. See http://www.rsc.org/suppdata/cc/b3/b303959e/

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We considered the possibility that the tribromopyrrole ring in compound **2** was being deprotonated upon addition of benzoate or acetate anions leading to an *apparently* very strong stability constant being observed. We have previously observed deprotonation of the NH group in pyrroles containing electron-withdrawing substituents upon addition of anions in dichloromethane-d_2 giving rise to sharp titration curves with unusual shapes.[14] In this case, the titrations with carboxylates reach a plateau after addition of one equivalent of the anion. If deprotonation had occurred, we might expect that the two sets of calixpyrrole NH protons still present in the macrocycle would resonate at identical chemical shifts upon addition of excess acetate or benzoate (as in both cases the deprotonated species in solution would be identical). Instead, the NH resonances reach a plateau in the NMR titration at 11.37 and 10.02 ppm in the case of benzoate and 11.15 and 10.47 ppm in the case of addition of acetate. This suggests to us that the species in solution are different in each case and hence are the benzoate and acetate complexes respectively. In addition, the carboxylate complexes were observed in negative electrospray MS in acetonitrile solution and the preliminary modeling studies do not suggest that deprotonation is occurring.

The strategy of increasing the anion affinity of a calix[4]pyrrole by increasing the number of hydrogen bond donor pyrrole groups in the macrocycle without increasing ring size has worked, with higher stability constants observed in dichloromethane-d_2 solution for a variety of anions. The selectivity for carboxylates displayed by compound **2** was unexpected. One possible explanation for this behaviour is that the functionalised calixpyrrole is capable of coordinating to both oxygen atoms of the carboxylate anion simultaneously[15] whilst the parent macrocycle is binding to only one oxygen atom.[9] Preliminary molecular modelling studies (using Spartan)[16] indicate the acetate complex of **2** to be more stable than the acetate complex of **1** by a significant margin (see ESI† and Fig. 3). We are still investigating the origin of this selectivity in addition to attempting to include pendant pyrrole groups at more than one *meso*-position to produce pyrrolic analogues of the extended cavity calix[4]pyrroles.[5] The results of these studies will be published in due course.

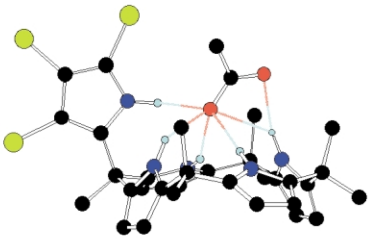

Fig. 3 Molecular model (AM1)[16] of compound **2**–acetate.

Table 1 Comparison of anion stability constants (M^{-1}) for **1** and **2** deteremined in deuteriated dichloromethane at 298 K.[a] **a**, **b** and **c** represent the three different NH groups present in **2**

		Compound **2**/M^{-1}		
	Compound **1**/M^{-1}	**a**	**b**	**c**
Cl^-	350^b	740	1042	1031
Br^-	10^b	36	27	27
$H_2PO_4^-$	97^b	br.^{c}	116	183
HSO_4^-	$< 10^b$	28	26	15
Benzoate	196	br.^{c}	$> 10^4$	$> 10^4$
Acetate	668	br.^{c}	$> 10^4$	$> 10^4$

[a] Anions added as tetrabutylammonium salts. All errors < 20%. [b] Data from reference 1. [c] In these cases the NH proton on the tribromopyrrole broadened and could not be followed.

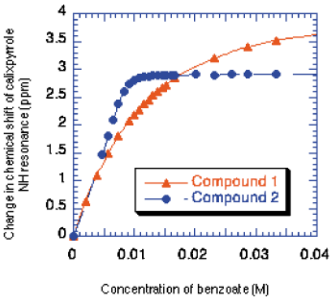

Fig. 2 ^1H NMR titration plot of calix[4]pyrrole NH resonance for compounds **1** and **2** upon addition of aliquots of tetrabutylammonium benzoate in dichloromethane-d_2 at 298 K.

