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ARTICLE

Deuterium Exchange of Pyrrolic NH Protons Accelerated by Fluoride and Bicarbonate in $CDCl_3$, CD_3CN, and DMSO-d_6†

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The anion binding features of pyrrole- and benzene-strapped calix[4]pyrroles **1** and **2**, in particular, for F^- and HCO_3^- have been examined by means of NMR spectroscopy in DMSO-d_6, $CDCl_3$, and CD_3CN, respectively. Receptors **1** and **2** were found to bind F^- and HCO_3^- tightly *via* slow binding/release equilibria in these solvents. A combination of ^1H and ^{19}F NMR spectroscopic analyses with mass spectrometry revealed that contacting calix[4]pyrroles **1** and **2** with F^- and HCO_3^- salts prompts deuterium exchange of the NH protons in the three nominally aprotic deuterated solvents considered in this study.

Introduction

An increasing appreciation of the critical roles anions play in biology, and chemistry, and the environment, has focused attention on the study of synthetic anion recognition systems.[1-3] Many of the better studied anion receptors contain hydrogen bond donors, e.g., amide, urea, pyrrole, indole, hydroxyl, or squaramide groups, and recognize anions by harnessing hydrogen bonding interactions involving what are typically Lewis basic anions.[4-19] Often, the hydrogen bonding interactions between the receptor and the target anions may be monitored by ^1H NMR spectroscopy.[4-19] In principle, the proton signals of the hydrogen atoms involved in stabilizing the receptor-anion hydrogen bonds are downfield-shifted in the ^1H NMR spectrum. In particular, hydrogen bonds to basic anions including F^- and HCO_3^- result in relatively large downfield shifts in the corresponding proton signals.[20-42] However, these and other anions are basic and can act to deprotonate the protons of the hydrogen bond donor motifs.[43-48] The presence of basic anions can also promote deuterium exchange with the solvent. This is true even in the case of nominally aprotic solvents. For instance, in 2004, the Bowman-James group demonstrated via ^1H and ^{19}F NMR spectroscopic analyses that in cryptands bearing multiple amide hydrogen bond donor groups interactions with the F^- anion in DMSO-d_6 (a solvent lacking relatively acidic protons but not necessarily rigorously dried) could trigger stepwise NH deuteration.[35-37] More recently, Mani et al. reported that pyrrolic NH hydrogens present in a cage-like anion receptor were sequentially replaced with deuterium from DMSO-d_6 after forming strong hydrogen bonds to the F^- anion.[38] However, to our knowledge, anion-induced deuterium exchange has not been explored in other aprotic deuterated solvents or with other anions than F^-. On the other hand, it has frequently been observed in aprotic solvents, such as chloroform-*d* and acetonitrile-d_3, that the proton signals of the receptor hydrogen bond donor moieties display reduced integration values or disappear completely while the intensity of the other proton signals remain relatively unchanged.[39-41] Similar ^1H NMR spectral changes have been observed in chloroform-*d* in the case of the bicarbonate anion.[42] While these ^1H NMR spectral changes may reflect deprotonation of the relatively acidic hydrogen bond donor protons,[39-42] the possibility exists that the observed features reflect deuterium exchange. Given this potential dichotomy, we sought to ascertain whether fluoride-mediated deuterium exchange would occur in the case of receptors **1** and **2** as monitored by ^1H and ^{19}F NMR spectroscopy in chloroform-*d* and acetonitrile-d_3, as well as DMSO-d_6 (Figure 1). The resulting ^1H and ^{19}F NMR spectra provided support for the conclusion that the binding of F^- to receptors **1** and **2** facilitates deuteration of the calix[4]pyrrole NH protons in all three solvents. The HCO_3^- anion was also found to accelerate deuterium exchanges of the pyrrolic NH protons in $CDCl_3$, as corroborated by a mass spectrometric analysis. Here, we report F^- and HCO_3^-–facilitated deuterium exchange of the pyrrolic NH protons in what are generally considered to be aprotic deuterated solvents.

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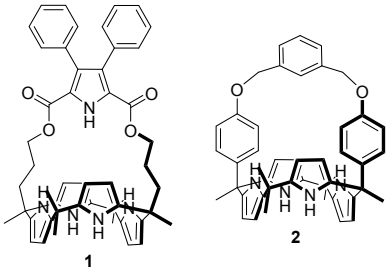

Fig. 1 Structures of anion receptors **1** and **2**.

Results and Discussion

Receptors **1** and **2** were synthesized following literature procedures reported by us (Figure 1).[32,43] The structure of receptor **2** was further confirmed by a single crystal X-ray diffraction analysis. In this case, the calix[4]pyrrole subunit of receptor **2** adopts the 1,3-alternate conformation in the solid state with no solvent molecules found to interact with the receptor (Fig. 2).

