

# Anion binding behavior of heterocycle-strapped calix[4]pyrroles

Dustin E. Gross · Dae-Wi Yoon · Vincent M. Lynch ·  
Chang-Hee Lee · Jonathan L. Sessler

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**Abstract** A comparative study of the halide and benzoate anion binding properties of a series of phenyl, pyrrole, and furan-strapped calix[4]pyrroles has been carried out. These receptors, which have previously been shown to bind the chloride anion (Yoon et al., *Angew. Chem., Int. Ed.* 47(27):5038–5042, 2008), were found to bind bromide and benzoate anion (studied as the corresponding tetrabutylammonium salts) with near equal affinity in acetonitrile, albeit less well than chloride, as determined from ITC measurements or NMR spectroscopic titrations. This stands in marked contrast to the parent octamethylcalix[4]pyrrole, where the carboxylate anion affinities are substantially higher than those for bromide anion under identical conditions. This finding is rationalized in terms of tighter binding cavity present in the strapped systems. For all three anions for which quantitative data could be obtained (i.e.,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{PhCO}_2^-$ ), the pyrrole-strapped system displayed the highest affinity, although the relative enhancement was found to depend on the anion in question. In the specific case of fluoride anion binding to the pyrrole-strapped receptor, two modes of interaction are inferred, with the first consisting of binding to the calix[4]pyrrole via NH-anion hydrogen bonds, followed by a process that involves

deprotonation of the strapped pyrrolic NH proton. A single crystal X-ray diffraction analysis provides support for the first of these modes and further reveals the presence of a methanol molecule bound to the fluoride anion.

**Keywords** Supramolecular chemistry · Anion recognition · Deprotonation · Calixpyrrole · Isothermal titration calorimetry

## Introduction

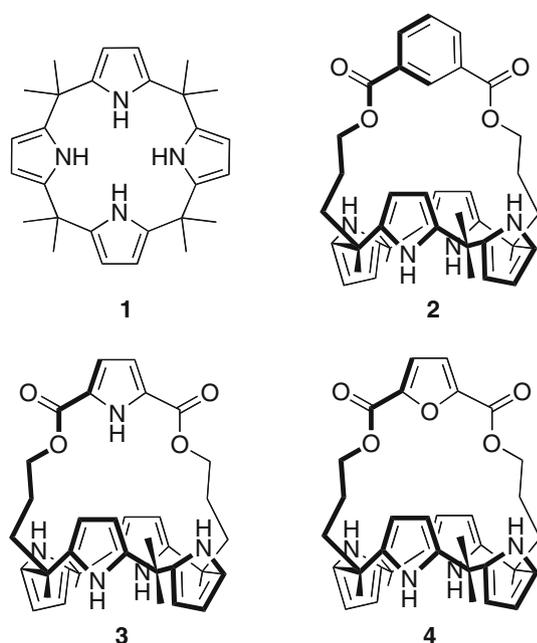
Tuning the selectivity and strength of anion–receptor interactions is one of the major goals in the field of anion recognition. In the case of oligopyrroles, a well-recognized class of anion-binding agents, these features are thought to be tunable on the basis of cavity size, number of H-bond donors, NH proton acidity, receptor charge, conformational flexibility, and the nature and directionality of ancillary electron donor or acceptor groups. Calixpyrroles are now a well-known class of anion receptors. In the specific case of calix[4]pyrroles, recent efforts to enhance the anion binding affinities, as well as to modulate the selectivity of this easy-to-make class of uncharged receptors, have led inter alia to the synthesis of strapped calix[4]pyrroles [1–3]. As detailed in a recent review [4], several strapped calix[4]pyrroles containing phenyl subunits within their respective straps display enhanced halide anion affinities. In some cases, these enhancements were as high as ca. 20× and 2,000× relative to **1** for bromide and chloride, respectively, as inferred from the corresponding  $K_{a(\text{Cl})}$  and  $K_{a(\text{Br})}$  values derived from ITC measurements carried out in  $\text{CH}_3\text{CN}$  [2]. More recently, it was shown that a pyrrole strapped calix[4]pyrrole system could be used to determine the concentration of anions in a commercial sports drink [5],

