Bis-cation salt complexation by *meso*-octamethylcalix[4]pyrrole: linking complexes in solution and in the solid state

Claudia Caltagirone,[a] Nathan L. Bill,[b] Dustin E. Gross,[b] Mark E. Light,[a] Jonathan L. Sessler*[b] and Philip A. Gale*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X
First published on the web Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

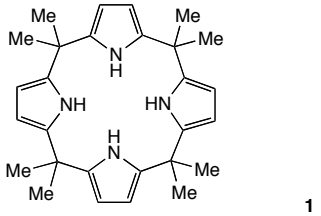
Pyridinium and imidazolium bis-cations are shown to link calix[4]pyrrole anion complexes both in solution and in the solid state. This is accomplished by binding of the bis-cations to the electron-rich bowl shaped cavities formed by two separate calixpyrrole – anion complexes. These resulting sandwich-type structures provide a new way of organising calix[4]pyrrole anion complexes in space.

Introduction

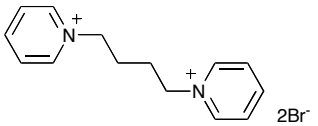
The development of ditopic ion-pair receptors has attracted intense interest recently.[1] Calix[4]pyrroles are tetrapyrrole macrocycles first synthesised by Baeyer in 1886[2] *via* the acid catalysed condensation of pyrrole and a ketone. In 1996, we reported that *meso*-octamethylcalix[4]pyrrole **1** forms complexes with anionic species in solution and in the solid state.[3] Subsequent studies have shown that members of this class of macrocycles can function both as anion sensors and anion separation agents.[4] In 2005, we discovered that calix[4]pyrroles can bind ion pairs such as caesium or 1,3-dialkylimidazolium halides salts with the anion bound to the pyrrole NH groups, locking the macrocycle into a cone conformation, and the large charge diffuse cation binding to the electron rich bowl-shaped cavity formed by the calix[4]pyrrole anion complex.[5] Subsequent studies in solution with a variety of salts have demonstrated a significant dependence of anion stability constants on both the nature of the solvent and cation used indicating that complexation cannot be regarded as a simple 1:1 (anion:calix[4]pyrrole) process but rather that the solvent and cation are intimately involved in the binding processes occurring in solution. This hypothesis is supported by evidence from a variety of solid-state structures showing cation inclusion in the calix[4]pyrrole cup.[6] It has also been shown that calixpyrroles can extract metal salts from aqueous solution[7] and transport caesium chloride salts across lipid bilayer membranes.[8]

We decided to investigate whether we could use cation complexation as a means of ordering calix[4]pyrrole anion complexes relative to one another as a first step towards producing ordered arrays of calixpyrrole ion-pair complexes. We therefore synthesised a series of bis-cation dibromide salts consisting of either two pyridinium or imidazolium groups linked *via* an alkyl chain (i.e. **2**-**5**) and studied whether the bis-cation would link calix[4]pyrrole anion complexes both in solution and the solid state.

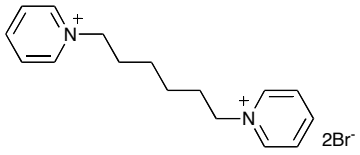
Please insert 1-5 here



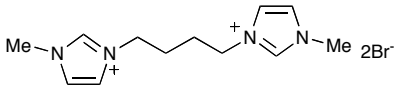
1



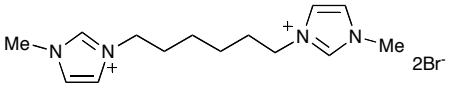
2



3



4



5

Results and discussion

meso-Octamethylcalix[4]pyrrole **1**,[3] as well as the pyridinium and imidazolium bis-cation salts **2**-**5** were synthesised *via* literature procedures.[9]

Solid state studies

Crystals of the 1,1'-(butane-1,4-diyl)bis(pyridin-1-ium bromide **2** complex of *meso*-octamethylcalix[4]pyrrole **1** were obtained by slow evaporation of a 1:1

dichloromethane/ethanol solution of the calixpyrrole in the presence of excess bromide salt. The structure of $\mathbf{1}_2 \cdot \mathbf{2}$ was elucidated by single crystal X-ray diffraction and reveals that the calix[4]pyrrole adopts the cone conformation binding bromide *via* four NH···Br$^-$ hydrogen bonds in the range 3.494(2) – 3.540(2)Å (Figure 1). The pyridinium groups of the bis-cation each residue in the bowl shaped calixpyrrole-anion complex cavity (which are equivalent by symmetry). The distance between carbon atoms C30 and C31 on the pyridinium ring and the centroid of the closest pyrrole ring (C15 C16 C17 C18 N3) are 3.531 and 3.796Å respectively (see ESI for more details).