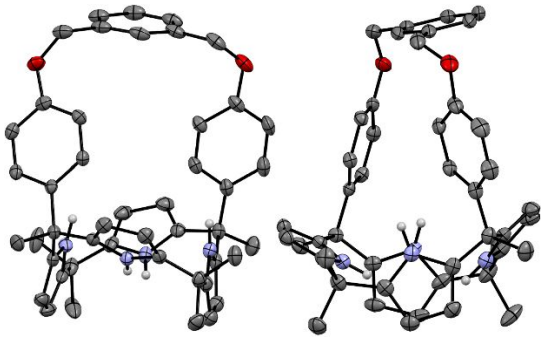

Fig. 2 Single crystal X-ray diffraction structures of receptor **2**. Most hydrogen atoms are removed for clarity. Displacement ellipsoids are scaled to the 50% probability level.

We previously reported the binding features of receptor **1** for the halide anions (as their tetrabutylammonium (TBA^+) salts) in DMSO-d_6.[43] By contrast, the capability of receptor **2** to bind the halide anions in DMSO-d_6 was not investigated. Thus, we examined the ability of receptor **2** to bind halide anions in DMSO-d_6 via ^{1}H NMR spectroscopy. Receptors **1** and **2** were also tested for their affinity for the bicarbonate anion (as its tetraethylammonium (TEA^+) salt) in the same solvent system. When receptor **1** was treated with the test anions including F^-, Cl^-, Br^-, I^- and HCO_3^- (ca. 10 equiv each) in DMSO-d_6, most of its proton resonances were found to experience a noticeable chemical shift change in ^{1}H NMR spectra (Fig. S1†). Specifically, the signal of the calix[4]pyrrole NH protons were significantly shifted into a downfield region in the presence of F^-, Cl^-, Br^-, and HCO_3^-, while the *β*-pyrrolic CH proton signal moved upfield. On the other hand, receptor **2** gave rise to ^{1}H NMR spectral changes consistent with anion binding in the cases of the F^-, Cl^-, and HCO_3^- anions (Fig. S2†), a finding which stands in contrast to what was seen in chloroform-*d* where receptor **2** complexes only F^- and HCO_3^-.[32] Both receptors (**1** and **2**) were also found to bind all the anions via slow association/dissociation kinetics on the NMR timescale (Fig. S3-S8†). The association constants (K_a) of receptor **1** in DMSO-d_6 were calculated from ^{1}H NMR spectral titrations to be $>10^5$ M^{-1}, $(1.2 \pm 0.1) \times 10^4$ M^{-1}, $(1.2 \pm 0.1) \times 10^3$ M^{-1}, and $(1.0 \pm 0.1) \times 10^4$ M^{-1} for F^-, Cl^-, Br^-, and HCO_3^-, respectively, while those of receptor **2** were estimated to be $(1.2 \pm 0.1) \times 10^4$ M^{-1}, $(1.1 \pm 0.1) \times 10^3$ M^{-1}, and $(9.2 \pm 0.1) \times 10^3$ M^{-1} for F^-, Cl^- and HCO_3^-, respectively (Table 1).[49] The high association constants seen for receptor **1** relative to receptor **2** are attributed to the auxiliary NH hydrogen bond donor on the strap subunit of **1** participating in anion binding.

Table 1 Association constants (K_a, M^{-1}) of receptors **1** and **2** for the halide and bicarbonate anions as evaluated by ^{1}H NMR spectroscopy in DMSO-d_6 at room temperature.

Anions[a]	1	2
F^-	$> 10^{5b}$	$(1.2 \pm 0.1) \times 10^4$
Cl^-	$(1.2 \pm 0.1) \times 10^4$	$(1.1 \pm 0.1) \times 10^3$
Br^-	$(1.2 \pm 0.1) \times 10^3$	< 5
I^-	-[c]	-[c]
HCO_3^-	$(1.0 \pm 0.1) \times 10^4$	$(9.2 \pm 0.1) \times 10^3$

[a] The tetrabutylammonium salt form was used for the halide anions and the tetraethylammonium salt for the HCO_3^- anion. [b] From ref. 43. [c] No appreciable binding.

As reported earlier, receptor **1** binds F^- via a two-step process involving deprotonation of the strap pyrrolic NH proton. In the presence of 1.0 or less anion equiv, the pyrrolic NH hydrogens of **1** form a strong hydrogen bonds to F^- leading to a 1:1 receptor-F^- complex (Fig. S3†). By contrast, further addition of F^- to the 1:1 fluoride complex of receptor **1** induces deprotonation of the strap pyrrole NH proton generating a new set of proton peaks in ^{1}H NMR spectra corresponding to the HF_2^- anion and the fluoride complex of the deprotonated receptor **1**, respectively (Fig. S3†). In this case, one fluoride equivalent remains encapsulated within the receptor cavity after deprotonation of the pyrrolic NH proton on the strap unit (Fig. S3). This conclusion was further supported by ^{19}F NMR spectral studies (*vide infra*).

