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Phenanthroline-Strapped Calix[4]pyrroles: Anion Receptors Displaying Affinity Reversal as a Function of Solvent Polarity

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Complete List of Authors:	Heo, Nam Jung; Gyeongsang National University, Chemistry Oh, Ju Hyun ; Gyeongsang National University, Department of Chemistry and Research Institute of Natural Sciences Lee, Jeong Tae; Hallym University, Department of Chemistry and Institute for Applied Chemistry He, Qing; University of Texas at Austin, Chemistry Sessler, Jonathan; Univ Texas Austin, Chemistry; Shanghai University, Kim, Sung Kuk; Gyeongsang National University, Department of Chemistry and Research Institute of Natural Sciences

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Method

Phenanthroline-Strapped Calix[4]pyrroles: Anion Receptors Displaying Affinity Reversal as a Function of Solvent Polarity

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Nam Jung Heo,‡[a] Ju Hyun Oh,‡[a] Jeong Tae Lee,[b] Qing He,*[c] Jonathan L. Sessler,*[d] and Sung Kuk Kim*[a]

Calix[4]pyrroles **1** and **2**, diametrically strapped with a phenanthroline via ester and amide linkages, respectively, have been synthesized as anion receptors. It was revealed by ^{1}H NMR spectroscopic analysis that receptors **1** and **2** possessing both hydrogen bonding donors and acceptors were able to bind the bicarbonate anion (as its tetraethylammonium (TEA^+) or sodium salt) in $CDCl_3$, as well as in 15% aqueous DMSO with high affinity and selectivity over other anions. The amide-based receptor **2** contains additional potential hydrogen bonding donors relative to its ester-based congener **1**. Nevertheless, in $CDCl_3$ receptor **1** was found to display a higher affinity for all test anions than receptor **2**. In contrast, in 15% aqueous DMSO solution the affinities of receptor **2** for anions, in particular chloride, bicarbonate, and dihydrogen phosphate, were enhanced, whereas those of receptor **1** were reduced dramatically with no appreciable interaction being seen in the case of most test anions considered in this study. These reversals in selectivity and affinities underscore the importance of solvent in regulating the recognition features of seemingly simply anion binding agents.

Introduction

Anions are ubiquitous in nature and play various roles in a wide range of biological and environmental, and chemical processes.[1-3] Not surprisingly, considerable ongoing effort is being devoted to the design and synthesis of anion receptors, particularly those with improved binding affinities and higher selectivities for specific anionic targets.[4-11] Key factors in determining the selectivity and affinity of anion receptors include good receptor-anion size matching and geometric complementarity between the specific recognition subunits that make up the receptor as a whole, as well as an appropriate level of preorganization.[1-12] Among the many anion receptors reported in recent years, calix[4]pyrroles have attracted attention as well-defined scaffolds that can be elaborated to provide systems with fine-tuned affinities and selectivities.[13-18] Typically, elaboration of the basic calix[4]pyrrole skeleton has involved functionalization at either the meso- or β-pyrrolic carbon atoms, or both.[15-17] Within the context of this general paradigm, the so-called strapped calix[4]pyrroles are noteworthy. Their anion selectivities and affinities can be modulated by controlling the size and rigidity of the linkers that make up the strap and which serve to connect two opposing meso carbons. The strapping strategy also allows introduction of introducing auxiliary recognition motifs into the linkers, including hydrogen bonding donors and acceptors.[15,16] Strapped calix[4]pyrroles also contain a 3-dimensional cryptand-like cavity that can help enhance anion affinities as the result of anion or ion pair encapsulation.[15-16]

In addition to the basic receptor design, the solvents chosen for anion binding studies can be critical. They can exert a great influence on the anion affinity and selectivity patterns seen for receptors.[19,20] As recently noted by Flood et al., it is taken as established fact that the anion binding affinities of receptors are highly dependent on the dielectric constants (ε_r) of solvents.[19] Namely, the association constants of a given receptor for a set of targeted anions decrease in inverse proportion to the ε_r values of the solvents. In the presence of water, the anion affinities decrease dramatically, a finding attributable to the strong competitive solvation of the anionic substrates by water.[19] In the case of calix[4]pyrrole-based receptors the anion affinities decrease noticeably in DMSO as compared to what is seen in less polar solvents, such as dichloromethane or acetonitrile.[20] A current challenge in the field is thus to design receptors capable of recognizing physiologically important anions in highly polar protic solvents, including water.[21] With these concepts in mind, we designed and synthesized two bicarbonate anion receptors, namely calix[4]pyrroles **1** and **2**. These systems contain phenanthroline moieties strapped across the meso positions of the core calix[4]pyrrole via ester and amide linkages, respectively.