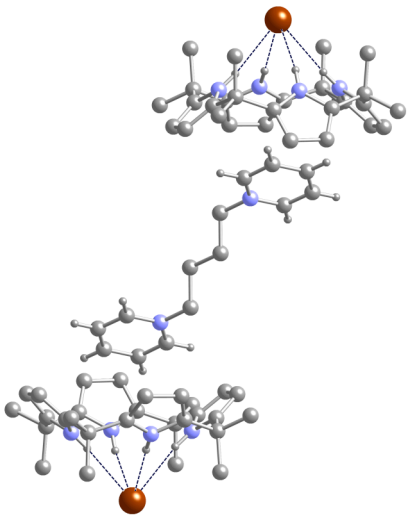


Figure 1 The X-ray crystal structure of the complex $\mathbf{1}_2.\mathbf{2}$. Selected hydrogen atoms and dichloromethane solvent molecules have been omitted for clarity. An inversion centre lies at the midpoint of the central bond of the cation..

Crystals of the 1,1'-(hexane-1,6-diyl)bis(pyridin-1-ium) bromide **3** complex of *meso*-octamethylcalix[4]pyrrole **1** were obtained by slow evaporation of a 1:1 dichloromethane/ethanol solution of the calixpyrrole in the presence of excess bromide salt. The structure of $\mathbf{1}_2.\mathbf{3}$ was elucidated by single crystal X-ray diffraction and reveals again that the calix[4]pyrrole adopts the cone conformation binding bromide *via* four NH···Br$^-$ hydrogen bonds in the range 3.438(3)-3.503(3)Å (Figure 2). As was observed in the structure of $\mathbf{1}_2.\mathbf{2}$, each pyridinium group resides in the bowl shaped cavity of the calix[4]pyrrole anion complex. The distance between carbon atoms C31 and C32 on the pyridinium ring and the centroid of the closest pyrrole ring (C1 C2 C3 C4 N1) are 3.640 and 3.679Å, respectively (see ESI for more details).

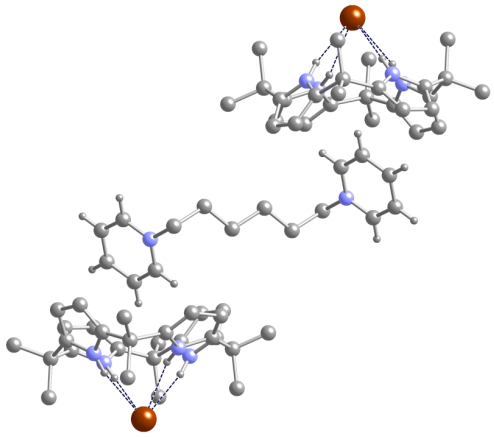


Figure 2 The X-ray crystal structure of the complex $\mathbf{1}_2.\mathbf{3}$. Selected hydrogen atoms have been omitted for clarity. An inversion centre lies at the midpoint of the central bond of the cation.

Crystals of the 3,3'-(hexane-1,6-diyl)bis(1-methyl-1*H*-imidazol-3-ium) **5** bromide complex of *meso*-octamethylcalix[4]pyrrole **1** were obtained by slow evaporation of a solution of the receptor in 1:1 acetonitrile/ethanol solution in the presence of excess bromide salt. The structure of $\mathbf{1}_2.\mathbf{3}$ was elucidated by single crystal X-ray diffraction and reveals again that the calix[4]pyrrole adopts the cone conformation binding bromide *via* four NH···Br$^-$ hydrogen bonds in the range 3.410(4)-3.500(4)Å (Figure 3). The distance between carbon atoms C30 in the imidazolium ring and the centroid of the closest pyrrole ring (C1 C2 C3 C4 N1) is 3.537Å (see ESI for more details).