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D. E. Gross · D.-W. Yoon · V. M. Lynch · J. L. Sessler (✉)  
Department of Chemistry and Biochemistry, Institute for Cellular and Molecular Biology, The University of Texas, 1 University Station-A5300, Austin, TX 78712-0165, USA  
e-mail: sessler@mail.utexas.edu

C.-H. Lee  
Department of Chemistry, Kangwon National University, Chun-Chon 200-701, Korea

and that, separately, a triazole strapped system was capable of affecting the transport of anions across lipid bilayer membranes [6]. Strapped calix[4]pyrroles have also proved instrumental in defining the importance of CH $\cdots$ anion interactions in supramolecular chemistry. With this latter consideration in mind, we previously reported the synthesis of the strapped calix[4]pyrroles **2–4** and their chloride anion binding properties [7]. Here, we extend our studies to include other anions, specifically fluoride, bromide and benzoate, and on this basis are able to confirm further the correlation between the size and shape of an anion with the affinity and selectivity of calix[4]pyrroles **1–4**. We also show that in the particular case of the fluoride anion and the pyrrole strapped receptor **3**, initial anion binding to the four NH protons of the calix[4]pyrrole core is followed by deprotonation of the strapping pyrrole NH proton.



## Results and discussion

Initially, NMR spectroscopy was used to study the binding of fluoride, bromide and benzoate to receptors **3–4** (see Table 1). Downfield shifts of the pyrrolic NH proton signals were seen upon the addition of these anions (as the corresponding tetra-*n*-butylammonium (TBA) salts in acetonitrile-*d*<sub>3</sub> and dimethylsulfoxide-*d*<sub>6</sub>). Unfortunately, as with the previous chloride studies [7], these anions displayed slow association/dissociation kinetics with compound **3**. This precluded an accurate measurement of  $K_a$  values. Nevertheless, structural insights could be inferred in the case of the non-spherical, benzoate anion, which displayed

a slightly different binding mode compared to what was seen in the case of halide anion binding. Specifically, when a slight excess of benzoate anion (ca. 1.4 equiv.) was added to a DMSO-*d*<sub>6</sub> solution containing this receptor, the calix[4]pyrrole NH signal originally present at 9.43 ppm was split into two singlets, which were seen at 11.84 and 9.93 ppm, respectively. In the case of TBAOAc (ca. 4 equiv.), these same signals were seen at 11.54 and 11.32 ppm. While not a proof, these observations are consistent with the intuitively reasonable notion that the bulky benzoate anion binds asymmetrically to the calix[4]pyrrole NH protons due to the limited size of the binding cavity.

In the course of studying the interaction of fluoride with strapped calix[4]pyrrole **3** via NMR spectroscopy, a disappearance of one set of signals (corresponding to free host, **3**) was noted, along with the appearance of a new set of signals (**3**·F<sup>−</sup> two doublets at 15.20 ppm ( $J = 50$  Hz) and 12.20 ppm ( $J = 33$  Hz) see Table 1) as up to one equivalent of fluoride anion was added. These observations are consistent with a strong 1:1 binding interaction and the inclusion of fluoride within the cavity of the pyrrole strapped calix[4]pyrrole **3**. However, the subsequent addition of excess fluoride anion produced a completely new set of signals, including a doublet at 13.1 ppm ( $J = 43$  Hz), ascribed to the calix[4]pyrrole NH resonance, as well as a triplet at 16.01 ppm ( $J = 120$  Hz) diagnostic of the [F–H–F]<sup>−</sup> anion [8]. We rationalize these findings in terms of deprotonation of the strapping pyrrole subunit in the presence of excess fluoride anion. Such an interpretation is consistent with the enhanced acidity expected for the pyrrole within the strap due to the electron withdrawing esters used to tether it to the rest of the receptor [9, 10].