Different binding behavior was seen for receptor **1** in case of the bicarbonate anion in DMSO-d_6. For instance, upon exposure of receptor **1** to up to 1.28 equiv of the bicarbonate anion (as its tetraethylammonium (TEA^+) salt), the proton signal of the calix[4]pyrrole NH protons originally appearing as a singlet at 9.33 ppm in the ^{1}H NMR spectrum undergo a downfield-shift and split into two discrete singlets appearing at 10.74 ppm ($\Delta\delta \approx 1.41$ ppm) and 11.29 ppm ($\Delta\delta \approx 1.96$ ppm), respectively (Fig. S4†). This finding presumably reflects the bicarbonate anion being bound asymmetrically to the cavity of receptor **1**. This presumption was further supported by the observation that the β-pyrrolic CH proton signal, originally a singlet, is split into two doublets that are upfield-shifted (Fig. S4†). This observance is attributable to the TEA^+ cation forming a tight ion pair with the bound bicarbonate anion that prevents the strap unit from swaying over the bicarbonate anions leading

to the presumed asymmetric binding modes (Fig. S4†). Further addition of ≥1.90 equiv of the bicarbonate anion led the split signals corresponding to the calix[4]pyrrole NH and β-pyrrolic CH proton signals to merge into a singlet in both cases with a further downfield shift for the NH signals and a upfield shift for the CH signals (Fig. S4†). By contrast, the strap pyrrole NH peak experienced a distinct upfield shift. These chemical shift changes are rationalized in terms of a binding mode change at relatively high anion concentrations. Namely, a tight ion pair of the initially bound $TEAHCO_3$ is separated by the receptor to form a receptor-separated ion pair complex where the TEA^+ counter cation being bound to the electron-rich calix[4]pyrrole cavity (Fig. S4†). In the latter binding mode, the bicarbonate anion is more tightly bound to the calix[4]pyrrole moiety with its weakened hydrogen bonding interaction with the pyrrole NH on the strap. As a result, the initial asymmetric bicarbonate binding mode becomes more symmetric, at least in a time averaged sense.

Receptor **2** was found to complex the fluoride and the bicarbonate anions with higher affinity in DMSO-d_6 than in $CDCl_3$ (K_a for F^- = 9.1 × 10^3 M^{-1} in $CDCl_3$ vs 1.2 × 10^4 M^{-1} in DMSO-d_6 and K_a for HCO_3^- = 2.3 × 10^3 M^{-1} in $CDCl_3$ vs 9.2 × 10^3 M^{-1} in DMSO-d_6) (Fig. S5 and S8†).[32,49] The higher anion affinity seen in DMSO-d_6 is ascribed to the initial salts, TBAF and $TEAHCO_3$, being subject to a lower level of ion pairing in DMSO-d_6 than in $CDCl_3$ and hence more dissociated and available for complexation.

Further evidence for receptor **1** complexing the bicarbonate anion was garnered from a single crystal X-ray diffraction analysis. Diffraction grade single crystals of the putative bicarbonate complex of receptor **1** were grown by subjecting a dichloromethane-ethanol solution of receptor **1** and excess $TEAHCO_3$ to slow evaporation. The resulting structure revealed complexation of the monoethyl carbonate ester as its TEA^+ salt. In analogy to what was seen in the case of a cationic calix[4]pyrrole derivative, formation of the carbonate ester was presumed to result from the reaction of the bicarbonate anion with ethanol under the conditions of crystallization. The monoethyl carbonate ester anion is asymmetrically complexed within receptor **1** as further inferred from ^{1}H NMR spectroscopic studies (Fig. S4†).[33,34] The N-H···O distances for the hydrogen bonding interactions between the receptor pyrrole NHs and the ethyl carbonate O atoms were found to fall in the range of 2.07 Å ~ 2.15 Å for the calix[4]pyrrole and to be 1.88 Å for the strap pyrrole, respectively (Fig. 3).

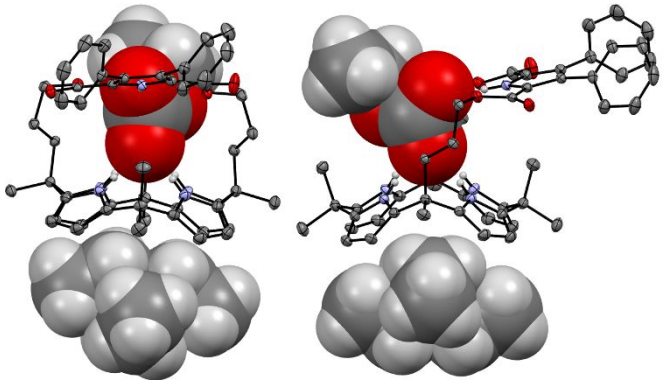

Fig. 3 Two views of the single crystal X-ray diffraction structure of the tetraethylammonium ethyl carbonate complex of receptor **1**. Most hydrogen atoms are omitted for clarity. Displacement ellipsoids are scaled to the 30% probability level.