Bicarbonate, a mildly alkaline anion, is a pivotal component of both the intracellular and extracellular pH buffering systems in the human body. It also plays vital roles in signal transduction and in the triggering of certain intracellular events.[22-26] The most common physiological bicarbonate salt is $NaHCO_3$, a species that occurs naturally, is noted for its role as a buffer

[a]*Department of Chemistry and Research Institute of Natural Science, Gyeongsang National University, Jinju 52828, Korea. E-mail: sungkukkim@gnu.ac.kr*
[b]*Department of Chemistry and Institute of Applied Chemistry, Hallym University, Chuncheon 24252, Korea*
[c]*State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P. R. China. E-mail: heqing85@hnu.edu.cn*
[d]*Department of Chemistry, The University of Texas at Austin, 105 E. 24th Street-Stop A5300, Austin, Texas 78712-1224, USA. E-mail: sessler@cm.utexas.edu*
‡*These two authors equally contributed to this work*
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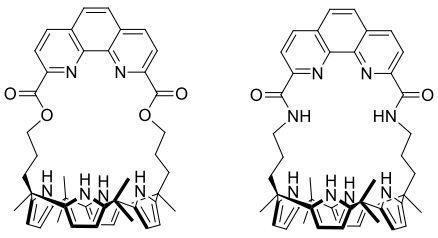
against pH changes in variety of physiologically critical systems.[22-26] Deviations from normal physiological pH levels can lead to severe tissue damage and to central nerve system failure.[27,28] In addition to its role as a physiological buffer, the bicarbonate anion is an important element in the natural carbon cycle.[29-31] For example, gaseous CO_2 generally dissolves in the oceans to reach equilibrium with CO_2 present in the atmosphere. When dissolved at or near neutral pH, CO_2 reacts with water to produce H_2CO_3 which is subsequently dissociates to give HCO_3^- and CO_3^{2-}.[29-31] The regulation of dissolved HCO_3^- is a key aspect of maintaining aquatic environments at a pH capable of supporting a wide range of living organisms. Despite its physiological and environmental importance, only a few receptors have been reported that are able to recognize the bicarbonate anion with high selectivity and affinity.[32-34] Here, we report the phenanthroline strapped calix[4]pyrrole receptors **1** and **2** and show that they can not only act as effective bicarbonate capture agents, but that their relative affinities can be fine-tuned through changes in the solvent polarity.

The bicarbonate anion is planar and possesses pseudo-trigonal symmetry. It also bears a single proton that may act potentially as a hydrogen bond donor. The Lewis basic phenanthroline subunits present in receptors **1** and **2** were designed to provide an additional binding motif for the bicarbonate anion. Likewise, it was thought that the amide linkers present in receptor **2** (but not receptor **1**) could act as ancillary hydrogen bonding donors and aid in anion recognition. In fact, as detailed below, in chloroform, receptor **1** was found to have a higher binding affinity for most test anions than receptor **2**. In contrast, in 15% aqueous DMSO solution, a more polar medium, the anion affinity of receptor **2** was enhanced while that of receptor **1** decreased to the point that no discernible interaction between the receptor and anions was observed. To our knowledge such a dramatic solvent-based reversal in selectivities has little precedent in the anion recognition literature.

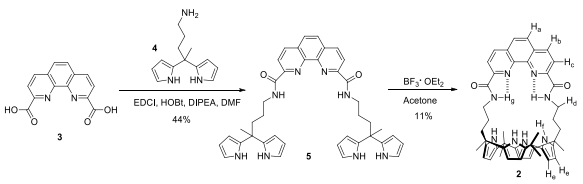


1 **2**

Results and Discussion

Synthesis and Characterization

Receptor **1** was synthesized according to our previous literature procedure.[35] The synthesis of receptor **2** is shown in Scheme **1**. In brief, the dicarboxylic acid-functionalized phenanthroline **3** was coupled with 4,4-di(1H-pyrrol-2-yl)pentan-1-amine (**4**) in the presence of EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide), HOBt (hydroxybenzotriazole), and DIPEA (N,N-diisopropyethylamine) in DMF. This produced the corresponding diamide **5** in 44% yield. Subsequent condensation reaction of the pyrrole groups with acetone in the presence of $BF_3{\cdot}OEt_2$ (≈1.0 equiv.) as a Lewis acid afforded the desired compound **2** in 11% yield. Receptor **2** was characterized by standard spectroscopic techniques, including ^{1}H NMR and ^{13}C NMR spectroscopy, as well as high-resolution mass spectrometry.



Scheme 1. Synthesis of receptor **2**

Studies of the interactions between receptors 1 and 2 and the bicarbonate anion

Evidence that receptors **1** and **2** were able to bind the bicarbonate anion in solution came from ^{1}H NMR spectroscopic analyses performed in $CDCl_3$ and, separately, in 15% aqueous DMSO solution. For example, when receptor **1** was subject to ^{1}H NMR spectroscopic titrations in $CDCl_3$ using the bicarbonate anion (as its tetraethylammonium (TEA^+) salt) as the putative guest, two sets of proton signals were seen for all observable proton signals corresponding to the phenanthroline CH ($H_{a\text{-}c}$), β-pyrrolic CH (H_e), and the methylene CH (H_d) protons before saturation became evident upon the addition of ≈ 3 equiv. of $TEAHCO_3$ (Figure S1). In contrast, the pyrrolic NH protons (H_d) experienced two different chemical shift changes, that is, a large downfield shift irrespective of the existing quantities of bicarbonate and small gradual downfield shifts that was found to depend monotonically on the quantity of added bicarbonate anion (Figure S1). This finding leads us to suggest that receptor **1** recognizes the bicarbonate anion *via* two different concurrent binding processes that involve equilibria that are slow and fast, respectively, on the NMR timescale. The slow binding/release equilibrium between receptor **1** and the bicarbonate anion presumably results from a strong binding interaction. This suggestion was further supported by the observation of a large downfield shift in the pyrrolic NH proton signal (Δδ = 4.55 ppm) and small upfield shift in the β-pyrrolic CH proton signal (Δδ = 0.24 ppm) (Figure S1). After saturation, further addition of the bicarbonate anion to receptor **1** caused the intensity of the pyrrolic NH proton signals to decrease gradually and eventually to broaden into the baseline. This finding is attributed to the increase in the basicity of the $CDCl_3$ solution containing receptor **1** as the bicarbonate anion concentration increases. Specifically, proton exchange between the basic bicarbonate anion and the relatively acidic pyrrolic NHs is facilitated. This leads to line broadening. Similar ^{1}H NMR spectral changes were observed when receptor **1** was subjected to titration with the basic fluoride anion in $CDCl_3$ (*vide infra*).

