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Real-time determination of chloride anion concentration in aqueous-DMSO using a pyrrole-strapped calixpyrrole anion receptor^{†,‡}

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Abstract

The use of a pyrrole-strapped calix[4]pyrrole (1) permits the determination of chloride anion concentrations in mixed aqueous DMSO-*d*₆-H₂O environments *via* proton NMR spectroscopy.

Anion recognition chemistry has attracted considerable attention of late.^{1,2} This interest has been driven in part by an appreciation that anions play a central role in biology. Over 70% of all cofactors and substrates involved in biological transformations are anionic in nature, while the maintenance of appropriate concentration of certain anions, including chloride, is now recognized as being essential to human health. A number of anions, including cyanide, phosphate, nitrate, and pertechnetate, are also appreciated as being real or potential threats to the environment, just as others, such as fluoride anion in the treatment of dental carries, are noteworthy for their beneficial effects at appropriate concentrations.¹ These and other considerations continue to animate efforts to produce artificial receptor systems that can mimic biological anion recognition and transport phenomena.² In this context, pyrrole-based and indole-based receptors are of particular interest since these neutral NH hydrogen bond-donating subunits are found in a number of naturally-occurring anion binding motifs.³ To date, uncharged receptors based on pyrroles and indoles have proved highly effective for the recognition and sensing of anions in purely organic solvents or in organic media containing trace quantities of water.⁴ Several have been described that act as carriers,⁵ extractants,⁶ or sensors⁷ under interfacial mixed-organic conditions. Others have been used as ion-selective electrode elements in the presence of water.⁸ However, with the exception of Gale's recent bis-indole urea receptor^{4g} that demonstrated H₂PO₄⁻ binding in DMSO containing up to

[†]This communication is dedicated to one of the great thought leaders in supramolecular chemistry, Professor Javier de Mendoza, on the occasion of his 65th birthday.

[‡]Electronic supplementary information (ESI) available: Proton NMR spectral titration of the pyrrole-strapped calix[4]pyrrole (1) with aq. NaF and corresponding water dependant proton NMR titration spectrum. See DOI: 10.1039/b818077f

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25% water ($K_a = 160 \text{ M}^{-1}$), we are unaware of any neutral pyrrole-type anion receptor that functions in a homogenous mixture containing > 45% water.

Here we report that the pyrrole-strapped calix[4]pyrrole **1**, a system originally prepared as a control for a recent study of CH–anion interactions,⁹ is able to bind fluoride and chloride anions effectively in 4 : 1 (v/v) DMSO–H₂O.

The pyrrole-strapped calix[4]pyrrole (**1**) is not soluble in water. However, it is soluble in DMSO–water (4 : 1 v/v). Therefore, studies of its potential ability to bind chloride in the

presence of water were carried out in DMSO- d_6 to which solutions of NaCl in H₂O were added.

Fig. 1 shows the proton NMR titration spectra produced as the result of such a titration. Inspection of this figure reveals that the pyrrolic NH signals undergo a downfield shift from $\delta = 11.58$ ppm (on the strap) and 9.43 ppm (calix[4]pyrrole) to $\delta = 12.86$ ppm and 10.90 ppm, respectively, upon the addition of ≥ 1.0 equiv. of aq. NaCl. This addition also induces an upfield shift in the pyrrolic β -H signals from $\delta = 5.77$ – 5.73 ppm to *ca.* 5.48–5.44 ppm. Finally, the free pyrrole-strapped calix[4]pyrrole (**1**) signals were found to disappear completely upon the addition of ≥ 1.0 equiv. of aq. NaCl solution (Fig. 1). These proton NMR spectroscopic results are very similar to those observed previously for chloride binding in pure DMSO- d_6 .⁹ On this basis we conclude that the binding stoichiometry is 1 : 1 and that anion complexation takes place within the cavity.⁹

The specific spectral features recorded in the presence of less than one full equivalent of chloride anion are consistent with a slow exchange system. This slow exchange precluded an accurate determination of the K_a values from an NMR titration. However, it was found that the amount of chloride anion-bound receptor is equal to the concentration of added chloride within the limits of the integration error through the addition of 1.0 equiv. of aq. NaCl. Also, complete binding is observed after the addition of 1.0 equiv. of NaCl. This leads us to suggest the binding stoichiometry is 1 : 1 and that the affinity constant is $\geq 10\,000\text{ M}^{-1}$ under these mixed and somewhat varying aqueous conditions. This value corresponds to the normal limit for NMR spectroscopy based K_a determinations.¹⁰

To probe in greater depth the effect, if any, that the presence of water had on the binding process, a proton NMR spectroscopic study was carried out in which the pyrrole-strapped calix[4]pyrrole (**1**) was first dissolved in a DMSO- d_6 solution (1.0 mL) to which 0.55 equiv. of aq. NaCl (20 μ L) had been added. Increasing quantities of water (D₂O) were then added to this initial solution (Fig. 2). The integrated ratios of the pyrrolic β -protons corresponding to the bound and unbound forms of the calix[4]pyrrole core were found to be unchanged during the course of this titration. This is consistent with the binding being exceptionally strong (*i.e.*, above the NMR spectroscopic K_a limit of *ca.* $10\,000\text{ M}^{-1}$) even in the highly polar environment consisting of 4 : 1 DMSO- d_6 -H₂O. Unfortunately, when the amount of water exceeded 20%, precipitation of calix[4]pyrrole **1** occurred. Thus, the limit at which the expected water-induced diminution in the affinity occurs could not be attained. Presumably, more solubilized versions of **1**, current synthetic targets, will allow such studies to be carried out.