Next, we explored whether receptors **1** and **2** would also undergo fluoride-mediated pyrrole NH deuterium exchange in DMSO-d_6. We also tested chloroform-*d* and acetonitrile-d_3 since these solvents are frequently used in anion binding studies. In a first study, receptor **1** was treated with 1.0 equiv of TBAF in DMSO-d_6. This led to the emergence of two distinct fluorine signals in the ^{19}F NMR spectrum at -94.28 ppm and -94.94 ppm as a quintet of doublets and a quintet, respectively (Fig. S9†). The splitting seen in the apparent quintet of the doublet resonance is attributable to ^{1}H-^{19}F coupling between the bound fluoride anion and all the five pyrrolic NH protons as inferred from ^{1}H NMR spectroscopic analyses (Fig. S3 and S9†). In contrast, the quintet signal (J = 20.61 Hz) is presumed to result from ^{1}H-^{19}F coupling between the mono-deuterated receptor (**1**-d_1) with the bound fluoride anion. Based on the signal pattern, it is inferred that the more acidic pyrrolic NH proton on the strap is replaced by a deuterium under these conditions. Consistent with what was suggested by Bowman-James, we suggest that the DMSO-d_6 solvent is the source of the incorporated deuterium. Upon addition of 6.0 equiv of F^- to receptor **1** in DMSO-d_6, the fluorine signals were downfield-shifted by Δδ = 15.41 ppm to -79.32 ~ -81.92 ppm appearing as a series of multiplets ranging from a quintet to a singlet. The multiplets appear at regular intervals (Δδ = 0.60 ppm) and have the same coupling constant J = 28.63 Hz (Fig. S9†). These observations are ascribed to a strengthening of the hydrogen bonding interactions between the fluoride anion and the remaining NH protons (i.e., those from the calix[4]pyrrole) as a result of full deprotonation of the strap pyrrole NH (as opposed to D-for-H exchange) and formation of the fluoride complex of the resulting species (referred to as [**1** - H^+]$^-$) concurrent with the hydrogen bifluoride anion (HF_2^-). This presumption was supported by the finding that the NH proton signal of the calix[4]pyrrole was shifted to lower field in the ^{1}H NMR spectrum, as well as the observation of a triplet signal at 16.15 ppm (J = 120.09 Hz) and a doublet signal at -142.95 ppm (J = 77.10 Hz) in the ^{19}F NMR spectrum (Fig. 4). The multiplet fluorine signals, ranging from a quintet to a singlet, are consistent with the H-F coupling patterns expected for a fluoride anion bound to the mono- ([**1** - H^+]$^-$•F^--d_1), di- ([**1** -

$H^+]^-\bullet F^-$-d_2), tri- ([**1** - $H^+]^-\bullet F^-$-d_3), and tetra-deuterated forms ([**1** - $H^+]^-\bullet F^-$-d_4) of deprotonated receptor **1** ([**1**-$H^+]^-\bullet F^-$), respectively. The initial doublet proton signal for the calix[4]pyrrole NH protons in the ^{1}H NMR spectrum also becomes more complex; this is as expected given the presumed presence of multi-deuterated forms of [**1**-$H^+]^-\bullet F^-$ (Fig. 4). After a DMSO-d_6 solution of receptor **1** (10 mM) was allowed to stand overnight in the presence of 6.0 equiv of fluoride anion, a greater percentage of fluorine signals corresponding to the more highly deuterated forms of **1** ([**1** - $H^+]^-\bullet F^-$-d_n) were seen, while the ^{19}F quintet signal disappears completely (Fig. 4 and S10†). Upon the addition of H_2O (10%) to a DMSO-d_6 solution containing various multi-deuterated forms of [**1** - $H^+]^-\bullet F^-$, a spectrum is produced that resembles that seen in the presence of 1.0 equiv of fluoride (Fig. 4 and S10†). This finding is rationalized in terms of the deprotonated strap pyrrole becoming re-protonated upon contact with H_2O. However, a portion of the calix[4]pyrrole NH protons remain deuterated even after this treatment (Fig. 4 and S10†) as inferred from the presence of quintet, quartet, triplet, and doublet signals, respectively.

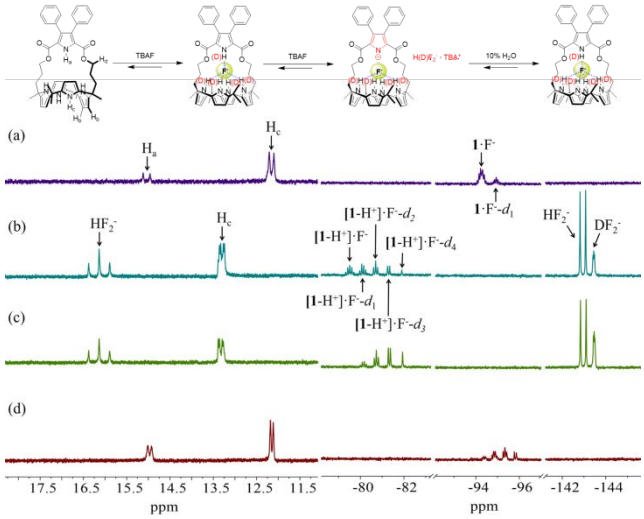

Fig. 4 Partial ^{1}H (left) and ^{19}F (right) NMR spectra of **1** (10 mM) recorded (a) in the presence of 1.0 equiv of TBAF in DMSO-d_6, (b) 6.0 equiv of TBAF in DMSO-d_6, (c) after allowing the solution in (b) to stand overnight, and (d) after adding 10% water to (c). Fluorobenzene (C_6H_5F, 16.2 mM) was used as an internal reference.