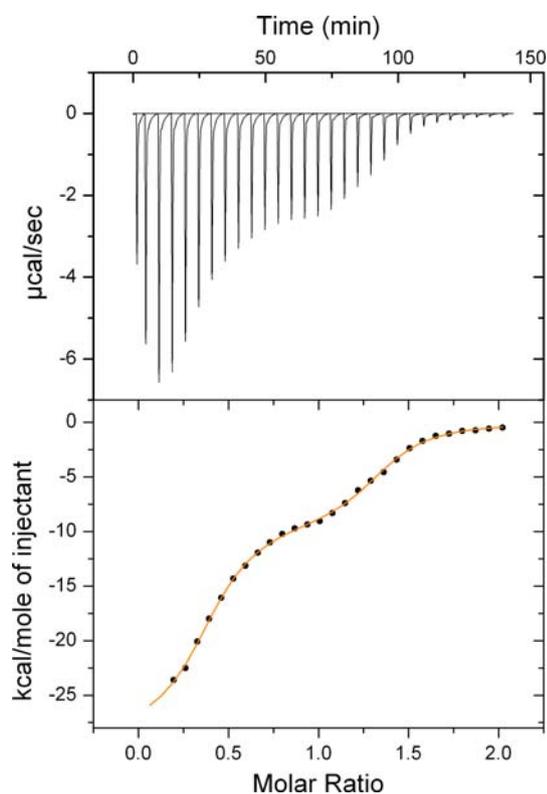
Given the above findings, an attempt was then made to quantify the binding of fluoride anion to strapped system **3** using ITC (isothermal titration calorimetry) in acetonitrile. As expected, plots consistent with an exothermic, two-step process were obtained (see Fig. 1). This result, which unfortunately could not be interpreted to obtain quantitative equilibrium values (i.e.,  $K_a$ 's), nevertheless supports the conclusion that anion binding to the calix[4]pyrrole core takes place initially followed by deprotonation of the pyrrolic NH strap proton as proposed on the basis of the NMR spectroscopic analyses (vide supra). Such a putative two-step process was not evident in the case of the other calixpyrrole receptors of this study (for any of the test anions) or when **3** was either treated with chloride, as shown in previous work, or with benzoate and bromide, as detailed further below.

A single crystal suitable for X-ray diffraction analysis was grown by treating receptor **3** with an excess of TBAF in CH<sub>2</sub>Cl<sub>2</sub> and layering with CH<sub>3</sub>OH. The resulting structural analysis revealed the formation of the fluoride anion inclusion complex **3**·F<sup>−</sup>·2CH<sub>3</sub>OH (see Fig. 2). In this 1:1 anion–receptor complex, the calix[4]pyrrole was found to exist in

**Table 1** Selected proton chemical shifts (ppm) for strapped calix[4]pyrroles **3** and **4**, and their respective anion complexes as recorded in DMSO-*d*<sub>6</sub>

	Strap NH	CP NH	Strap β-H	CP β-H
<b>3</b> <sup>a</sup>	11.58	9.43	6.93	5.76, 5.74
<b>3</b> ·F <sup>b</sup> <b>3</b> ·F(-H) <sup>c</sup>	15.20(16.09)	12.20(13.21)	6.93(6.48)	5.51, 5.49 (5.34, 5.31)
<b>3</b> ·Cl <sup>d</sup>	12.87	10.92	6.93	5.48, 5.45
<b>3</b> ·Br <sup>e</sup>	12.81	10.48	6.89	5.48, 5.45
<b>3</b> ·OBz <sup>f</sup>	16.03	11.84, 9.93	6.72	5.54, 5.49, 5.45, 5.39
<b>3</b> ·OAc <sup>g</sup>	15.97	11.54, 11.32	6.80	5.50, 5.44, 5.40, 5.35
<b>4</b> <sup>h</sup>	–	9.39	7.42	5.71, 5.69
<b>4</b> ·F <sup>i</sup>	–	13.03	7.36	5.38, 5.36
<b>4</b> ·Cl <sup>j</sup>	–	11.47	7.28	5.41, 5.39
<b>4</b> ·Br <sup>k</sup>	–	9.44	7.38	5.63
<b>4</b> ·OBz <sup>l</sup>	–	10.08	7.33	5.61, 5.59