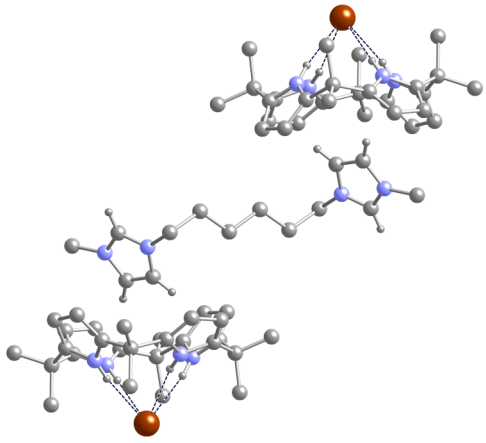


Figure 3 The X-ray crystal structure of the complex $\mathbf{1}_2.\mathbf{5}$. Selected hydrogen atoms have been omitted for clarity. An inversion centre lies at the midpoint of the central bond of the cation.

^{1}H NMR spectroscopic analyses

Proton NMR experiments were conducted with bis-imidazolium bromide **5** and compound **1** in aceotnitrile-d_3. Compound **1** was titrated into a solution of the salt and the resulting NMR spectra are shown in Figure 4. The results show that in the presence of increasing quantities of the macrocycle, the imidazolium CH protons become shielded and move to lower field (e.g., proton originally resonating at *ca.* 9.41 ppm). Such a finding is consistent with, but not proof of, inclusion of the imidazolium cation in the bromide-induced calix[4]pyrrole cup-shaped cavity. While we favor such an interpretation, which is accord with the X-ray structural analyses discussed above, it is important to appreciate that the observed shielding effect may be due to sequestration of the bromide anion by the calixpyrrole.

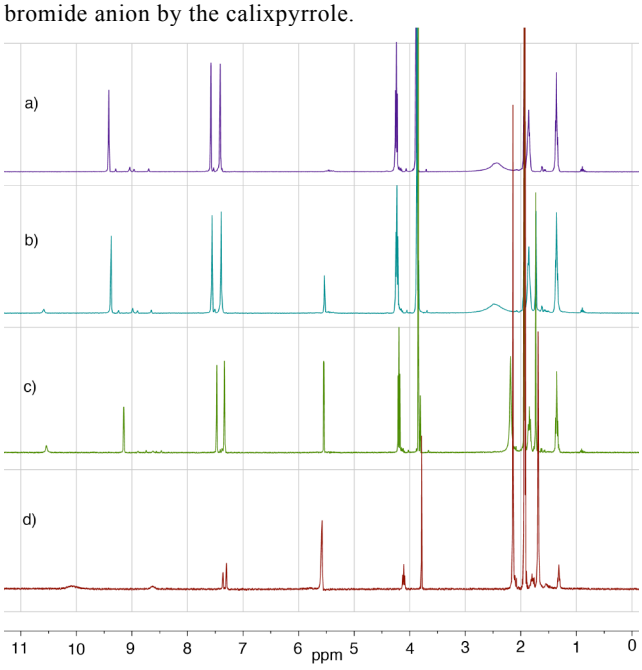


Figure 4 Proton NMR spectra of bis-imidazolium bromide **5** (a) in the absence of calix[4]pyrrole,, (b) 8:1 molar ratio (salt:calixpyrrole), (c) 4:1 molar ratio (salt:calixpyrrole), and (d) 1:3 molar ratio (salt:calixpyrrole) in acetonitrile-d_3. The NMR spectra in question reveal increased shielding of the imidazolium CH groups in the presence of calixpyrrole.

Isothermal titration calorimetry (ITC)

In an attempt to quantify the energetics associated with calixpyrrole:bis-cation complex formation, we turned to ITC. Unfortunately the bis-pyridinium salts (**2** and **3**) were not sufficiently soluble in acetonitrile or dichloromethane to allow for ITC analyses in these solvents. When titrations were attempted in DMSO a very weak interaction was observed (K_a<10^2 M^{-1}), as would be expected from the previous reports on chloride binding in DMSO and bromide binding in dichloromethane.[3,6]

The bis-imidazolium salts **4** and **5** were sufficiently soluble in acetonitrile to permit ITC titrations. Representative titrations are shown below in Figure 5. From the position of the inflection point (*ca.* 0.5 molar ratio; see Figure 5) we infer that the binding stoichiometry of the interaction is 1:2 (bisimidazolium salt:calixpyrrole). When fit to a sequential binding site model (i.e., defining the salt as having two independent binding sites) a good fit is obtained (see Table S1 in the ESI for complete thermodynamic data).