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Notes and references

‡ The sample crystallised as non-merohedral twins and the data were treated accordingly using DirAx,[17] EVALCCD[18] and SADABS.[19] Crystal data for **4**: $C_{14}H_{12}N_3Br_3$, M_r = 462.00, T = 120(2) K, monoclinic, space group $P2_1/c$, a = 17.13(4), b = 10.965(8), c = 17.450(15) Å, β = 114.25(7)°, V = 2989(7) Å^3, ρ_{calc} = 2.053 g cm^{-3}, μ = 8.090 mm^{-1}, Z = 8, reflections collected: 13791, independent reflections: 3468 (R_{int} = 0.0742), final R indices [$I > 2\sigma I$]: $R1$ = 0.0480, $wR2$ = 0.0952, R indices (all data): $R1$ = 0.0915, $wR2$ = 0.1081. CCDC 208974. See http://www.rsc.org/suppdata/cc/b3/b303959e/ for crystallographic data in CIF or other electronic format.

1 P. A. Gale, J. L. Sessler, V. Král and V. Lynch, *J. Am. Chem. Soc.*, 1996, **118**, 5140.
2 A. Baeyer, *Ber. Dtsch. Chem. Ges.*, 1886, **19**, 2184.
3 B. Turner, M. Botoshansky and Y. Eichen, *Angew. Chem., Int. Ed.*, 1998, **37**, 2475; G. Cafeo, F. H. Kohnke, G. L. L. Torre, A. J. P. White and D. J. Williams, *Angew. Chem., Int. Ed.*, 2000, **39**, 1496; J. L. Sessler, P. Anzenbacher Jr., J. A. Shriver, K. Jursíková, V. M. Lynch and M. Marquez, *J. Am. Chem. Soc.*, 2000, **122**, 12,061.
4 P. A. Gale, J. L. Sessler, W. E. Allen, N. A. Tvermoes and V. Lynch, *Chem. Commun.*, 1997, 665.
5 P. Anzenbacher Jr., K. Jursíková, V. M. Lynch, P. A. Gale and J. L. Sessler, *J. Am. Chem. Soc.*, 1999, **121**, 11020; S. Camiolo and P. A. Gale, *Chem. Commun.*, 2000, 1129.
6 D.-W. Yoon, H. Hwang and C.-H. Lee, *Angew. Chem., Int. Ed.*, 2002, **41**, 1757.
7 P. Anzenbacher Jr, K. Jursíková and J. L. Sessler, *J. Am. Chem. Soc.*, 2000, **122**, 9340.
8 P. A. Gale, M. B. Hursthouse, M. E. Light, J. L. Sessler, C. N. Warriner and R. S. Zimmerman, *Tetrahedron Lett.*, 2001, **42**, 6759.
9 J. L. Sessler, A. Andrievsky, P. A. Gale and V. Lynch, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2782.
10 E.-H. Kim, B.-S. Koo, C.-E. Song and K.-J. Lee, *Synth. Commun.*, 2001, **31**, 3627.
11 B. J. Littler, M. A. Miller, C.-H. Hung, R. W. Wagner, D. F. O'Shea, P. D. Boyle and J. S. Lindsey, *J. Org. Chem.*, 1999, **64**, 1391.
12 F. P. Schmidtchen, *Org. Lett.*, 2002, **4**, 431.
13 M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311.
14 S. Camiolo, P. A. Gale, M. B. Hursthouse, M. E. Light and A. J. Shi, *Chem. Commun.*, 2002, 758; P. A. Gale, K. Navakhun, S. Camiolo, M. E. Light and M. B. Hursthouse, *J. Am. Chem. Soc.*, 2002, **124**, 11228.
15 P. A. Gale, S. Camiolo, C. P. Chapman, M. E. Light and M. B. Hursthouse, *Tetrahedron Lett.*, 2001, **42**, 5095; P. A. Gale, S. Camiolo, G. J. Tizzard, C. P. Chapman, M. E. Light, S. J. Coles and M. B. Hursthouse, *J. Org. Chem.*, 2001, **66**, 7849; S. Camiolo, P. A. Gale, M. B. Hursthouse and M. E. Light, *Tetrahedron Lett.*, 2002, **43**, 6995.
16 Spartan '02, Wavefunction Inc., Irvine CA, USA.
17 A. J. M. Duisenberg, *J. Appl. Crystallogr.*, 1992, **25**, 92–96.
18 A. J. M. Duisenberg, L. M. J. Kroon-Batenburg and A. M. M. Schreurs, *J. Appl. Crystallogr.*, 2003, **36**, 220–229.
19 G. M. Sheldrick, SADABS: Program for Empirical Absorption correction of Area Dectector Data, Univ. of Gottingen, Germany, 1996.