Receptor **2** was also titrated with the bicarbonate anion under the same conditions as above using $CDCl_3$ as the solvent. In

this case, saturation was reached more quickly (i.e., upon the addition of *ca*. 1.26 equiv. of $TEAHCO_3$; Figure 1). Under these conditions, both the amide NH proton signal and the pyrrolic NH signals shift to lower field ($\Delta\delta$ = 4.74 ppm and $\Delta\delta$ = 1.54 ppm for the pyrrolic NH and amide NH signals, respectively). This finding leads us to suggest that the amide NH protons of receptor **2** participate in bicarbonate anion binding, which in turn was expected to enhance the affinity relative to receptor **1**. On the basis of ^{1}H NMR spectroscopic titrations, the association constants (K_a) for receptors **1** and **2** and the bicarbonate anion were estimated to be 1,330 M^{-1} and 4,880 M^{-1}, respectively.[36]

Studies analogous to the above were also carried out in a more polar medium consisting of 15% D_2O in DMSO-d_6. Upon subjecting receptor **1** to a ^{1}H NMR spectral titration in this solvent system, saturation was not reached until an excess of $TEAHCO_3$ (> 10 equiv.) was added (Figure S2). This finding leads us to suggest that the affinity of receptor **1** for the bicarbonate anion is drastically decreased in 15% D_2O in DMSO-d_6 relative to $CDCl_3$. Unfortunately, the binding affinity of receptor **1** for the bicarbonate anion could not be quantified in this solvent system because of the poor solubility of receptor **1** and the fact that it appeared to undergo decomposition or precipitation over the course of the requisite ^{1}H NMR spectral titrations.

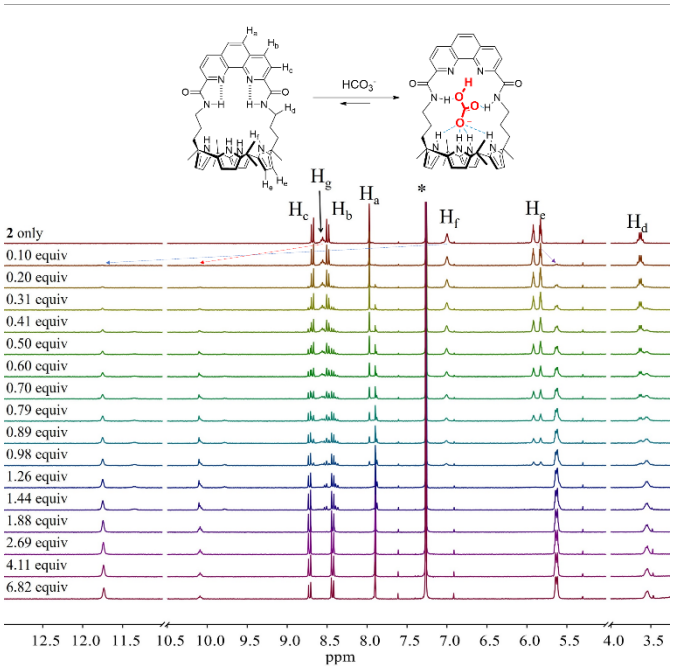


Fig. 1 Proposed binding interactions between receptor **2** and the bicarbonate anion (top) and partial views of the ^{1}H NMR spectra recorded during the titration of **2** (3 mM) with tetraethylammonium bicarbonate ($TEAHCO_3$) in $CDCl_3$ (bottom). *Denotes the solvent peak.

In sharp contrast to what was seen with receptor **1**, the binding affinity of receptor **2** for the bicarbonate anion was enhanced in 15% D_2O in DMSO-d_6 relative to what was seen in $CDCl_3$. Specifically, during the titration of receptor **2** with the bicarbonate anion in 15% D_2O in DMSO-d_6, two sets of separate proton resonances were observed for the pyrrolic NH protons and the β-pyrrolic CH protons before saturation took place upon the addition of ≈ 1 equiv. of $TEAHCO_3$ (Figure S3). By contrast, the amide NH signal disappeared, presumably as a result of deuterium exchange with the D_2O present in the medium. From this ^{1}H NMR spectral titration, the association constant of receptor **2** for the bicarbonate anion was approximated to be > 10,000 M^{-1}.[36] ^{1}H NMR spectral titration experiments also revealed that receptor **2** can bind the presumably more hydrophilic bicarbonate salt, $NaHCO_3$, with high affinity in 15% D_2O in DMSO-d_6 (Figure 2). In this case, a ^{1}H NMR spectral titration revealed that the proton signals of the calix[4]pyrrole moiety, as well as those of the phenanthroline subunit, underwent significant chemical shift changes consistent with the interaction between **2** and the bicarbonate anion. The association constant of receptor **2** for $NaHCO_3$ was calculated from these spectral studies to be K_a = 21,300 M^{-1} (Figures 2 and S5).[37]