<sup>a</sup> Concentration of **3** = 9.0 mM; <sup>b</sup> 1.12 equiv. of TBAF; <sup>c</sup> 5.59 equiv. of TBAF; <sup>d</sup> 1.46 equiv. of TBACl; <sup>e</sup> 1.29 equiv. of TBABr; <sup>f</sup> 1.38 equiv. of TBAOBz; <sup>g</sup> 3.91 equiv. of TBAOAc; <sup>h</sup> Concentration of **4** = 11.4 mM; <sup>i</sup> 1.22 equiv. of TBAF; <sup>j</sup> 1.12 equiv. of TBACl; <sup>k</sup> 3.44 equiv. of TBABr; <sup>l</sup> 4.01 equiv. of TBAOBz

**Fig. 1** ITC plot of the interaction of **3** [1.08 mM] with TBAF [0.094 mM] in acetonitrile

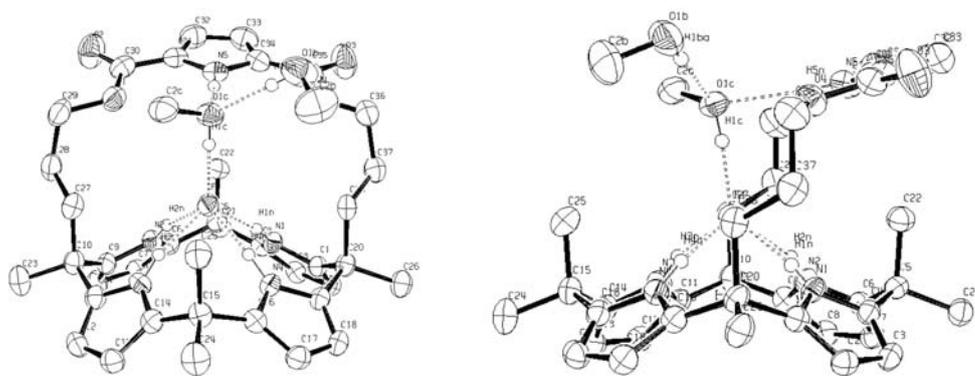
the cone conformation with four NH hydrogen bonds interacting with the fluoride anion (1.817, 1.932, 2.024, 2.067 Å). However, it also revealed that the strapped pyrrolic NH was neither deprotonated nor directly bound to the fluoride anion. Rather, this particular donor site was found to interact with a molecule of methanol, which in turn was bound to the fluoride anion (N–H···O<sub>MeOH</sub> = 1.990 Å,

O–H<sub>MeOH</sub>···F<sup>–</sup> = 1.679 Å). Such a bridging interaction stands in marked contrast to what is seen in the case of the chloride anion complex of **3**, whose structure was reported earlier [7] and which is reproduced in Fig. 3 for the sake of comparison. Presumably, this difference reflects the smaller and more highly solvated nature of the fluoride anion, which makes it less able to bind fully within the pentaaza cavity of **3** without inducing an energetically unfavorable distortion in the receptor structure, at least in the absence of an ancillary donor group (methanol in the present instance). Unfortunately, efforts to obtain diffraction grade crystals under more forcing conditions, i.e., an excess of fluoride anion that might favor deprotonation, proved unsuccessful. Thus, we have no direct structural proof for the existence of the species that we believe is produced at the end of the NMR spectroscopic and ITC titrations.