In analogy to what was observed for receptor **1**, receptor **2** undergoes deuteration of its pyrrolic NH protons in the presence of the fluoride anion. For instance, after allowing a DMSO-d_6 solution of receptor **2** to stand overnight in the presence of 6.0 equiv of fluoride as the TBA^+ salt, a series of fluorine multiplet signals is seen at -90.94 ~ -93.75 ppm in the ^{19}F NMR spectrum with the singlet signal dominating. This finding is consistent with the successive replacement of the respective pyrrolic NH protons in receptor **2** by deuterium from the DMSO-d_6 solvent (Fig. S11-S13†). The singlet signal is attributable to the fluoride anion bound to **2**•F^--d_4 (Fig. S12 and S13†).

Chemical shift changes in the ^{1}H NMR spectra comparable to what was seen in DMSO-d_6 were also observed when receptors **1** and **2** in CD_3CN were treated with the fluoride anion. For instance, when receptor **1** was subjected to a ^{1}H NMR spectroscopic titration with the fluoride anion as its TBA^+ salt, saturation was reached upon addition of 1.19 equiv with initial deprotonation of the strap pyrrole being observed at 2.73 equiv (Fig. S14†). The integration intensities of both the calix[4]pyrrole and strap pyrrole NH proton signals steadily decreased upon addition of >2.73 equiv and were all but absent in the presence of 13.33 equiv of TBAF (Fig. S14†). These findings are attributed to deuterium exchange between the pyrrolic NH protons and the CD_3CN solvent. This inference was further supported by ^{19}F NMR spectroscopic studies (Fig. S15-S17†). In analogy to what was seen in DMSO-d_6, in the presence of <2 equiv of the fluoride anion, a quintet of doublets and a quintet fluorine signal are seen at -95.93 ppm and -96.59 ppm (J = 18.57 Hz), respectively, in the ^{19}F NMR spectrum (Fig. S15†). By contrast, upon exposure of receptor **1** to 2.0 ~ 12.0 fluoride anion equivalents, a series of multiplet signals were seen in the -95.7 ~ -98.5 ppm and -83.1 ~ -85.2 ppm spectral range, respectively (Fig. S15†). These signals are ascribed to H-F coupling of the receptor-bound fluoride anion with the various deuterated forms of **1**•F and [**1** - $H^+]^-\bullet F$, respectively. In the presence of excess TBAF, only two broad singlet fluorine signals at -85.8 ppm and -98.3 ppm are seen in the ^{19}F NMR spectrum of **1** (Fig. S15†). This finding is consistent with 1) all five pyrrolic NH proton of receptor **1** and its deprotonated form ([**1** - $H^+]^-$) being replaced with deuterium from CD_3CN and 2) the fact that the strap NH proton is not completely deprotonated in the presence of excess fluoride anion. Subsequent addition of H_2O to a mixture of **1**•F^--d_5 and [**1** - $H^+]^-\bullet F^-$-d_4 in CD_3CN led to re-protonation of the strap pyrrole and re-exchange of the pyrrolic ND deuteriums with protons (Fig. S16 and S17†).

In the case of receptor **2**, the addition of >1.46 equiv of fluoride anion as its TBA^+ salt in CD_3CN caused the singlet corresponding to the NH proton originally at 7.38 ppm to shift to lower field ($\Delta\delta$ = 5.27 ppm) and split into a doublet (J = 27.48 Hz). A weakening in the signal intensity was seen upon the addition of increasing quantities of fluoride anion before this doublet was no longer observed in the presence of an excess of the fluoride anion (Fig. S18†). These findings are consistent with the fluoride anion both being strongly bound to receptor **2** and replacement of the pyrrolic NH protons by deuterium occurring in the presence of excess anion.

