Bis(amido)calix[4]arenes in the pinched cone conformation as tuneable hydrogen-bonding anion receptors

Beth R. Cameron and Stephen J. Loeb*†

Department of Chemistry and Biochemistry, University of Windsor, Windsor, Ontario, Canada N9B 3P4

Calix[4]arene units functionalized at the 1,3-positions of the upper rim with amido groups, –NHC(O)X, act as neutral, hydrogen-bonding receptors for hydrogen sulfate, dihydrogen phosphate, acetate, benzoate, nicotinate, oxalate, terephthalate, isophthalate and fumarate with binding strength and selectivity tunable by varying the electron-withdrawing ability of the terminal substituent X (X = CH_2Cl, $CHCl_2$, CCl_3).

Increased interest in the molecular recognition of anionic substrates has led to the synthesis and evaluation of a variety of anion receptors.[1] The most common employ ammonium or guanidinium binding sites while recently electron-deficient, Lewis acid centres such as tin,[2] boron,[3] mercury,[4] silicon[5] and the uranyl ion[6] have received attention. Although some of these systems are quite efficient receptors, it is interesting to note that anion binding by proteins is most commonly achieved *via* neutral amide functions employing the hydrogen-bond accepting properties of the amido NH group.[7] Indeed, some very efficient anion (Cl^-, $H_2PO_4^-$) receptors containing both Lewis acidic centres and amide binding sites have been reported recently.[6,8]

A major disadvantage to employing the amide function –NHC(O)– is the rigid directionality of the NH group which makes if difficult to incorporate into a highly structured framework such as a macrocycle.[9] This problem can be overcome by including the amide function as a terminal group on the upper-rim of a calix[4]arene framework.[10] We report herein the syntheses of bis(amido)calix[4]arene-based anion receptors which exhibit a selectivity for carboxylate ions, particularly benzoate derivatives, over tetrahedral oxyanions.

Receptors **2** and **3** were prepared by the reaction of 5,17-bis-(amino)-25,26,27,28-tetrapropoxycalix[4]arene with 2.5 equiv. of dichloroacetyl chloride or trichloroacetyl chloride in a manner similar to the published procedure for **1**.[11]‡§

Initially, the anion complexation properties of receptor **1** were investigated using ^{1}H NMR spectroscopy and association constants were measured for a variety of simple anions (Table 1). In each case, the anion–receptor stoichiometry was confirmed to be 1 : 1 by a Job plot. These results indicate a preference for the Y-shaped carboxylate anions acetate and benzoate over tetrahedral-shaped anions, $H_2PO_4^-$, ReO_4^- and HSO_4^-. For example, addition of 1 equiv. of $[Bu_4N^+][C_6H_5CO_2^-]$ to a 10^{-3} mol dm^{-3} solution of **1** in $CDCl_3$ resulted in a dramatic downfield shift of 1.33 ppm for the amide NH proton and a moderate downfield shift of 0.12 ppm for the CH_2Cl resonance. Whereas, the same experiment using $H_2PO_4^-$ resulted in much smaller downfield shifts of 0.90 and a 0.07 ppm for the NH and CH_2Cl resonances.

It is reasonable to assume that increasing the acidity of the amide proton by introducing more effective electron-withdrawing groups in the terminal position would enhance anion binding. This was investigated by measuring the binding of benzoate ion with a series of receptors differing only in the terminal substituent X, in the NHC(O)X group (X = CH_2Cl, $CHCl_2$, CCl_3) (Table 2). Receptor **2** exhibits the highest association constant with downfield shifts of 2.38 and 0.73 ppm observed for the NH and $CHCl_2$ resonances in the ^{1}H NMR spectrum of **2** upon addition of 1 equiv. of benzoate anion. The replacement of hydrogen by chlorine results in a *ca*. 50-fold increase in association constant.

The benzoate anion binds in a bidentate fashion to the two amide protons present on the upper rim of the calix[4]arene (Fig. 1). In order for this to occur, the calix[4]arene must exist in the pinched cone conformation in which the rings bearing the amide groups are essentially parallel. This is clearly demonstrated by observed changes in the ^{1}H NMR spectra upon anion binding. The ^{1}H NMR spectrum of **2** exhibits a singlet for the four aromatic protons on the amido substituted rings and an unresolved multiplet for the six protons on the unsubstituted rings. Addition of benzoate ion results in an upfield shift of the substituted ring protons and a downfield shift and resolution of

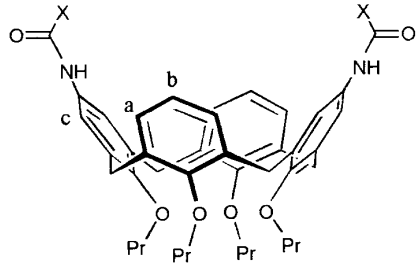
Table 1 K_{ass} Values of receptor **1**

Anion	$H_2PO_4^-$	HSO_4^-	ReO_4^-	$CH_3CO_2^-$	$C_6H_5CO_2^-$
K_{ass} 1	22	27	< 10	88	107

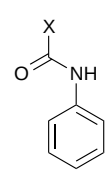
Table 2 K_{ass} Values of benzoate anion with receptors **1**–**6**

Receptor	**1**	**2**	**3**[a]	**4**	**5**	**6**[a]
K_{ass} 1	107	5160	—	81	210	—

[a] No binding is observed.