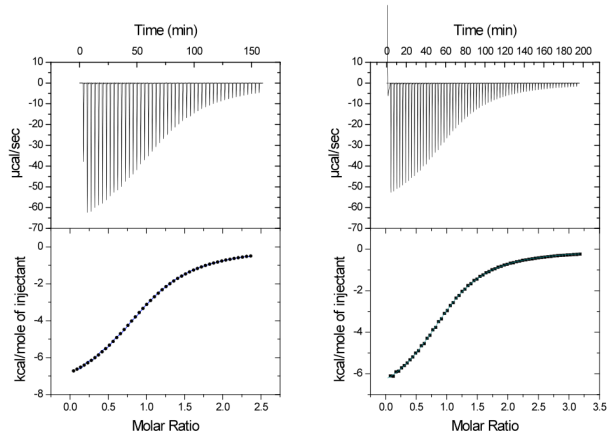


Figure 5. Left: Onesite binding fit of 1,4-bis-(3-methylimidazolium)butane dibromide salt: **4** [30.9 mM effective] titrated into **1** [3.3 mM] and right: onesite binding fit of 1,4-bis-(3-methylimidazolium)hexane dibromide salt **5** [45.3 mM effective] titrated into calix[4]pyrrole **1** [2.9 mM]

Table 1. ITC titrations of various organic chloride and bromide salts with calix[4]pyrrole **1** carried out in acetonitrile.

See end of document for table 1

For comparison, the data obtained for bis-imidazolium salts **4** and **5** was also fitted to a one site binding equation. This model can give an accurate representation of multiple binding sites provided the sites are identical to one another. Again a good fit is obtained using this method, and the data is summarized in Table 1 (see ESI for complete thermodynamic data). This data reveals that within experimental error there are no differences in the energetics of binding for studies involving the linked species **4** and **5.**

As a control study, designed to probe the effect that tethering two imidazolium salts has on the binding energetics, the mono-imidazolium salts, 1-butyl-3-methyl imidazolium chloride (BMIMCl) and 1-butyl-3-methyl imidazolium bromide (BMIMBr), were investigated by ITC in acetonitrile at similar concentrations as used above. In these cases the inflection point occurs near a molar ratio of 1.0, a finding that is consistent with a 1:1 (**1**:BMIM salt) binding interaction. This behavior is also in accord with previous data[6] obtained in dichloromethane (see Table 1 and Figure 6).

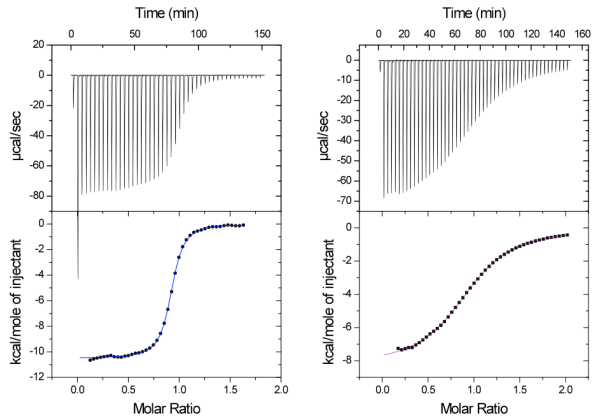


Figure 6. ITC heat signatures and associated binding curves obtained when BMIMCl [31.0 mM] is titrated into **1** [3.3 mM] (left) and BMIMBr [37.8 mM] titrated into **1** [3.5 mM] (right).