The above inference was further supported by ^{19}F NMR spectroscopic analyses. For instance, the broad fluorine signal seen in the presence of 1.00 equiv of fluoride (TBA^+ salt) was separated into a string of distinct multiplets ranging from a quintet (δ = -89.40 ppm) to a singlet (δ = -92.10 ppm) upon the addition of additional fluoride anion equivalents (Fig. S19†). After the CD_3CN solution of receptor **2** was allowed to stand overnight in the presence of excess fluoride, only a singlet was seen at δ = -92.10 ppm in the ^{19}F NMR spectrum. This finding was rationalized in terms of all the four NH protons of receptor **2** being replaced with deuteriums from the CD_3CN solvent. This interpretation was further supported by the complete

disappearance of the doublet NH proton signal in the ^{1}H NMR spectrum (Fig. 5 and S19†). Additional evidence came from the observance of two peaks at m/z = 690 and 691 in the FAB mass spectrum of receptor **2** recorded in CD_3CN in the presence of 20.0 equiv of TBAF (Fig. S20†). These peaks are assigned to M + 4 ([**2**+H$^+$]-d_3) and M + 5 ([**2**+H$^+$]-d_4) species, respectively. Upon the addition of H_2O (10%) to the fluoride complex of the tetra-deuterated **2** (**2**•F$^-$-d_4), no fluorine signals were seen in the ^{19}F NMR spectrum; this is consistent with the decomplexation that would be expected to occur in this polar medium (Fig. 5).

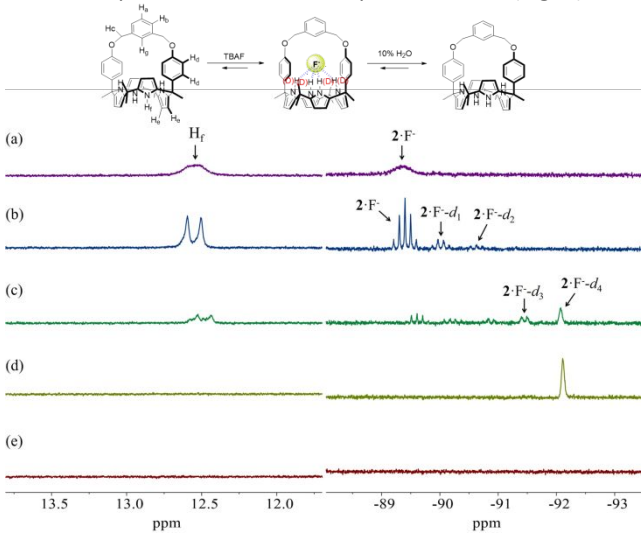

Fig. 5 Partial ^{1}H (left) and ^{19}F (right) NMR spectra of **2** (5 mM) recorded (a) with 1.0 equiv of TBAF in CD_3CN, (b) with 2.0 equiv of TBAF in CD_3CN, (c) with excess TBAF in CD_3CN, (d) after allowing the (c) solution to stand overnight, and (e) after adding 10% water to (d). Fluorobenzene (C_6H_5F, 16.2 mM) was used as an internal reference.

When receptors **1** and **2** were exposed to the fluoride anion in $CDCl_3$, respectively, similar spectral changes were seen in the ^{1}H NMR and ^{19}F NMR spectra as observed in CD_3CN and DMSO-d_6. However, in the case of receptor **1**, no signals corresponding to HF_2^- could be identified in the ^{1}H NMR and ^{19}F NMR spectra. These findings lead us to suggest that the strap pyrrole NH proton does not undergo deprotonation in this relatively less-polar medium (Fig. S21-S23†). This suggestion was further supported by the observation that, after saturation was achieved (i.e., upon adding ca. 1.0 equiv of the fluoride anion), no further spectral changes are seen upon the addition of up to 5.38 equiv; this stands in sharp contrast to what was seen in DMSO-d_6 and CD_3CN (Fig. S21†; cf. Fig. S3 and S14†). In the case of receptor **2**, the calix[4]pyrrole NH proton signal, which was shifted to lower field and split into a doublet upon initial treatment with fluoride, displayed a weakened intensity upon adding increasing quantities of fluoride before vanishing completely (Fig. S24†). These spectral changes are rationalized in terms of deuteration of the pyrrolic NH protons of receptors **1** and **2** by $CDCl_3$. Such an interpretation was further supported by ^{19}F NMR spectroscopic titration experiments. For instance, when receptor **2** was titrated with fluoride in $CDCl_3$, a fluorine signal appears as a broad quintet at δ = -89.4 ppm in the ^{19}F NMR spectrum in the presence of 0.5 equiv of fluoride. This quintet signal is ascribed to coupling between the bound fluoride anion and the four NH protons of receptor **2** (Fig. S25†). By contrast, the addition of > 1.0 equiv of fluoride to receptor **2** gives rise to a series of multiplet fluorine signals between δ = -89.4 ppm and -93.3 ppm (Fig. S25†). These signals run the gamut from a quintet to a singlet and are, as above, attributable to H-F couplings between the bound fluoride anion and the mono-, di-, tri-, and tetra-deuterated forms of receptor **2**. Upon addition of increasing quantities of fluoride to receptor **2** in $CDCl_3$, the relative intensity of the quintet signal decreases while that of the singlet signal increases (Fig. S25†). This finding is consistent with deuterium exchange of the pyrrolic NH protons with $CDCl_3$, a process that is facilitated by fluoride anion binding (Fig. S25†). After receptor **2** was allowed to stand overnight in the presence of an excess of the fluoride anion in $CDCl_3$, a singlet fluorine resonance, along with a relatively weak doublet signal, was seen in the ^{19}F NMR spectrum (Fig. 6 and S25†). This leads us to suggest that at least three, and likely all four, pyrrolic NH protons of receptor **2** were replaced by a deuterium from the $CDCl_3$ solvent. Upon addition of CH_3OH (10%) to the deuterated forms of the **2**•F$^-$ complex in $CDCl_3$, no fluorine signals corresponding to a fluoride anion complex were visible in the ^{19}F NMR spectrum. As above, this is rationalized in terms of release of the bound fluoride anion into the polar medium (Fig. 6). Consistent with this suggestion, the β-pyrrolic CH proton signal is downfield-shifted in the ^{1}H NMR spectrum relative to what was seen for the **2**•F$^-$ complex (Fig. S26†).