Experiments similar to those summarized in Fig. 1 and 2 were carried using aqueous NaF and were found to give rise to similar results (see ESI[†]). Again, the ¹H NMR titration spectrum indicated slow association/dissociation kinetics and, as in the case of aq. NaCl, the NH proton signal disappeared upon the addition of ≥ 1.0 equiv. of fluoride anion. Likewise, precipitation was observed if the amount of water exceeded 20%. Other anions, including dihydrogenphosphate and hydrogensulfate, were also tested; however, no evidence of binding was observed by NMR spectroscopic analysis.

Due to the slow exchange observed in the above NMR spectroscopic analyses, isothermal titration calorimetry (ITC) was used to quantitate the interaction between chloride anion and **1**. The conclusion reached above, namely that the chloride affinity is greater than 10^4 M^{-1} in DMSO–water (4 : 1 v/v), was confirmed by titrating either tetra-*n*-butylammonium (TBA) chloride or NaCl into a DMSO–water solution of **1** (see ESI[†]). The resulting K_a values (estimated errors of $< 10\%$) were determined to be $26\,000\text{ M}^{-1}$ and $24\,000\text{ M}^{-1}$, respectively. Additionally, the affinity of receptor **1** for F[−] (studied as the TBA salt) was

found to be 20 times greater than that for Cl^- (*i.e.*, $K_{\text{fluoride}} = \text{ca. } 500\,000\text{ M}^{-1}$). Related studies revealed no evidence that either the dihydrogenphosphate or benzoate anions (studied as the corresponding TBA salts) were bound (*cf.* ESI†). This binding behaviour (affinity and selectivity) stands in marked contrast to what is seen in the case of the bis-indole urea receptor^{4g} for which analogies in structure and measurement conditions invite comparisons.

The above findings led us to consider that system **1** could be used to determine directly the concentration of chloride anions in unknowns, as long as the latter could be dissolved in the 20% aqueous DMSO mixture needed to carry out an analysis *via* proton NMR spectroscopy. An example of how such an analysis could be carried out is presented in Fig. 3; it shows the ^1H NMR spectrum of the pyrrole-strapped calix[4]pyrrole (**1**) recorded in the presence of a high-ion sports drink (Pocari Sweat™; 100 μL added to a solution of **1** in 1.0 mL of $\text{DMSO}-d_6$). Also shown in this figure are the spectra of **1** recorded in the presence of known concentrations of NaCl and NaF.

The proton NMR spectrum recorded in the presence of the sports drink (spectrum b) is clearly distinguished from the unbound form of pyrrole-strapped calix[4] pyrrole (**1**), as well as the 100% chloride and fluoride anion-bound forms. Specifically, peaks corresponding to both the unbound and chloride-bound forms were present. Thus, it was concluded that (*i*) this sports drink did not contain an appreciable amount of fluoride anion and (*ii*) it contained a chloride anion concentration of 17.7 mmol L^{-1} , as inferred from the proton NMR integration ratios (and a knowledge of the total receptor concentration; see ESI†). This latter value compares well with the 16.5 mmol L^{-1} indicated on the package label and matches even more closely to the $[\text{Cl}^-]$ value of $17.0 \pm 0.4\text{ mM}$ determined for the actual test sample of Pocari Sweat using ion chromatography.¹¹ Thus, receptor **1** appears to allow for the direct analysis of chloride anion in aqueous mixtures and in real time on the NMR time scale.

In summary, we have been able to demonstrate that neutral receptors containing only pyrrole NH hydrogen bond donors may be used to effect the binding of halide anions (Cl^- and F^-) under highly polar conditions. To the best of our knowledge, this is the first time such binding has been demonstrated in mixed aqueous organic media at H_2O levels $> 5\%$ in the absence of ancillary amide or urea motifs. Current work is focused on studying systems such as **1** under interfacial conditions, as well as preparing new analogues that would allow for the recognition and detection of anions in pure water.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

Proton NMR spectra of (a) pyrrole-strapped calix[4]pyrrole (**1**) ([**1**] = 18.65 mM, DMSO-*d*₆ = 0.800 mL), (b) after adding 0.34 equiv. of aq. NaCl (0.010 mL; after addition: H₂O 1.2% by volume), (c) 0.68 equiv. of aq. NaCl (0.020 mL; after addition: H₂O 2.4% by volume), and (d) 1.02 equiv. of aq. NaCl (0.030 mL; after addition: H₂O 3.6% by volume).

Fig. 2.

Water-dependent proton NMR spectral titration of the pyrrole-strapped calix[4]pyrrole (**1**) chloride complex. In this study, compound **1** was dissolved in 1.00 mL of DMSO-*d*₆ (16.04 mM) containing 20 μL of aq. NaCl solution (0.55 equiv.). D₂O was then added such that the percent water in each spectrum was as follows: (a) 5%, (b) 11%, (c) 15%, (d) 21%, and (e) 24%. The numbers on the spectra are the integrated ratios for the sets of peaks in question. Note that precipitation occurs under the conditions of spectrum (e).

Fig. 3. Proton NMR spectrum of (a) pyrrole-strapped calix[4]pyrrole (**1**) dissolved in 1.0 mL of DMSO- d_6 , (b) after adding 100 μ L of a high-ion sports drink (Pocari SweatTM), (c) spectrum of chloride complex produced by adding 1.10 equiv. of aq. NaCl to solution (a), (d) spectrum of fluoride complex (produced by adding 1.1 equiv. of aq. NaF to solution (a)). Note: ■ = peaks due to non-calixpyrrole organic species present in the sports drink.