Conclusions

Equations predicated on first a sequential binding interaction and then a single set of binding sites were both used to fit these data for the complexation of bisimidazolium salts **4** and **5** with calix[4]pyrrole. The results obtained allowed some limited conclusions about the complexation process in solution to be drawn. For example, the position of the inflection point can be indicative of the binding stoichiometry, which in the case of the bisimidazolium salts was found to occur around a molar ratio of 0.5. Such a molar ratio is expected for a 2:1 (calixpyrrole:guest) binding interaction. In contrast, the mono-imidazolium salts BMIMCl and BMIMBr were found to interact with calix[4]pyrrole in a 1:1 binding stoichiometry.[6] Although the nature of the interaction is not fully defined, the solution data are consistent with the notion that binding of the bisimidazolium salts occurs such that a 1:2 salt: calixpyrrole complex forms wherein the cationic portions of the two-component substrate are bound within the calixpyrrole cup. Such an inference is fully supported by the single crystal X-ray diffraction analyses, which reveal the inclusion of the cation into the calixpyrrole cup and the formation of a 5-membered anion-calixpyrrole-biscation-calixpyrrole-anion supramolecular ensemble in the solid state.

Acknowledgements

PAG thanks the EPSRC for funding and for access to the crystallographic facilities at the University of Southampton. JLS thanks the National Institutes of Health (GM 58907) for financial support. CC would like to thank Italian Ministero dell'Istruzione, dell'Università e della Ricerca Scientifica (MIUR) for financial support (Project PRIN-2007C8RW53).

Notes and references

[a] *School of Chemistry, University of Southampton, Southampton, SO17 1BJ, UK. E-mail: philip.gale@soton.ac.uk; Fax: +44 (0)23 8059 6805; Tel:+ 44 (0)23 8059 3332*

[b] *Departament of Chemistry and Biochemistry, The University of Texas at Austin, 1 University Station A5300, Austin TX 78712, USA. E-mail: sessler@mail.utexas.edu*

† Electronic Supplementary Information (ESI) available: Experimental, tabulated ITC data, original ITC plots and crystallographic data. See DOI: 10.1039/b000000x/

1 For recent contributions and reviews see for example: (a) C. Caltagirone and P. A. Gale, *Chem. Soc. Rev.*, 2009, **38**, 520-563; (b) M. D. Lankshear, I. M. Dudley, K.-M. Chan, A. R. Cowley, S. M. Santos, V. Felix and P. D. Beer, *Chem. Eur. J.,* 2008, **14**, 2248-2263; (c) P.A. Gale, S.E. García-Garrido and J. Garric, *Chem. Soc. Rev.* 2008, **37**, 151-190; (d) M. Cametti, M. Nissinen, A. Dalla Cort, L. Mandolini, and K. Rissanen *J. Am. Chem. Soc.,* 2007, **129**, 3641-3648; (e) J. M. Mahoney, K. A. Stucker, H. Jiang, I. Carmichael, N. R. Brinkmann, A. M. Beatty, B. C. Noll and B. D. Smith, *J. Am. Chem. Soc.,* 2005, **127**, 2922-2928; (f) F. Oton, A. Tarraga, A. Espinosa, M. D. Velasco, P. Molina, *Dalton Trans.,* 2006, 3685-3692; (g) J. L. Sessler, P. A. Gale, and W. S. Cho, *Synthetic Anion Receptor Chemistry*; Royal Society of Chemistry: London, 2006; Chapter 6, pp 259-293; (h) B. D. Smith, In *Macrocyclic Chemistry: Current Trends and Future Perspectives*; K. Gloe, Ed.; Springer: Dordrecht, 2005; pp 137-151; (i) G.J. Kirkovits, J.A. Shriver, P.A. Gale and J.L. Sessler, *J. Inc. Phenom. Mol. Recognit. Chem.* 2001, **41**, 69-75.

2 A. Baeyer, *Ber. Dtsch. Chem. Ges*. 1886, **19**, 2184-2185.

3 P.A. Gale, J.L. Sessler, V. Král, V. Lynch, *J. Am. Chem. Soc.* 1996, **118**, 5140-5141.

4 (a) J.L. Sessler, P. Anzenbacher Jr., H. Miyaji, K. Jursikova, E.R. Bleasdale and P.A. Gale, *Ind. Eng. Chem. Res.* 2000, **39**, 3471-3478; (b) J.L. Sessler, A. Gebauer and P.A. Gale, *Gazz. Chim. Ital.* 1997, **127**, 723-726; (c) J.L. Sessler, P.A. Gale and J.W. Genge, *Chem. Eur. J.* 1998, **4**, 1095-1099;

5 R. Custelcean, L. H. Delmau, B. A. Moyer, J. L. Sessler, W.-S. Cho, D. E. Gross, G. W. Bates, S. J. Brooks, M. E. Light, and P. A. Gale, *Angew. Chem. Int. Ed.,* 2005, **44**, 2537-2542.

