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Fluoride recognition in 'super-extended cavity' calix[4]pyrroles†

Salvatore Camiolo and Philip A. Gale*

Department of Chemistry, University of Southampton, Southampton, UK SO17 1BJ. E-mail: philip.gale@soton.ac.uk

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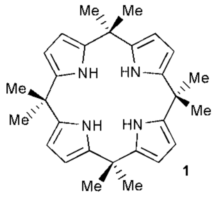
Extended cavity ester (4) and amide (5) calix[4]pyrrole macrocycles have been synthesised and shown to bind fluoride exclusively in deuteriated DMSO solution.

The coordination chemistry of anionic species by abiotic receptor species is an area of supramolecular chemistry that continues to attract the attention of coordination chemists.[1] One of the major goals in molecular recognition is to produce receptors that are highly selective in their guest binding properties. The discovery that calix[4]pyrroles (such as *meso*-octamethylcalix[4]pyrrole (**1**)) are effective anion binding agents[2] in solution has led to the synthesis of a variety of new calixpyrrole macrocycles that have been used for anion binding,[3] sensing[4] and in new anion separation technologies.[5] Recently Sessler and co-workers[6] and Floriani and co-workers[7] have independently reported the syntheses of extended cavity calix[4]pyrroles derived from 4-hydroxyacetophenone. The $\alpha\alpha\alpha\alpha$-isomer of this species (**2**) possesses an array of phenol moieties that resembles that present in lower-rim unfunctionalised calix[4]arenes in the cone conformation. Sessler and co-workers have studied the anion recognition properties of the isomers of **2** together with OMe derivatives (**3**) and found anion selectivity trends in line with those observed for other calix[4]pyrrole species.[6] We have modified the phenol groups of compound **2** with a variety of 'longer' and bulkier functional groups than methyl and have obtained tetra-ester (**4**) and -amide (**5**) macrocycles with 'super-extended cavities'. These macrocycles show interesting highly selective anion coordination properties in solution that are atypical of calix[4]pyrrole macrocycles.



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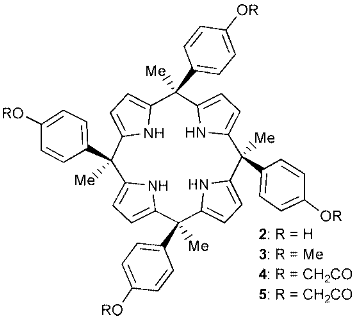

2: R = H
3: R = Me
4: R = CH_2COOEt
5: R = CH_2CONEt_2

Compound **4** was synthesised by reaction of compound **2** with ethylbromoacetate in dry acetone in the presence of K_2CO_3 with heating at reflux for 5 days. The tetra-ester derivative was isolated as a white powder in 76.5% yield. Compound **5** was synthesised by reaction of compound **2** with 2-chloro-*N*,*N*-diethylacetamide and potassium iodide in dry acetone with stirring for 5 days and was isolated in 50% yield. These compounds may be regarded as pyrrolic analogues of the lower-rim functionalised calix[4]arenes synthesised and studied in the 1980s by McKervey, Ungaro and co-workers.[8]

Solution binding properties of **4** and **5** were investigated using ^{1}H NMR titration techniques in deuteriated DMSO solution. Previous studies in deuteriated dichloromethane with compound **1**[2] and deuteriated acetonitrile with compounds **1**, **2** and **3**[6] have shown downfield shifts of the calix[4]pyrrole NH proton on addition of chloride and dihydrogen phosphate anions consistent with the formation of 1:1 receptor–anion solution complexed species. However, it was found that addition of 20 equivalents of Cl^-, Br^-, I^-, $H_2PO_4^-$ or HSO_4^- anions (as tetrabutylammonium salts) to deuteriated DMSO solutions of **4** and **5** caused *no changes* in the NMR spectra of these calixpyrroles.[9] Compounds **4** and **5** therefore *do not interact* with these putative anionic guests in DMSO solution. On the other hand, upon addition of fluoride anions, new resonances (for the N*H*, Ar*H*, pyrrole C*H* and ArOC*H*$_2$C protons) were observed in the ^{1}H NMR spectra of **4** and **5** corresponding to the formation of fluoride complexes with slow complexation/decomplexation kinetics relative to the NMR timescale (Fig. 1). In addition, coupling is observed between the NH protons of the calixpyrroles and the bound fluoride anions (confirmed by ^{19}F NMR spectroscopy) at room temperature (21 °C) with coupling constants of 47 Hz for both compounds **4** and **5**. This coordination coupling has only previously been observed in a

