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Anion sensing using colorimetric amidourea based receptors incorporated into a 1,3-disubstituted calix[4]arene

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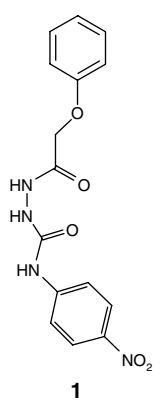
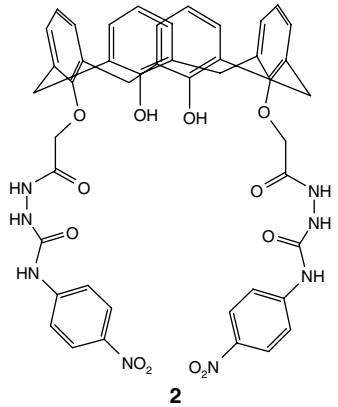
Abstract—The synthesis of amidourea-based colorimetric anion sensors **1** and **2** and the evaluation of these sensors using anions such as acetate ($CH_3CO_2^-$), fluoride (F^-), hydrogen phosphate ($H_2PO_4^-$) and hydrogenpyrophosphate (*pyr*) in DMSO is described. While **1** has a single amidourea moiety, **2** has two such receptors incorporated into a lower-rim 1,3-disubstituted calix[4]arene scaffold. Whilst both sensors gave rise to red shifts in their absorption spectra upon anion recognition, the sensing of F^- and *pyr* gave rise to large changes with concomitant colour changes from yellow to purple, which were visible to the naked eye.

The recognition of anions using luminescent or colorimetric methods has become an active area of research.[1,2] In particular, charged or charge neutral receptors such as metal based macrocycles,[3] amides,[4] carbamides,[5] ureas[6] or thioureas[7] have been employed for the selective recognition of anions in relatively simple structural motifs.[8] Such binding sites have also been incorporated into structural frameworks such as steroids,[9] calixarenes[10] and polynorbornanes[11] giving rise to more preorganized anion recognition motifs. Moreover, such designs can give rise to larger supramolecular assemblies as demonstrated elegantly by Gale et al.,[12] Kruger et al.[13] and Beer et al.[14] to name just a few. Anion receptors have also been employed for medicinal purposes and as biological mimics for the transport of anions or ion pairs across cell membranes.[15]

We are interested in the development of sensors for anions and have demonstrated such sensing based on the use of charge neutral photoinduced electron transfer (PET) sensors[16] as well as colorimetric anion sensors based on the use of internal charge transfer chromophores.[17,18] In this letter, we build upon these earlier successes and present **1**, which can also be incorporated into a preorganized scaffold, such as at the lower-rim of a 1,3-disubstituted calix[4]arene, for example, **2**.[19] Our receptors are based on a simple amidourea structure that can hydrogen bond to anions such as acetate, phosphate and potentially halides. Furthermore, using 4-nitrobenzene as part of the receptor enables us to monitor this binding spectroscopically in the visible region. We have previously used related amidothioures as a part of naphthalimide based colorimetric sensors.[20] Similarly, both Gale et al., using pyrrolylamidoureas,[21] and Jiang et al.[22] using *N*-benzamido-thiourea, have developed many excellent examples of receptors for anion recognition. However, to the best of our knowledge, **2** is the first example of an amidourea based 1,3-disubstituted calix[4]arene based colorimetric sensor for anions.



1



2

The synthesis of **1** was achieved in two steps as shown in Scheme 1. This involved the use of 2-phenoxy-acetohydrazide **3**, which was made from ethyl 2-phenoxyacetate

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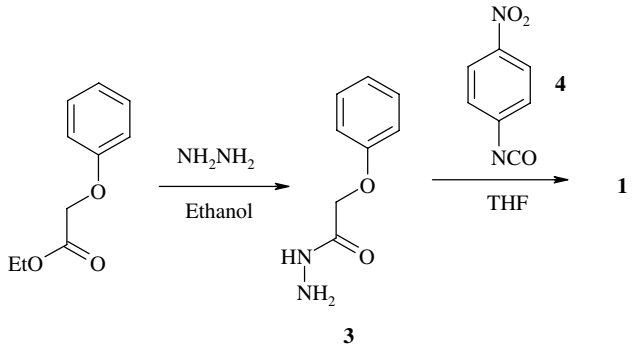