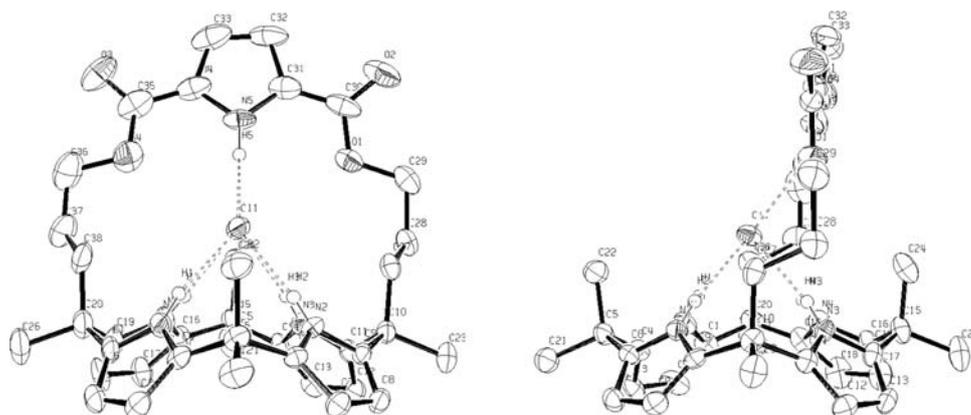
As noted above, NMR spectroscopic titrations of **3** with benzoate anion carried out in acetonitrile-*d*<sub>3</sub> revealed slow exchange kinetics. The same proved true for bromide anion (both species were studied in the form of their respective TBA salts). Thus, we turned to ITC as an alternative method to determine the binding affinities of **3** for these two species. We have previously shown that under appropriate conditions the *K*<sub>a</sub> value for a 1:1 binding interaction derived from NMR spectroscopy and ITC titration data is comparable [12]. In the case of **3**, the ITC analyses in acetonitrile were “clean” and the resulting data fit well to a 1:1 binding profile. This allowed *K*<sub>a</sub> values of 4.5 × 10<sup>5</sup> M<sup>–1</sup> and 7.9 × 10<sup>5</sup> M<sup>–1</sup> to be derived for bromide and benzoate, respectively (cf. Table 2).

In the context of these studies, we were also able to obtain the previously elusive affinity of **2** for bromide (*K*<sub>a</sub> = 2.1 × 10<sup>3</sup> M<sup>–1</sup> in acetonitrile; Table 2) by increasing the titration concentration. This bromide anion

**Fig. 2** Front (*left*) and side (*right*) views of the single crystal X-ray structure of the anion complex **3**·F<sup>−</sup>·2MeOH. Displacement ellipsoids are scaled to the 50% probability level. Structure deposited to The Cambridge Crystallographic Data Centre (CCDC-737942). These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)



**Fig. 3** Front (*left*) and side (*right*) views of the single crystal X-ray structure of the anion complex **3**·Cl<sup>−</sup> (*right*). Displacement ellipsoids are scaled to the 50% probability level. This structure was originally published in ref. [7]



affinity is notable in that it is more than 2 orders of magnitude lower than that recorded for **3** under identical conditions. Presumably, this reflects entropy and enthalpy terms for **3** that are more favorable.<sup>1</sup> This relative enhancement in favor of **3** over **2** was extended to benzoate anion as well, as can be seen by an inspection of Table 2.

In contrast to what was seen in the case of **3**, NMR spectroscopic investigations of the anion binding behavior of receptor **4** revealed that the system was under fast exchange in the case of bromide and benzoate; therefore, association constants could be determined by standard curve fitting methods. Specifically, by following the shift in the furanyl protons as a function of anion concentration and using Wilcox's 1:1 binding profile [11] (this reference first appears in a footnote to Table 2) we determined the binding constants for bromide ( $K_{Br} = 54 \text{ M}^{-1}$ ) and benzoate ( $K_{OBz} = 46 \text{ M}^{-1}$ ; see Table 2) in acetonitrile.

With the binding data for **4** in hand, the selectivity ratios for chloride/bromide and chloride/benzoate could be analyzed across the series of receptors **1–4**. Specifically, from the data included in Table 2, chloride/bromide selectivity ratios,  $K_{Cl}/K_{Br}$ , of 64, 1048, 40, and 3518 could be

<sup>1</sup> In fact, the interaction of calixpyrrole **3** with TBABr actually has a favorable  $T\Delta S$ ; while further analysis is required, this finding could reflect a solvation energy for bromide anion that is relatively small as compared to that of other anions considered in this study.