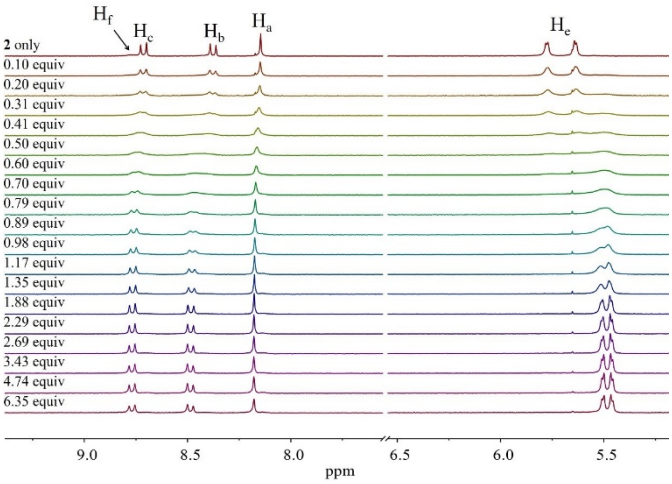


Fig. 2 Partial ^{1}H NMR spectra recorded during the titration of **2** (3 mM) with sodium bicarbonate ($NaHCO_3$) in aqueous DMSO-d_6 solution (15% D_2O in DMSO-d_6).

DFT optimized structures of the bicarbonate complexes of receptors 1 and 2

In order to obtain further insights into the anion binding behaviour of receptors **1** and **2**, we optimized the structures of their bicarbonate complexes and estimated the binding energies using gas phase density functional theory (DFT) calculations carried out at the x3lyp/6–31g*//x3lyp/6–31g* level. The resulting optimized structures revealed that receptors **1** and **2** bind the bicarbonate anion via different binding modes and with different binding energies. For example, the case of the bicarbonate complex of receptor **1** is stabilized by two different kinds of hydrogen bonding interactions involving the pyrrolic NHs and the bicarbonate anion. Specifically, three pyrrolic NH protons interact with one of the bicarbonate oxygen atoms, whereas the remaining pyrrolic NH proton interacts with a different oxygen atom (Figure 3). In addition, the proton of the bicarbonate anion was

found to form a hydrogen bond with the nitrogen atoms of the phenanthroline group in accord with our design expectations. In the case of receptor **2**, the bound bicarbonate anion was further stabilized via additional hydrogen bond interactions involving the amide NH protons of the strap. In contrast to what was seen in the case of **1**, for the bicarbonate anion complex of **2**, all four pyrrolic NH protons interact with one bicarbonate oxygen atom, while the other two bicarbonate oxygen atoms interact with the respective amide NH protons (Figure 3). The binding energy of receptor **2** for the bicarbonate anion was calculated to be -73.40 kcal/mol while that of receptor **1** was about -56.30 kcal/mol. This finding provides support for the notion that receptor **2** should bind the bicarbonate anion more effectively than its ester-containing congener **1**.

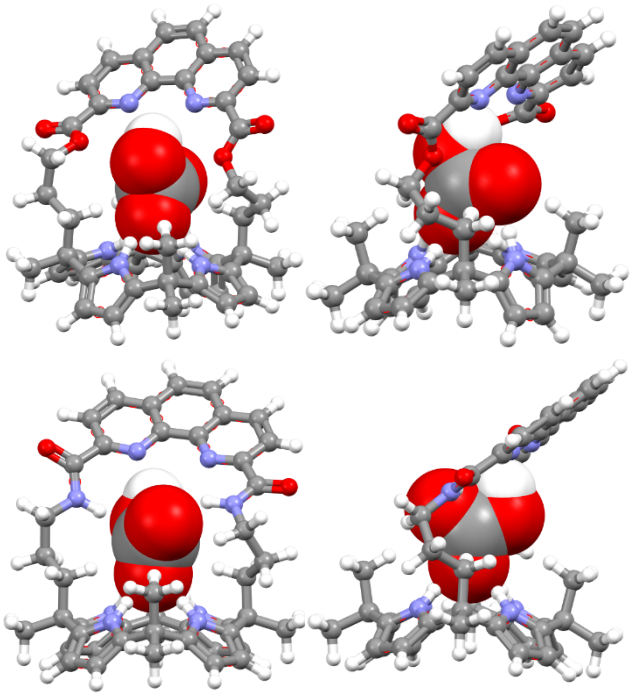


Fig. 3 Two different views of the optimized geometries of the complexes, **1**·HCO_3^- (top) and **2**·HCO_3^- (bottom).

Studies of the interactions between receptors 1 and 2 and representative other anions in chloroform-*d*

In an effort to ascertain whether the relatively enhanced K_a value for $TEAHCO_3$ seen for receptor **2** in 15% D_2O in DMSO-d_6 as compared to $CDCl_3$ was a general phenomenon, receptors **1** and **2** were subject to titrations with a variety of other test anions, including F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, $HP_2O_7^{3-}$, HSO_4^-, and SO_4^{2-} (as their tetrabutylammonium (TBA^+) salts). Depending on the choice of a solvent system, namely $CDCl_3$ or 15% D_2O in DMSO-d_6, receptors **1** and **2** displayed different binding features when treated with F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, $HP_2O_7^{3-}$, HSO_4^-, and SO_4^{2-} (TBA^+ salts). As a general rule, upon the exposure of receptor **1** to an excess of these anions in in $CDCl_3$, the NH proton signal of the calix[4]pyrrole moiety were shifted to lower field, with the extent of chemical shift varying with the anion in question (Figures S6-S13). This finding is consistent with receptor **1** being able to bind to all the test anions considered to a greater or lesser extent,