1 X = CH_2Cl
2 X = $CHCl_2$
3 X = CCl_3



4 X = CH_2Cl
5 X = $CHCl_2$
6 X = CCl_3

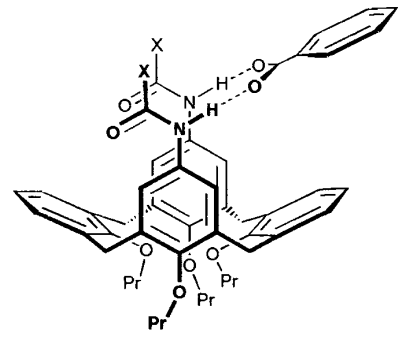


Fig. 1

the protons on the unsubstituted ring. Also, the OCH_2 resonances which overlap in **2** resolve into two distinct triplets and the $CHCl_2$ protons are systematically shifted downfield upon anion binding (Fig. 2). These changes can be attributed to a perturbation of the see-saw motion between the two pinched cone conformers of the calix[4]arene skeleton. This conformational isomerism is usually ignored in calix[4]arene chemistry, although the energy barrier to this interconversion was measured to be *ca*. 40 kJ mol^{-1}.[12] Thus, anion coordination freezes the calixarene unit in the pinched cone conformation with the substituted rings parallel and allows for two linear hydrogen bonding interactions between receptor and anion.

Surprisingly, the presence of three chloro substituents results in absolutely no binding of the anion as is evident from the absence of any change in the ^{1}H NMR spectrum. Since the model compound **6** also showed no change in the ^{1}H NMR spectrum with the addition of 10 equiv. of benzoate anion, it is likely that the amide protons in receptors **3** and **6** are inaccessible for the approach of the anion due to steric crowding of the trichloromethyl substituents rather than an inability of **3** to achieve the appropriate pinched cone conformation.

Association constants for various other mono-carboxylate anions with receptor **2** are given in Table 3 These results demonstrate that receptor **2** is not only selective for carboxylate ions but has a particular affinity for the benzoate ion. Examination of CPK models suggested a more open conformation might provide a suitable geometric fit for some dicarboxylates. The binding of receptor **2** with dicarboxylate ions was investigated and results are also given in Table 3.

A Job plot of receptor **2** with oxalate anion showed 1 : 1 complexation. The changes evident in the aromatic region of the spectrum of **2** are opposite to those demonstrated with the benzoate anion. This suggests that the calix[4]arene exists in a pinched cone conformation in which the unsubstituted rings are parallel. This allows accommodation of the dianion and still maintains a 1 : 1 stoichiometry. In contrast, the larger dicarboxylate anions (isophthalate, terephthalate, fumarate) were found by Job plots to bind with an anion–receptor ratio of 1 : 2. ^{1}H NMR Spectra show the same trends observed for benzoate and suggest that the calixarene receptors can be assembled around the anion with a similar coordination mode for each carboxylate group.

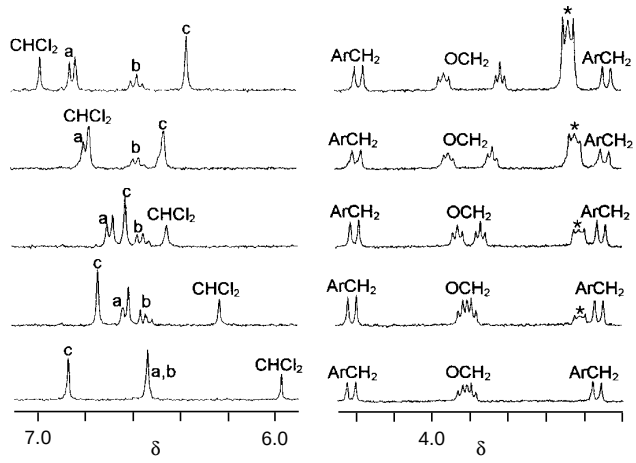


Fig. 2 ^{1}H NMR spectra of stepwise addition of 0.0 (bottom), 0.25, 0.50, 1.0 and 2.0 equiv. of $[Bu_4N][C_6H_5CO_2]$ to receptor **2** (* = peak due to Bu_4N^+ cation). Aromatic H-atoms a, b and c are assigned as in Fig. 1.

Table 3 K_{ass} Values of **2** with monocarboxylate and dicarboxylate anions

Anion	Benzoate[a]	Nicotinate[a]	Acetate[a]	Oxalate[a]	Isophthalate[b]	Terephthalate[b]	Fumarate[b]
K_{ass} 1	5160	821	609	707	$> 10^6$	$> 10^6$	$> 10^6$

[a] Stoichiometry is 1 : 1. [b] Stoichiometry is 1 : 2 and values are $\beta(K_1K_2)$.