Scheme 1. Synthesis of **1**.

by reaction with hydrazine hydrate in ethanol under reflux for 3 h, followed by cooling to room temperature overnight, upon which a solid was formed. Reacting **3** with 4-nitrophenyl isocyanate **4** under an inert atmosphere at room temperature overnight gave **1** as a light yellow precipitate in a 62% yield after filtration and washing with methanol. The ^{1}H NMR (400 MHz, in DMSO-d_6) clearly showed the presence of the two urea protons, and the amide urea proton.[†]

The rationale behind **2** was to incorporate two anion receptors into a single calixarene scaffold with the aim of achieving colorimetric sensing of anions such as phosphate or pyrophosphate, where the binding of the anion would be in a 1:1 stoichiometry. The synthesis of the desired sensor **2**, commenced with the synthesis of the hydrazine intermediate **6**, which was achieved in one-step from 25,27-bis[(ethoxy-carbonyl)methoxy]-26,28-dihydroxy calix[4]arene, **5**, previously synthesized by Reinhoudt et al.,[23] through treatment with an excess of hydrazine hydrate. Following cooling to room temperature, the solution was evaporated to dryness under reduced pressure and the resulting residue triturated with methanol, collected by suction filtration and washed with distilled water providing **6** in a 94% yield as a white powder. We have also employed this method for the conversion of the tetra ester of calix[4]arene into the tetra hydrazidocarbonyl in good yield. The synthesis of the desired sensor was then achieved by reacting **6** in dry THF with 2 equiv of **4**. The mixture was stirred overnight at room temperature after which it was quenched by the addition of methanol, and the off-yellow precipitate filtered and washed with methanol to yield **2** as a pale yellow powder in a 95% yield.[†] The ^{1}H NMR (400 MHz, DMSO-d_6) of **2**, Figure 1, shows the formation of the desired amidourea sensor with characteristic resonances appearing at 10.17, 9.59 and 8.62 ppm for the three N–H protons. Figure 1 also shows the simplicity of the ^{1}H NMR caused by the C_2 symmetry of **2** (see Scheme 2).

The ability of both **1** and **2** to recognize anions was evaluated in DMSO by observing the changes in the absorption spectra of both compounds. For the current study,

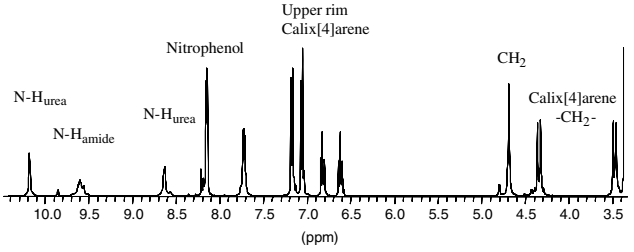
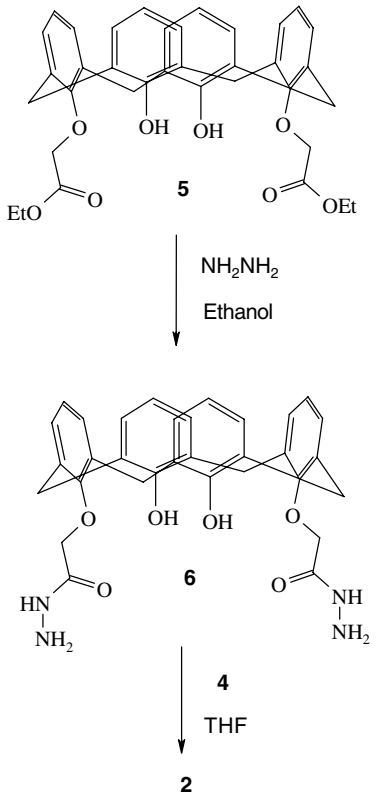


Figure 1. The ^{1}H NMR (400 MHz, DMSO-d_6) of **2**.



Scheme 2. Synthesis of **2**.