In the specific case of the fluoride anion, two sets of distinct proton resonances were observed for the β-pyrrolic CH signals when receptor **1** was subjected to titration with TBAF in $CDCl_3$ before saturation was reached upon the addition of ≈ 2 equiv. (Figure 4). By contrast, the pyrrolic NH protons (labelled as H_f in Figure 4) underwent two distinct chemical shift changes, which is analogous to what was seen with the bicarbonate anion (Figure S1). A large downfield shift is seen that proved essentially independent of the quantity of fluoride added once ca. 0.20 equiv. had been added. A separate signal was seen that underwent gradual downfield shifts as a function of increasing fluoride anion concentration through the addition of ca. 1.88 equiv. (Figure 4). This finding leads us to suggest that receptor **1** recognizes the fluoride anion via two different binding modes, one of which is subject to slow exchange on the NMR timescale with the other reflecting a fast equilibrium with the unbound form. Consistent with this suggestion is the finding that the lower field NH signal (shifted downfield by Δδ = 5.31 ppm relative to **1**) is split into a doublet (J = 39.70 Hz), as would be expected for equivalent protons split by the bound $^{19}F^-$ centre (Figure 4).[38]

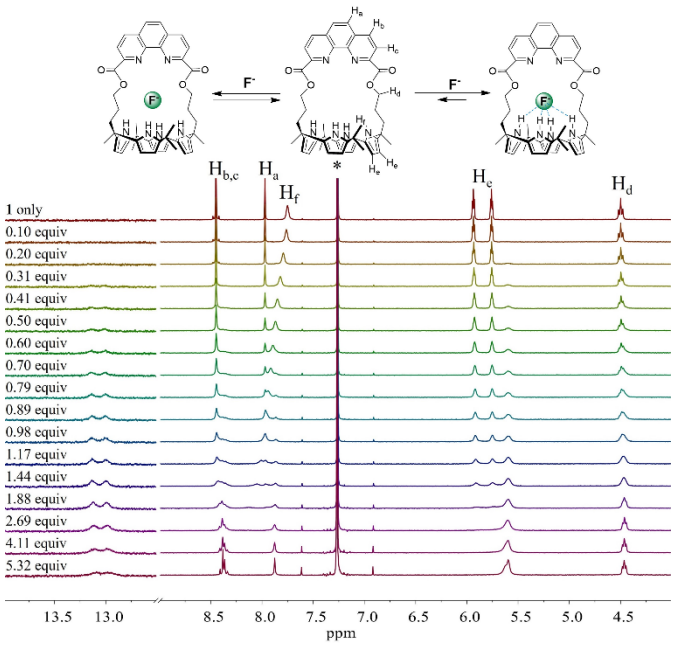


Fig. 4 Putative binding interactions involving receptor **1** and the fluoride anion (top) and partial ^1H NMR spectra recorded during the titration of **1** (3 mM) with tetrabutylammonium fluoride (TBAF) in $CDCl_3$ (bottom).

In contrast to what was seen in the case of **1**, appreciable chemical shift changes in both the pyrrolic and amido NH proton signals of receptor **2**, as well as in the β-pyrrolic CH proton signals, are seen in the corresponding ^1H NMR spectra when this amide-based strapped system is titrated with F^-, Cl^-, Br^-, $H_2PO_4^-$, $HP_2O_7^{3-}$, and SO_4^{2-} in $CDCl_3$ (TBA^+ salts) but not for

I^- or HSO_4^- (Figure S14). Specifically, when receptor **2** was titrated with the fluoride anion, both the pyrrolic NH and amide NH proton resonances shifted progressively to lower field while the pyrrolic CH resonances experienced an upfield shift (Figure 5). This finding is consistent with receptor **2** interacting with the fluoride anion via a fast anion binding/release equilibrium process on the NMR timescale. It is also taken as evidence that both the pyrrolic NH and amide NH protons take part in fluoride anion binding (Figure 5). More specifically, over the course of the titration, the NH proton signals of both the amide and pyrrole subunits became increasingly broadened before 1.17 equiv. of the fluoride anion was add. These resonances then sharpened again as further quantities of fluoride anion were added. These chemical shift changes are as expected when the binding affinity of a receptor for an anion is moderate. Before saturation is reached, the observed peak broadening occurs because binding/release of the fluoride anion by the receptor (calix[4]pyrrole **2** in the present instance) is intermediate on the NMR timescale. On the other hand, in the presence of excess fluoride anion, the rates, which reflect a bimolecular event, increase. The result is a sharpening of the peaks. Under conditions of the titration, singlet signal of the pyrrolic NH proton becomes split into a doublet reflecting coupling with the bound fluoride anion. In contrast, the amide NH signal remains as a triplet, which is consistent with the fluoride anion interacting relatively more strongly with the calix[4]pyrrole NH protons.