In the case of receptor **1**, after 30% CH_3OH was added to its fluoride complex in $CDCl_3$, the pyrrolic NH proton signals remained downfield-shifted and presented as a broad singlet in ^{1}H NMR spectrum. Meanwhile, the fluorine signals completely disappeared in the ^{19}F NMR spectrum. These findings are interpreted in terms of the fluoride anion remaining encapsulated within receptor **1** but via weakened pyrrolic NH—F$^-$ hydrogen bonds in this polar medium (Fig. S23†).

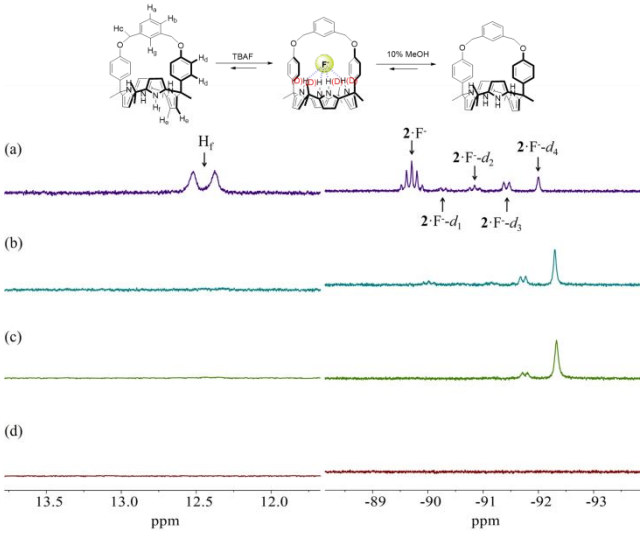

Fig. 6 Partial ^{1}H (left) and ^{19}F (right) NMR spectra of **2** (10 mM) recorded (a) in the presence of 2.0 equiv of TBAF in $CDCl_3$, (b) with excess equiv of TBAF in $CDCl_3$, (c) after allowing the (b) solution to stand overnight, and (d) after adding 10% methanol to (c). Fluorobenzene was used as an internal reference.

In analogy to what was seen with the fluoride anion, the bicarbonate anion was found to accelerate the replacement of the receptor NH protons with deuterium from $CDCl_3$. For instance, when receptor **1** was treated with increasing quantities of the bicarbonate anion, new peaks corresponding to the strap pyrrole NH, the calix[4]pyrrole NH and the β-CH protons of the pyrroles were seen at δ = 12.47 ppm (Δδ = 2.91 ppm), δ = 11.54 ppm (Δδ = 4.45 ppm), and δ = 5.62 ppm (Δδ = 0.37 ppm), respectively (Fig. 7). Concurrently, the integrated intensities of the proton resonances for receptor **1** in its ion-free form steadily decreased before these signals completely disappeared upon the addition of 1.15 equiv of bicarbonate. The corresponding association constant was calculated to be K_a = 9.2 × 10^3 M^{-1}.[49] Both pyrrolic NH proton signals of **1**•HCO_3^- became less prominent upon the addition of >1.49 equiv of bicarbonate. This finding leads us to conclude that one or more of the NH protons is being replaced with a $CDCl_3$-derived deuterium. Further evidence for the deuteration of the receptor NH protons came from a FAB mass spectrometric analysis of a $CDCl_3$ solution of receptor **1** recorded in the presence of 3.50 equiv of bicarbonate. Only two peaks at m/z = 790 and 792 corresponding to M + 3 ([**1**+H^+]-d_2) and M + 5 ([**1**+H^+]-d_4), respectively, were readily observable in the mass spectrum (Fig. 8b). In contrast, the mass spectrum recorded in the absence of bicarbonate showed no peaks attributed to any deuterated forms of receptor **1** (Fig. 8a).