[†] Compound **1**: Mp 208–211 °C. Anal. Calcd for $C_{15}H_{14}N_4O_5 \cdot 0.3$THF: C, 55.36; H, 4.74; N, 15.81. Found: C, 55.41; H, 4.41; N, 16.24%. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 10.11 (s, 1H, NH), 9.55 (s, 1H, NH), 8.54 (s, 1H, NH), 8.18 (d, $J = 9.0$ Hz, 2H, Ar–H(nitrophenyl)), 7.73 (d, $J = 7.0$ Hz, 2H, Ar–H(nitrophenyl)), 7.32 (t, $J = 8.0$ Hz, 2H, Ar–H_{ortho}), 7.00 (m, 3H, Ar–$H_{meta,para}$), 4.63 (s, 2H, OCH_2C(O)). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 167.8, 157.7, 146.4, 141.1, 129.5, 125.0, 121.2, 118.0, 117.8, 114.7,66.0. IR ν_{max} (cm^{-1}, solid): 3326, 3228, 3107, 2903, 1728, 1720, 1676, 1660, 1616, 1598, 1567, 1508, 1459, 1412, 1426, 1343, 1333, 1300, 1239, 1202, 1175.

Compound **2**: Mp 242–245 °C Anal. Calcd for $C_{46}H_{40}N_8O_{12} \cdot CH_3OH$: C, 60.77; H, 4.77; N, 12.06. Found: C, 60.26; H, 4.48; N, 12.09%. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 10.17 (s, 2H, NH_{urea}), 9.59 (s, 2H, NH_{urea}), 8.62 (s, 2H, NH_{amide}), 8.14 (d, $J = 9$ Hz, 4H, Ar–$H_{nitrophenyl}$), 7.71 (d, $J = 9$ Hz, 4H, Ar–$H_{nitrophenyl}$), 7.17 (d, $J = 7$ Hz, 4H, ArH), 7.05 (d, $J = 7$ Hz, 4H, ArH), 6.81 (t, $J = 8.0$ Hz, 2H, Ar–H), 6.62 (t, $J = 7.0$ Hz, 2H, Ar–H), 4.68 (s, 4H, ArO–CH_2–C(O)), 4.33 (d, $J = 13$ Hz, 4H, Ar–CH_2–Ar), 4.46 (d, $J = 13$ Hz, 4H, Ar–CH_2–Ar). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: Quaternary not visible, 152.4, 152.3, 146.2, 141.2, 133.5, 129.1, 128.7, 127.5, 125.6, 125.4,125.0, 119.3, 117.8, 73.3, 30.6. IR ν_{max} (cm^{-1}, solid): 3314, 3097, 1658, 1633, 1595, 1567, 1510, 1466, 1434, 1329, 1302, 1215.

tetrabutylammonium (TBA) anions such as acetate ($CH_3CO_2^-$), fluoride (F^-), hydrogenphosphate ($H_2PO_4^-$) and hydrogenpyrophosphate (*pyr*) were employed. In DMSO, the two receptors **1** and **2** had absorptions bands centred at 338 nm ($\varepsilon = 17{,}641\ cm^{-1}\ M^{-1}$) and 336 nm ($\varepsilon = 29802\ cm^{-1}\ M^{-1}$), respectively. These were assigned to the internal charge transfer (ICT) nature of the chromophore. Both compounds showed significant changes in their absorption spectra upon addition of the above anions, demonstrating the formation of an anion-receptor complex utilizing hydrogen bonding. Figure 2 shows the changes observed for the titration of **1** with acetate. Here, significant spectral changes were observed for the 336 nm transition, which was hypsochromically shifted upon anion recognition. The changes in the 440 nm wavelength were used to evaluate the binding affinity of **1** and these changes are shown as an inset in Figure 2. Fitting these changes using the nonlinear least squares regression program SPECFIT, gave a good fit, with two binding constants, $\log\beta_1 = 4.20$ (± 0.03) and $\log\beta_2 = 3.21$ (± 0.09). This indicates that the binding of acetate is not a 1:1 stoichiometry as might be expected. Examining the changes in the main transition in Figure 2, it can be seen that no clear isosbestic point is observed, which suggest that there is more than one simple 1:1 binding process occurring. This can possibly be viewed as one of the anions forming linear hydrogen bonds to the urea part of the receptor, with a second binding occurring at the amide.