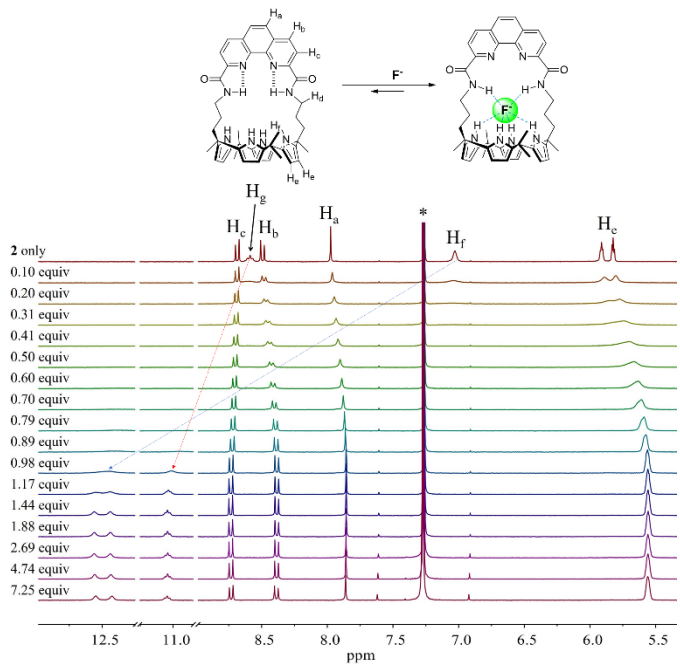


Fig. 5 Proposed interactions between receptor **2** and a bound fluoride anion guest (top) and partial view of the ^{1}H NMR spectra recorded during the titration of **2** (3 mM) with tetrabutylammonium fluoride (TBAF) in $CDCl_3$ (bottom).

For other anions, including Cl^-, Br^-, $H_2PO_4^-$, $HP_2O_7^{3-}$, and SO_4^{2-} (as their TBA^+ salts), the NH proton signals of both the calix[4]pyrrole and the amide of receptor **2** were seen to broaden over the courses of the respective ^{1}H NMR spectral titrations, presumably as the result of relatively weak anion binding interactions (Figures S15-S21).

The association constants (K_a) in $CDCl_3$ for receptors **1** and **2** and the anions considered in this study were estimated from the various ^{1}H NMR spectral titrations, with the resulting values listed in Table 1. As can be seen from an inspection of this table, as a general rule receptor **1** showed higher affinities for all the test anions other than chloride and bicarbonate than receptor **2**. This was unexpected in light of the fact that the amide strap in **2** provides two additional potential hydrogen bond donor groups. These results are rationalized in terms of the amide NH protons in receptor **2** forming strong intramolecular hydrogen bonds with the phenanthroline nitrogen atoms in $CDCl_3$.[39] To the extent this occurs, it would constitute an internal interaction that would compete with hydrogen bond-based anion recognition. Evidence for formation of these presumed intramolecular hydrogen bonds came from the observation that the amide NH proton resonance of **2** appears at lower field (δ = 8.5 ppm) than a normal amide NH proton signal or for the corresponding resonances in the case of amide strapped calix[4]pyrroles bearing benzene, as opposed to phenanthroline, subunits.[40,41] Further support for these proposed intramolecular hydrogen bond interactions came from ^{1}H NMR spectral studies carried out at different concentrations of receptor **2** in $CDCl_3$. No concentration dependent change in the chemical shift of the amide NH proton signal was seen (Figure S22).

Table 1. Association constants (K_a, M^{-1})[a] corresponding to the interactions between receptors **1** and **2** and various test anions as estimated by ^{1}H NMR spectroscopic titrations in $CDCl_3$ and 15% aqueous DMSO solution at room temperature.

Anions	**1** (K_a, M^{-1})		**2** (K_a, M^{-1})	
	$CDCl_3$	15% D_2O in DMSO-d_6	$CDCl_3$	15% D_2O in DMSO-d_6
F^-	580[b]	444 ± 31	-[c]	> 10,000
Cl^-	121 ± 11	No Binding	181 ± 16	1,868 ± 129
Br^-	338 ± 25	No Binding	56 ± 4	168 ± 6
I^-	312 ± 23	No Binding	No Binding	No Binding
$H_2PO_4^-$	174 ± 17	No Binding	105 ± 5	> 10,000
$HP_2O_7^{3-}$	447 ± 24	-[d]	120 ± 9	203 ± 24
HCO_3^-	1,330[b]	-[d]	4,880	> 10,000
HSO_4^-	364 ± 47	No Binding	53 ± 11	No Binding
SO_4^{2-}	565 ± 86	No Binding	8	No Binding

[a]Anions were used in the form of the tetraethylammonium (TEA^+) salt for bicarbonate and tetrabutylammonium (TBA^+) salts for all other anions. [b]Association constants for slow anion binding/release equilibrium. [c]No reliable

fit to a 1:1 binding profile could be made. [d]K_a values could not be determined because hydrolysis or precipitation occurred during the titration.

Interactions between receptors 1 and 2 in 15% aqueous DMSO

In order to test the assumption that intramolecular amide NH-phenanthroline interactions exert an influence on anion binding in the case of receptor **2**, receptors **1** and **2** were studied in more polar solvent systems than $CDCl_3$. In DMSO-d_6, the proton signal of the pyrrolic NHs of receptor **2** were relatively downfield-shifted while that of the amide NHs remained relatively unchanged compared to what was seen in $CDCl_3$ (Figure S24(a,b)). We interpret this finding in terms of the intramolecular hydrogen bond between the amide NHs and the phenanthroline of receptor **2** being retained in DMSO-d_6 and the pyrrolic NHs interacting with the DMSO-d_6 medium resulting in a downfield shift in the latter NH proton signal. On the contrary, upon the addition of 15% D_2O to a DMSO-d_6 solution of receptor **2**, the amide NH peak underwent a noticeable downfield shift ($\Delta\delta$ = 0.82 ppm), a finding ascribed to hydrogen bonding interactions between the amide NHs protons and the bulk medium (Figure S24(c)). These presumed solvent - amide proton interactions are expected to break or at least weaken the amide NH-phenanthroline intramolecular hydrogen bonds making the strapped calix[4]pyrrole **2** more effective as an anion receptor.