6 (a) J. L. Sessler, D. E. Gross, W.-S. Cho, V. M. Lynch, F. P. Schmidtchen, G. W. Bates, M. E. Light, and P. A. Gale, *J. Am. Chem. Soc.,* 2006, **128**, 12281-12288; (b) G. W. Bates, P. A. Gale, M. E. Light, *CrystEngComm.,* 2006, **8**, 300-302; (c) D.E. Gross, F.P. Schmidtchen, W. Antonius, P.A. Gale, V.M. Lynch and J.L. Sessler, *Chem. Eur. J.,* 2008, **14**, 7822-7827; (d) G. W. Bates, P. A. Gale, M. E. Light, *Supramol. Chem.,* 2008, **20**, 23-28. (e) C.-H Lee, J.S. Lee, H.K. Na, D.W. Yoon, H. Miyaji, W.S. Cho, J.L. Sessler, *J. Org. Chem.* **70**, 2067-2074 (f) D.W. Yoon,, D.E. Gross, V.M. Lynch, J.L. Sessler, B.P. Hay, C.H. Lee, *Angew. Chem. Int. Ed.,* 2008, **47**, 5038-5042

7 (a) M. P. Wintergerst, T. G. Levitskaia, B. A. Moyer, J. L. Sessler, and L. H. Delmau, *J. Am. Chem. Soc.,* 2008, **130**, 4129-4139. For an examples of calix[4]pyrrole decorated polymers see: (b) A. Aydogan, D. J. Coady, V. M. Lynch, A. Akar, M. Marquez, C. W. Bielawski and J. L. Sessler, *Chem. Commun*. 2008, 1455-1457; (c) A. Aydogan, D.J. Coady, S. K. Kim, A. Akar, C.W. Bielawski, M. Marquez and J.L. Sessler, *Angew. Chem. Int. Ed.* 2008, **47**, 9648-9652; (d) G.V. Zyryanov, T.H.. Kinstle and P. Anzenbacher Jr. *Syn Lett.* 2008, 1171-1174.

8 (a) M.G. Fisher, P.A. Gale, J.R. Hiscock, M.B. Hursthouse, M.E. Light, F.P. Schmidtchen and C.C. Tong, *Chem. Commun.* 2009, 3017-3019; (b) C.C. Tong, R. Quesada, J.L. Sessler and P.A. Gale, *Chem. Commun.,* 2008, 6321-6323.

9 R. Hazard, J. Cheymol, J.A. Gautier, E. Corteggiani and E. Leroi, *Arch. Int. Pharm.* 1952, **90**, 271-275. See also R.E. Lyle

and J.J. Gardikes, *J. Am. Chem. Soc.* 1955, **77**, 1291-1292;
V.V. Namboodiri and R.S. Varna, *Org. Lett.* 2002, 3161-3163.

Table 1. ITC titrations of various organic chloride and bromide salts with calix[4]pyrrole **1** in acetonitrile.

salt	N[a]	n[a]	$\Delta\Gamma$	ΔH	$T\Delta S$	K_a
			kcal/mol	kcal/mol	kcal/mol	M^{-1}
4	6	0.502 ± 0.004	–2.44 ± 0.05	–7.74 ± 0.35	–5.30 ± 0.34	1 790 ± 320
5	5	0.486 ± 0.012	–2.42 ± 0.03	–7.75 ± 0.61	–5.32 ± 0.59	2 220 ± 230
BMIMBr		1.01	–4.83	–7.99	–3.16	3 500
BMIMBr[b]			–	–	–	280
BMIMCl		0.91	–6.67	–10.51	–3.84	75 000
BMIMCl[b]			–	–	–	6 000
TBABr[c]			–	–	–	3 400
TBACl[d]			–7.29	–10.16	–2.91	22 000

[a] N = number of independent titrations, n = stoichiometry at equivalence point (salt:calix[4]pyrrole) [b] Data from NMR titration in dichloromethane-d_2[6d]. [c] Data obtained at 303 K[6e]. [d] Data from reference[6f]