In a similar manner, the titration of F^- revealed some interesting results, as here the binding was determined to be mostly 1:1. Figure 3 shows the changes observed in the absorption spectra upon the addition of F^-. As can be seen from these changes the absorption band at 338 nm is significantly reduced in intensity, with concomitant formation of a new band centred at ca. 420 nm and an isosbestic point at 369 nm. This signifies a 1:1 binding interaction, which is somewhat surprising.[17] Given the fact that F^- is a strong Lewis base and can deprotonate one, or more, of the N–H protons of the receptor (as previously demonstrated by ourselves[17] and Gale et al.,[24] and more recently by Fabbrizzi et al.[25]), one would have expected that such a deprotonation should occur within the addition of the 2 equiv of F^- to **1**. However, this does not seem to be the case and only upon addition of a large excess of F^- (>40 equiv) does such deprotonation occur. Such deprotonation would give rise to the formation of HF_2^-[8] with concomitant changes in the absorption spectra, which would be shifted to longer wavelengths.[17] Indeed this was found to be the case for **1** at such high F^- concentrations. Hence, we can conclude that for F^-, the binding occurs only through hydrogen bonding within the concentration range shown in Figure 3. From these changes at 440 nm (Inset Fig. 3), a $\log\beta = 3.31$ (± 0.03) value was determined, which is significantly smaller than that observed for $CH_3CO_2^-$. However, in contrast to the $CH_3CO_2^-$ titration, the changes in the absorption spectra were also clearly visible to the naked eye, where a yellow colour was observed upon binding of the anion to the receptor. When these titrations were repeated using chloride or bromide, no significant binding was observed. In a similar manner, using $H_2PO_4^-$ gave rise to changes in the absorption spectra. However, in contrast to that observed above, the changes in the absorption spectra were smaller. For $H_2PO_4^-$, only a small red shift was observed, from which a binding constant value $\log\beta_1 = 4.73$ (± 0.17) was determined. It was also possible to determine a second binding constant from these changes, assigned to the formation of 2:1 complex between two anions and **1**, with $\log\beta_2 = 3.55$ (± 0.30), however, these values carry a significant error.

In contrast to these results, titration with *pyr*, gave rise to large changes in the absorption spectra (Fig. 4), similar to those observed for F^-. However, analysis of these data using a 1:1 stoichiometry gave, on all occasions, unsatisfactory results, where the fitted data carried a large error. Hence, alternative binding modes were considered. The best data fit was observed for the scenario where 2 equiv of **1** and a single anion formed a complex. The speciation distribution diagram for this fitting is

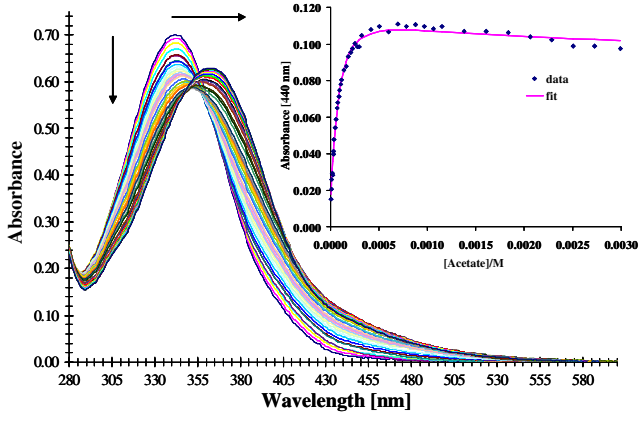


Figure 2. Changes in the absorption spectra upon titration with acetate in DMSO. The arrows show the red shift observed upon anion-complex formation. Inset: The changes at 440 nm and the fitted data observed using SPECFIT.

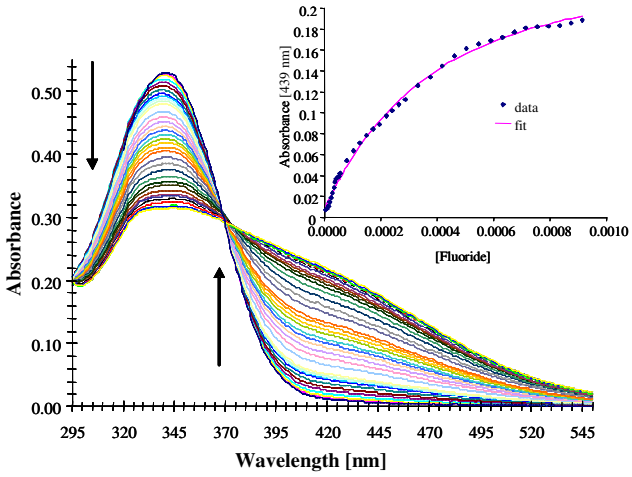


Figure 3. The changes in the absorption spectra of **1** upon titration with fluoride in DMSO. Inset: The changes at 439 nm and the result of fitting the data to 1:1 binding using SPECFIT.