In fact, in 15% D_2O in DMSO-d_6 solution, receptors **1** and **2** displayed binding behaviour towards the test anions that differed dramatically compared to what was observed in $CDCl_3$. For instance, when receptor **1** was exposed to an excess of the anion sets in 15% D_2O in DMSO-d_6, no appreciable changes in the initial ^{1}H NMR spectra were observed in the case of Cl^-, Br^-, $H_2PO_4^-$, SO_4^{2-}, and HSO_4^- (Figure S25). This finding is interpreted in terms of anion binding that is too weak to be observed by ^{1}H NMR spectral methods. As seen for most anion receptors, this weakened binding affinity is thought to result from the effects of competing solvation. In contrast, the addition of TBAF to receptor **1** in 15% D_2O in DMSO-d_6 solution induced ^{1}H NMR spectral changes consistent with fluoride anion binding in analogy to what was seen in $CDCl_3$. The corresponding association constant was estimated to be 444 M^{-1}, which is lower than that measured in $CDCl_3$ (Figure S26). The addition of pyrophosphate anion also ^{1}H NMR spectral shifts consistent with decomposition or precipitation of receptor **1** (Figure S28).

In contrast to what was seen for **1**, when receptor **2** was treated with F^-, Cl^-, Br^-, $H_2PO_4^-$ and $HP_2O_7^{3-}$ (TBA^+ salts) in 15% D_2O in DMSO-d_6 solution remarkable chemical shift changes in the pyrrolic NH, CH, and NH protons of receptor **2** were observed in the corresponding ^{1}H NMR spectra (Figure S29). These findings are taken as evidence that receptor **2** interacts with these test anions. Specifically, when receptor **2** was titrated with the fluoride anion in 15% aqueous DMSO solution, two sets of discernible proton resonances were observed for all the proton signals before saturation occurred upon the addition of ≈ 1.0 equiv. of TBAF (Figure 6). In this case, the singlet proton signal corresponding to the pyrrolic NHs shifts to lower field and becomes split into a doublet, which as above is interpreted in terms of formation of NH-F hydrogen bonds. In addition, the amide NH proton signals also shift to lower field; again, this is ascribed to NH-F hydrogen bonding (Figure 6). From this set of ^{1}H NMR spectral titrations, the association constant (K_a) corresponding to the interaction between receptor **2** and the fluoride anion was approximated to be > 10,000 M^{-1}.[36] This value is at least 2x larger than what was seen in $CDCl_3$ (cf. Table 1). A notable (*ca*. 10x) increase in the K_a value of receptor **2** was also seen for chloride (as its TBA salt) in 15% aqueous DMSO solution. Increases were also noted in the case of the bromide and the pyrophosphate anions as shown in Table 1 (*cf*. ESI for supporting spectral studies).

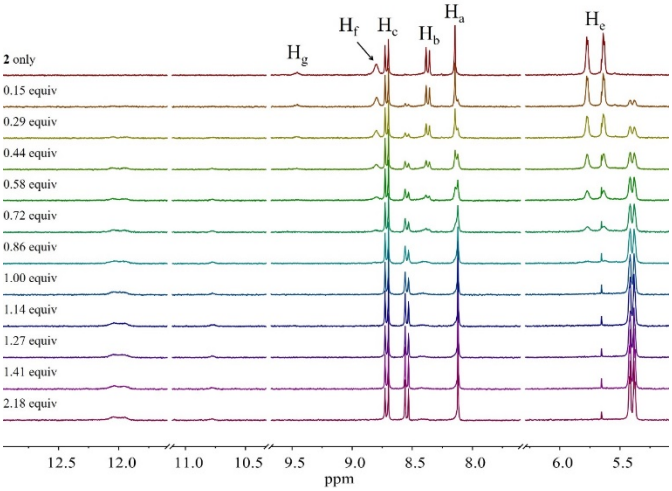


Fig. 6 Partial ^{1}H NMR spectra recorded during the titration of **2** (3 mM) with tetrabutylammonium fluoride (TBAF) in 15% aqueous DMSO-d_6 solution.

The most dramatic change in the anion binding property of receptor **2** in 15% D_2O in DMSO-d_6 solution relative to $CDCl_3$ was observed from the dihydrogen phosphate anion (Figure 7). For example, in contrast to what was seen in $CDCl_3$, when receptor **2** was subject to an ^{1}H NMR spectral titration with $TBAH_2PO_4$ in this solvent system, two sets of proton peaks were observed for the pyrrolic NH and CH signals in ^{1}H NMR spectra recorded before saturation rapidly took place upon the addition of ≈ 1 equiv. of dihydrogen phosphate (Figure 7). This ^{1}H NMR spectral change is consistent with receptor **2** forming a strong complex with the dihydrogen phosphate anion that is characterized by a slow equilibrium on the NMR timescale. The affinity of receptor **2** for the dihydrogen phosphate anion was found to be enhanced by more than 100-fold in 15% D_2O in DMSO-d_6 relative to $CDCl_3$ (105 M^{-1} vs > 10,000 M^{-1}; Table 1). In contrast, no evidence for the binding of the sulphate and hydrogen sulphate anions by receptor **2** was seen in 15% D_2O in DMSO-d_6; presumably, this reflects the relatively high hydration energies and lower relative basicities of these anions.[42] In the event, this finding leads us to suggest that receptor **2** is able to discriminate in favour of certain oxoanions, at least under appropriately chosen solvent conditions.