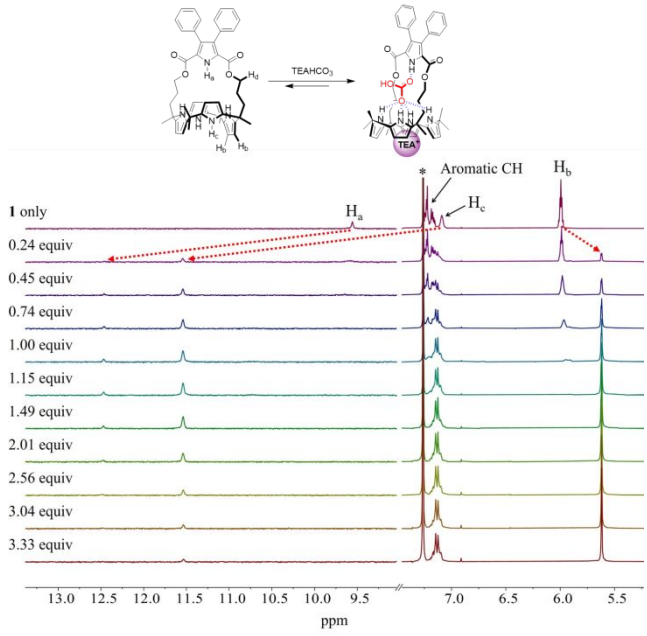

Fig. 7 ^{1}H NMR spectra recorded during the titration of **1** (3 mM) tetraethylammonium bicarbonate ($TEAHCO_3$) in $CDCl_3$. *denotes the residual $CHCl_3$ peak in the NMR solvent.

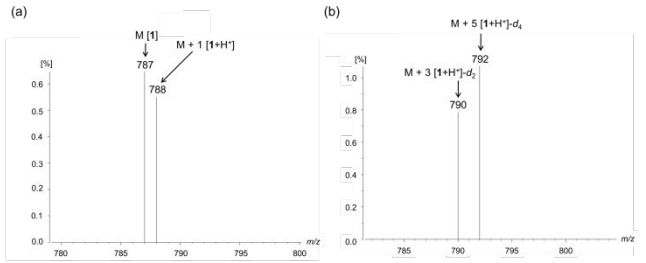

Fig. 8 FAB mass spectra of receptor **1** recorded in the absence (a) and presence (b) of $TEAHCO_3$ (3.5 equiv) in $CDCl_3$.

Receptor **2** was also found to undergo deuteration of its pyrrole NH protons from $CDCl_3$ accelerated by bicarbonate binding as inferred from the observance of the pyrrolic NH proton signal disappearing during the ^{1}H NMR spectral titration (Figure S27). The presence of peaks corresponding to molecular weights of [**2**+H^+]-d_1, [**2**+H^+]-d_2, [**2**+H^+]-d_3, and [**2**+H^+]-d_4 in the FAB mass spectrum provided further support for the notion that the bicarbonate anion promotes deuteration of the pyrrolic NH protons (Figure S28). In contrast to what was seen with $CDCl_3$, no evidence for deuteration of the pyrrole NH protons of receptors **1** and **2** was seen upon treatment with the bicarbonate anion in DMSO-d_6 or CD_3CN (Figures S4, S8, S29 and S30). These findings are attributable to the high acidity of $CDCl_3$ and its great ability to interact with anions relative to DMSO-d_6 and CD_3CN.[50]

The deuterium exchange of the receptor NH hydrogens seen upon exposure to the fluoride and bicarbonate anions in DMSO-d_6, $CDCl_3$, and CD_3CN is attributed to weakened N-H covalent bonds resulting from the formation of strong hydrogen bonds to the basic anions. This hydrogen bonding interaction is thought to make the pyrrolic NHs more acidic. In addition, the interactions of the anions with the deuterated solvents in question via hydrogen bonds are also presumed to contribute to the accelerated deuterium exchanges to some extent by enhancing the solvent acidity.

Conclusions

In conclusion, the F^- and HCO_3^- anion binding properties of the pyrrole- and benzene-strapped calix[4]pyrroles **1** and **2** have been investigated. Receptors **1** and **2** were found to bind F^- and HCO_3^- strongly *via* slow binding/release equilibria in DMSO-d_6, $CDCl_3$, and CD_3CN. A combination of ^{1}H and ^{19}F NMR spectroscopic analyses, along with FAB mass spectrometric data, provided support for the conclusion that fluoride and bicarbonate anion binding to receptors **1** and **2** facilitates exchange of the receptor pyrrolic NH protons with deuteriums arising from the deuterated solvents considered in this study.

Data availability

All data, including synthetic details, ^{1}H and ^{19}FNMR spectroscopic analyses, and single crystal X-ray diffraction analyses of **2** (CCDC2376015) and **1**•$TEA^+CH_3CH_2OCO_2^-$ (CCDC2248755), are available in the ESI.†

Author contributions

SKK and JLS conceived and supervised the project. NJH synthesized the compounds. NJH and JHO performed ion binding studies using ^{1}H and ^{19}F NMR spectroscopy. NJH carried out the X-ray diffraction analysis. SKK and JLS wrote the manuscript. All authors contributed to the editing of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Data availability

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