In summary, neutral, hydrogen-bonding anion receptors can be derived from a pair of terminal amido groups built into a calix[4]arene framework. The pinched cone conformation is flexible enough to allow for the binding of a variety of anions and the acceptor properties of the amido group can be tuned by varying the electron-withdrawing nature of the terminal substituent. These new receptors are selective for Y-shaped carboxylate ions over tetrahedral anions and show a particular preference for benzoate derivatives.

We thank the Natural Science and Engineering Council of Canada and the Petroleum Research Fund administered by the American Chemical Society for financial support of this research.

Footnotes

† E-mail: loeb@uwindsor.ca

‡ All new compounds were successfully characterized by ^{1}H and ^{13}C NMR spectroscopy, LSIMS and elemental analysis. ^{1}H NMR Titrations: varying amounts of stock solutions of anionic guests (0.0125 mol dm^{-3}) were added to 0.1 cm^3 aliquots of host solutions (0.005 mol dm^{-3} stock solutions) and were made up to 0.5 cm^3 with solvent to maintain a constant volume and thus a constant host concentration of 0.001 mol dm^{-3}. Anion–receptor ratios were varied from 0.1–10. K_{ass} Values were determined using the chemical shift of the amide proton as the probe. Values were fitted using the program EQNMR[13] with errors < 10% for K_{ass} > 100 and errors < 5% for K_{ass} < 100.

§ *Selected data* for **2**: ^{1}H NMR ($CDCl_3$) δ 7.87 (s, NH, 2 H), 6.87 (s, ArH, 4 H), 6.54 (s, ArH, 6 H), 5.97 (s, $CHCl_3$, 2 H), 4.43 (d, $ArCH_2$, 4 H), 3.82 (m, OCH_2, 8 H), 3.13 (d, $ArCH_2$, 4 H), 1.91 (m, CH_2, 8 H), 0.97 (m, Me, 12 H); ^{13}C NMR ($CDCl_3$) δ 161.62, 156.10, 154.90, 136.24, 134.07, 129.87, 128.14, 122,36, 121.29, 76.84, 66.96, 31.00, 23.23, 23.14, 10.36, 10.20; LSIMS *m/z* $[M + H]^+$ = 845. For **3**: ^{1}H NMR ($CDCl_3$) δ 8.23 (s, NH, 2 H), 7.19 (s, ArH, 4 H), 6.37 (m, ArH, 6 H), 4.45 (d, $ArCH_2$, 4 H), 3.95 (t, OCH_2, 4 H), 3.73 (t, OCH_2, 4 H), 3.15 (d, $ArCH_2$, 4 H), 1.91 (m, CH_2, 8 H), 1.05 (t, Me, 6 H), 0.92 (t, CH_3, 6 H); ^{13}C NMR ($CDCl_3$) δ 159.15 (CO), 155.61, 155.59, 137.27, 133.21, 129.65, 127.87, 122.43, 120.98 (ArC), 93.06 (CCl_3), 77.05, 76.85 (OCH_2), 31.08 ($ArCH_2$), 23.45, 23.08 (CH_2), 10.67, 10.05 (CH_3); LSIMS *m/z* $[M]^+$ = 913.

References

1 B. Dietrich, *Pure Appl. Chem.*, 1993, **65**, 1457; C. Seel and J. de Mendoza, in, *Comprehensive Supramolecular Chemistry*, ed. F. Vogtle, Elsevier Science, New York, 1996, vol. 2, ch. 17, pp. 519–552.
2 M. Newcomb, J. H. Horner, M. T. Blanda and P. J. Squattrito, *J. Am. Chem. Soc.*, 1989, **111**, 6294.
3 M. T. Reetz, C. M. Niemeyer and K. Harms, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1472.
4 X. Yang, C. B. Knobler and M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1507.
5 H. E. Katz, *J. Am. Chem. Soc.*, 1986, **108**, 7640.
6 D. M. Rudkevich, W. Verboom, Z. Brzozka, M. J. Palys, W. P. R. V. Stauthamer, G. J. van Hummel, S. M. Franken, S. Harkema, J. F. J. Engbersen and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1994, **116**, 4341.
7 D. Voet and J. G. Voet, *Biochemistry*, Wiley, New York, 1995.
8 P. D. Beer, *Chem. Commun.*, 1996, 689; D. M. Rudkevich, J. D. Mercer-Chalmers, W. Verboom, R. Ungaro, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1995, **117**, 6124.
9 S. Valiyaveettil, J. F. J. Engbersen, W. Verboom and D. N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 900.
10 Y. Morzherin, D. M. Rudkevich, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.*, 1993, **58**, 7602; J. Scheerder, J. P. M. van Duynhoven, J. F. J. Engbersen and D. N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1090.
11 D. M. Rudkevich W. Verboom and D. N. Reinhoudt, *J. Org. Chem.*, 1994, **59**, 3683.
12 A. Arduini, M. Fabbi, M. Mantovani, L. Mirone, A. Pochini, A. Secchi and R. Ungaro, *J. Org. Chem.*, 1995, **60**, 1454.
13 M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311.

Received, 13th November 1996; Com. 6/07726I