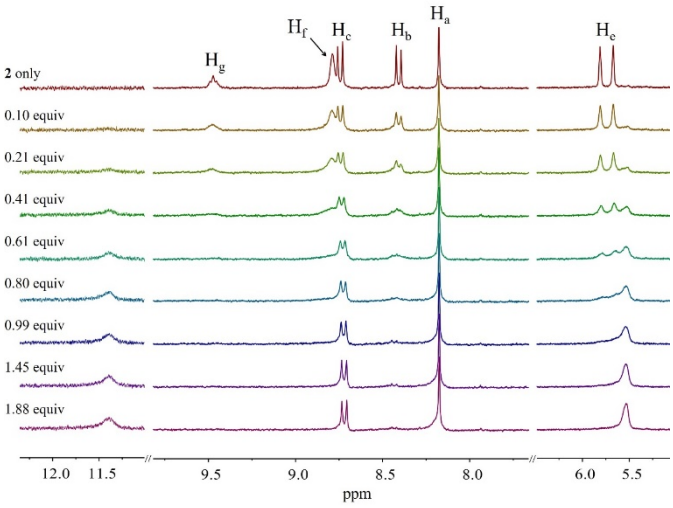


Fig. 7 Partial ^{1}H NMR spectra recorded during the titration of **2** (3 mM) with tetrabutylammonium dihydrogen phosphate ($TBAH_2PO_4$) in 15% aqueous DMSO-d_6 solution.

Single crystal X-ray diffraction analysis of the Cl^- complex of receptor 2

Further evidence that receptor **2** can act as an anion receptor came from a single crystal X-ray diffraction analysis of the chloride anion complex. The resulting crystal structure revealed that both the pyrrolic NH and amido NH protons of receptor **2** support hydrogen bonding interactions with the chloride anion. In the solid state, the NH···Cl- distances were found to be 2.46 – 2.55 Å and 2.68 – 2.86 Å for the calix[4]pyrrole and the amide groups, respectively (Figure 8).

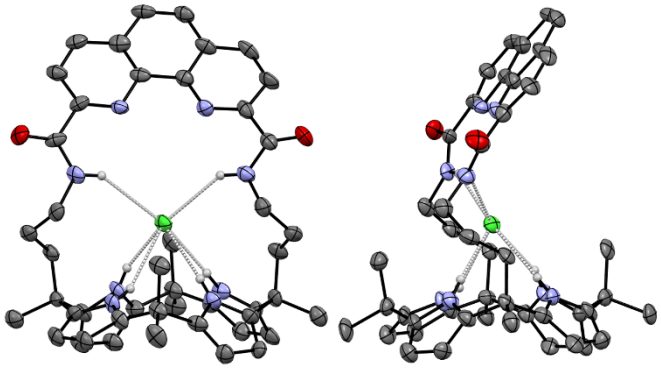


Fig. 8 Two different views of the single X-ray crystal structure of the TBACl complex of receptor **2**. Dashed lines indicate presumed hydrogen bonds. Thermal ellipsoids are scaled to the 30% probability level. Most hydrogen atoms and the TBA^+ cations sitting in the cone-shaped calix[4]pyrrole cavities have been omitted for clarity.

Conclusions

The phenanthroline-strapped calix[4]pyrroles **1** and **2**, bearing ester and amide linkers, respectively, act as effective anion receptors for the bicarbonate anion. The DFT calculations revealed that both receptors **1** and **2** formed energetically favorable complexes with the bicarbonate anion in which the phenanthroline group acts as a hydrogen bond acceptor and thus also participates in bicarbonate anion recognition. In $CDCl_3$ solution both receptors **1** and **2** were able to bind the bicarbonate anion with good selectively over other anions, including F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, $HP_2O_7^{3-}$, HSO_4^-, and SO_4^{2-}. Under these solvent conditions, receptor **2** exhibited a higher affinity for the bicarbonate anion than receptor **1**. In contrast, and in spite of the presence of two potential auxiliary hydrogen bond donor sites (the amide NH protons), receptor **2** was found to bind most other anions less effectively than receptor **1** in $CDCl_3$. This latter finding was rationalized in terms of the presence of competing intramolecular hydrogen amide NH-phenanthroline hydrogen bonding interactions bonds in the case of receptor **2**. Dramatic differences between receptors **1** and **2** and between what was observed in $CDCl_3$ were seen when the medium was changed to 15% D_2O in DMSO-d_6. In this highly polar protic solvent system, the affinity of receptor **1** for anions drastically decreased whereas receptor **2** was found to bind a number of anions with significantly improved affinities. This finding was rationalized in term of a weakening of the intramolecular amide NH-phenanthroline hydrogen bonding effects, allowing for an effective reversal in the anion affinities upon moving from $CDCl_3$ to the more polar (and protic) medium comprised of in 15% D_2O in DMSO-d_6. The current work thus serves to demonstrate how the solvent polarity may be used to modulate the anion affinities of appropriately designed receptors increasing in favorable circumstances both the affinities and selectivities of a given anion recognition system.

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