**Table 2** Thermodynamic data for the interaction of calix[4]pyrroles **1–4** with chloride, bromide, and benzoate anions

Guest	Host	$T\Delta S$	$\Delta H$	$\Delta G$	$K_a (\text{M}^{-1})$	$K_a/K_{\text{furan}}^d$
Cl <sup>−a</sup>	1	−2.9	−10.2	−7.3	$2.2 \times 10^5$	1.2
	2	−1.9	−10.5	−8.6	$2.2 \times 10^6$	12
	3	−1.4	−11.3	−9.9	$1.8 \times 10^7$	95
	4	−1.7	−8.9	−7.2	$1.9 \times 10^5$	1
Br <sup>−b</sup>	1 <sup>b</sup>	–	–	–	$3.4 \times 10^3$	63
	2	−2.9	−7.4	−4.5	$2.1 \times 10^3$	39
	3	0.48	−7.2	−7.7	$4.5 \times 10^5$	8,333
	4 <sup>c</sup>	–	–	–	$5.4 \times 10^1$	1
BzO <sup>−</sup>	1	−4.4	−11.4	−7.0	$1.4 \times 10^5$	3,043
	2	−3.3	−7.4	−4.2	$1.1 \times 10^3$	24
	3	−4.5	−12.6	−8.0	$7.9 \times 10^5$	17,179
	4 <sup>c</sup>	–	–	–	$4.6 \times 10^1$	1

Units of  $T\Delta S$ ,  $\Delta H$ , and  $\Delta G$  are ( $\text{kcal mol}^{-1}$ ); titrations were run at 25 °C in acetonitrile, and the anions were used in the form of their respective tetrabutylammonium (TBA) salts

<sup>a</sup> From reference [7]; <sup>b</sup> From reference [2] at 30 °C; <sup>c</sup> Derived from NMR spectroscopic titrations using standard curve fitting procedures [11]; <sup>d</sup>  $K_a/K_{\text{furan}}$  is the affinity enhancement ratio relative to the furan-strapped system **4**

calculated for compounds **1–4**, respectively. All three strapped systems **2–4** also proved selective for chloride over benzoate, with this selectivity being especially apparent in

the case of compounds **2** and **4**. Interestingly, the preference for chloride anion seen in the three strapped systems stands in contrast to what is observed in the case of the parent calixpyrrole **1**, where the affinities for chloride and benzoate are essentially the same, i.e.,  $1.4$  and  $2.2 \times 10^5 \text{ M}^{-1}$ , respectively. We ascribe this difference between the parent calix[4]pyrrole **1** and the modified systems **2–4** to the better preorganization of the strapped calix[4]pyrroles. These latter are characterized by a less flexible binding pocket, which allows them to be able to accommodate better the small, spherical chloride anion than the larger benzoate anion. The detailed NMR spectroscopic studies carried out in the case of **3** (vide supra) are fully consistent with such an interpretation.

## Conclusion

In previous studies, we were able to show that an order of magnitude increase in the chloride affinity relative to that of the unfunctionalized parent calix[4]pyrrole system **1** could be attained by using strap that contained a putative CH donor site (i.e., by switching to receptor **2**). Conversely, we were able to show that the furan equivalent **4**, a “negative control,” displayed a lower chloride anion affinity relative to both the phenyl-strapped receptor **2** and its pyrrole-containing congener **3** by ca. 1 and 2 orders of magnitude, respectively. In the present work, we have extended these studies to other representative anionic guests and have found that the affinities of both bromide and benzoate anions are enhanced in the phenyl- and pyrrole-strapped systems **2** and **3** relative to the furan-containing control **4**, but not relative to simple *meso*-octamethylcalix[4]pyrrole **1**. Finally, in the case of the pyrrole-strapped system **3**, but not the phenyl or furan analogues **2** and **4**, the interaction with fluoride was found to be a two-step process, as inferred from ITC and NMR spectroscopic measurements. Based on an analysis of the NMR spectroscopic data recorded in acetonitrile- $d_3$ , this two-step process is ascribed to anion binding followed by deprotonation. On the other hand, solid state structural data, obtained using a single crystal grown in the absence of excess fluoride anion, revealed “standard” binding of the fluoride anion by the calix[4]pyrrole core (i.e., four  $\text{N-H}\cdots\text{F}^-$  hydrogen bonds) complemented by a bridging solvent interaction involving the strapped pyrrole NH proton.

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