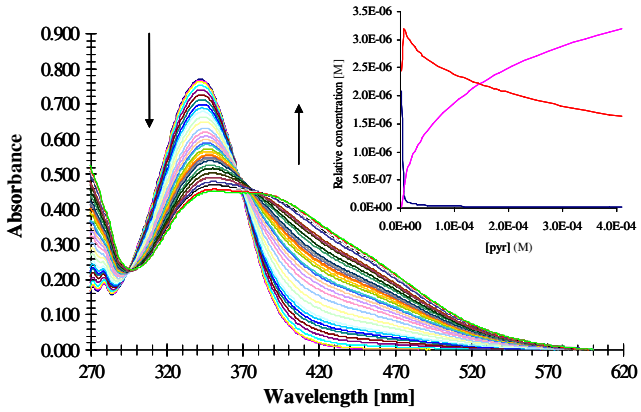


Figure 4. The changes in the absorption spectra of **1** upon titration with *pyr* in DMSO. Inset: Speciation distribution diagram for the titration of **1** with *pyr* in DMSO: —— **1**; —— 1:1 and —— 2:1.

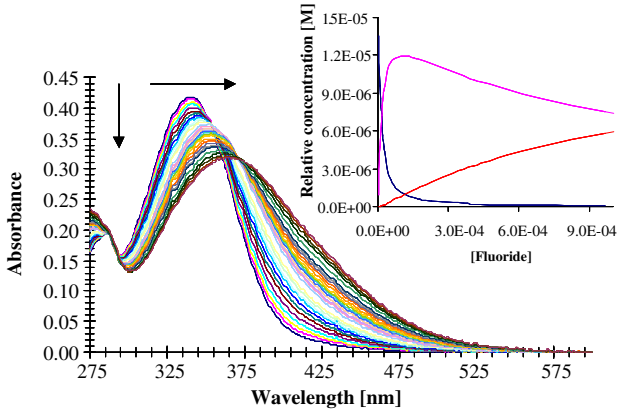


Figure 5. Changes in the absorption spectra of **2** upon titration with fluoride in DMSO. Inset: The species distribution diagram for the titration: —— **2**, —— 1:1 and —— 2:1 (anion:**2**).

seen as an inset in Figure 4. From this fit, two binding constants can be determined for 2:1 (**1**:anion) and 1:1 anion binding, where at a lower concentration, the 2 equiv of **1** bind to *pyr*, but with increasing concentration of the anion, the self-assembly brakes down to give the 1:1 complex as the dominant stoichiometry (Fig. 4). For the 1:1 binding, a value of $\log\beta = 5.78$ (± 0.30) was determined, which is quite strong binding; while for the 2:1 self-assembly, a binding constant of $\log\beta = 7.59$ (± 0.8) was determined. However, it is worth pointing out that this latter binding carries a large error.

Having established the ability of **1** to interact with anions in 1:1, 2:1 or 1:2 stoichiometries, we investigated the use of **2** under identical conditions. In the case of **2**, the anion receptors are more preorganized, and as such should be able to bind anions such as $H_2PO_4^-$ or *pyr* in a more cooperative manner, giving rise to an exclusive 1:1 binding of these anions. We first evaluated the ability of **2** to sense $CH_3CO_2^-$, which would be expected to bind in a 2:1 manner (anion:**2**) as each of the amidoureas would be expected to act independently. Upon titration with $CH_3CO_2^-$, the absorption spectrum of **2** was shifted to longer wavelengths in a similar manner to that observed for **1**. Analysis of the changes at 440 nm indeed revealed two binding constants for the 1:1 and the 1:2 (**2**:anion) complexes, with $\log\beta_1 = 5.64$ (± 0.07) and $\log\beta_2 = 4.39$ (± 0.27), both of which are significantly larger than observed for **1**. However, unlike that seen for **1**, we believe that these binding constants represent binding of the acetate directly to the urea parts of the receptors alone (cf. results from **1** above). In a similar manner, the titration of **2** with F^- gave rise to significant spectral changes (Fig. 5), that were also clearly visible to the naked eye. From these changes, it can be seen that the 1:1 complex is initially formed exclusively, but after addition of ca. one equiv of F^-, the 2:1 complex was also formed. As in the case of **1**, we do not seem to have a direct evidence for the deprotonation of the receptor moieties of **2** by F^- within the concentration range shown in Figure 5. Consequently, we can conclude that F^- is being recognized as the hydrogen bonding complex, mirroring that observed for **1**. From these changes a value of $\log\beta = 5.1$ (± 0.05) was determined for the 1:1 complex formation, with a $\log\beta = 3.24$ (± 0.15) value being determined for 2:1 complex.