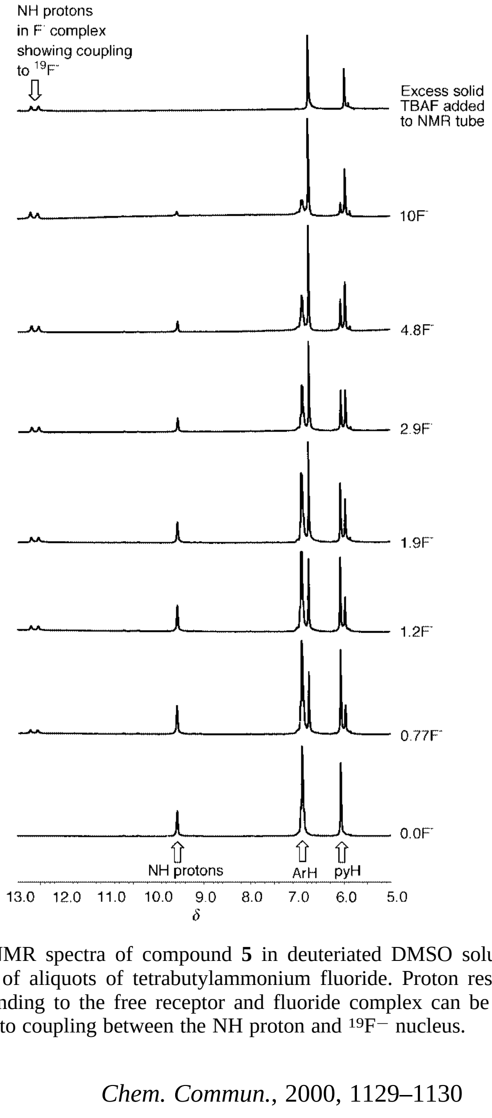

Fig. 1 NMR spectra of compound **5** in deuteriated DMSO solution on addition of aliquots of tetrabutylammonium fluoride. Proton resonances corresponding to the free receptor and fluoride complex can be seen in addition to coupling between the NH proton and $^{19}F^-$ nucleus.

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† Electronic supplementary information (ESI) available: synthesis details, NMR and MS, and titration curves. See http://www.rsc.org/suppdata/cc/b0/b003229h/

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calix[4]pyrrole–fluoride complex at low temperature (193 K) in deuteriated dichloromethane solution.[10] The concentration profiles of compounds **4** and **5** and their fluoride complexes during the NMR titrations (calculated by integration of the relevant NH resonances in the NMR spectra) are shown in Fig. 2.

In order to compare the solution binding properties of **4** and **5** with *meso*-octamethylcalix[4]pyrrole **1** and the extended cavity calix[4]pyrrole **2**, titrations of these species with fluoride and chloride anions were conducted in deuteriated DMSO solution. In the case of compound **1**, upon addition of fluoride anions, a broadening of the 'free' NH resonance at 9.4 ppm occurred and the appearance of a new resonance at 12.8 ppm (after the addition of 1.4 equivalents of fluoride) was observed. Upon addition of chloride anions to solutions of **1** in the same solvent, shifts of the NH proton were observed with a maximum shift to 11.1 ppm after 3.3 equivalents of chloride. Least squares non-linear fitting of the titration results (pyrrole CH protons) with fluoride and chloride to a 1 : 1 anion/calixpyrrole binding model with the EQNMR computer program[11] afforded stability constants of 1060 and 1025 M^{-1} (errors estimated to be $< 15\%$) with compound **1** and fluoride and chloride respectively. Similar behaviour was observed with compound **2** and chloride, however the shift of the NH proton was small (a downfield shift of 0.1 ppm after seven equivalents of chloride) and the binding profile did not reach a plateau. This suggests that only a weak interaction is occurring with chloride, making the accurate calculation of a stability constant difficult. The evolution of new resonances corresponding to a solution complexed species was observed upon addition of fluoride anions to compound **2** in deuteriated DMSO solution.

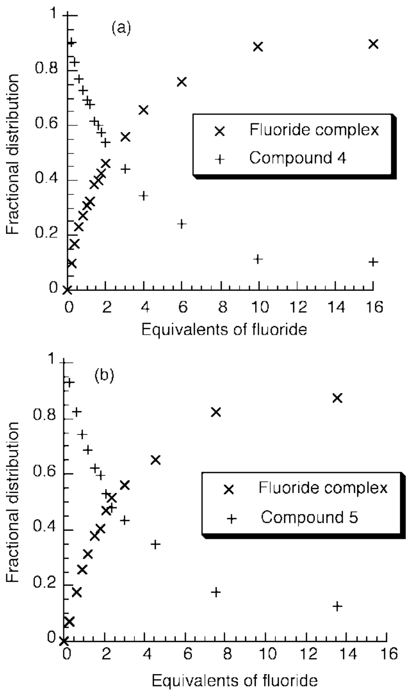

Fig. 2 Concentration profiles for (a) compound **4** and its fluoride complex and (b) compound **5** and its fluoride complex during ^{1}H NMR titrations in deuteriated DMSO solution at room temperature (21 °C).

Compounds **4** and **5** therefore show unique solution anion binding properties in that they *only bind fluoride* in deuteriated DMSO solution. These receptors do not interact with the other anions studied, behaviour not observed with other calix[4]pyrroles. It appears that the presence of an extended cavity in compound **2** and a 'super-extended' cavity in compounds **4** and **5** serves to decrease (**2**) and switch off (**4** and **5**) the affinity of this class of receptor for anions other than fluoride in DMSO solution. We are currently continuing to study the unusual coordination properties of these and other new calix[4]pyrroles in deuteriated DMSO. The results of this work will be reported in due course.

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9 Solubility problems prevented anion binding studies being conducted with compound **5** in deuteriated acetonitrile solution. It was therefore decided to conduct all binding studies in deuteriated DMSO (estimated water content approx. 0.02%) in order to give a consistent set of results and to minimise the chances of ion-pair formation in solution (which may occur with low polarity and poor donor/acceptor solvents such as dichloromethane). It should be noted however that ^{1}H NMR titrations of compound **4** with fluoride or chloride anions in deuteriated acetonitrile solution resulted in the appearance of new resonances corresponding to solution complexed species (slow exchange conditions in contrast to compound **2** which displays fast exchange with anions under these conditions (see ref. 6)).

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