The titrations of **2** using $H_2PO_4^-$ also gave rise to hypsochromic shifts in the absorption spectra. However, as for the titration of **1**, these changes were not as pronounced as those for $CH_3CO_2^-$ and F^-. However, here the preorganization of the sensor was evident as only 1:1 binding was observed, with $\log\beta = 4.86$ (± 0.03) being determined. This is somewhat stronger binding than that observed for **1**, demonstrating the advantage of the use of the receptors as part of the calix[4]arene scaffold.

The most striking results were however, once again observed for the titration with *pyr*. The changes in the absorption spectra are shown in Figure 6, and clearly show that the band centred at 336 nm is initially shifted to longer wavelengths, in a similar manner to that seen for **1** giving rise to the formation of a new band at ca. 377 nm, and a shoulder at ca. 500 nm. However, at a higher concentration (not shown), the 377 nm absorption gave way to even further changes with the formation of two new bands at 346 and 384 nm, respectively. Moreover, the shoulder previously ob-

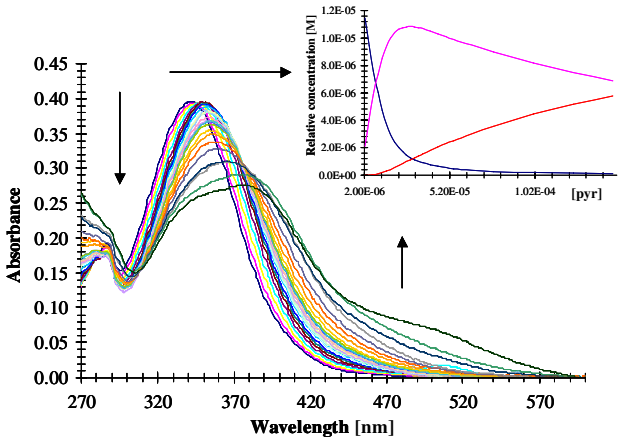


Figure 6. The changes in the absorption spectra of **2** upon titration with *pyr* in DMSO. Inset: The species distribution diagram for the titration of **2** with pyrophosphate: —— **2**, —— 1:1 and —— 1:2 (anion:**2**).

served at 500 nm developed into a full transition. We attribute these overall changes to: (i) formation of the hydrogen bonding anion:receptor complex, at lower concentrations, (ii) deprotonation of the anion receptors at higher *pyr* concentrations. Such deprotonation has also been shown to be possible with anions other than F^- by Gale et al.[21]

Analysis of the initial changes in Figure 6, showed that the *pyr* is bound to **2** in the desired 1:1 stoichiometry, with $\log\beta = 5.72$ (± 0.11). This binding can possibly occur in such a manner that the *pyr* anion bridges the two receptors in **2**, across the calix[4]arene cavity. However, a second binding constant can also be determined from these changes, assigned to the 1:2 (**2**:anion) stoichiometry, with $\log\beta = 3.81$ (± 0.31). The speciation distribution diagram for the binding of *pyr* to **2** is shown in Figure 6 as an inset. From these changes, it can be seen that the recognition of *pyr* initially involves the formation of a 1:1 self-assembly, with the formation of the 1:1 and the 1:2 binding stoichiometries at higher concentrations. We are currently evaluating these binding possibilities in a greater detail.

In summary, we have developed calixarene **2** as a novel colorimetric sensor for anions, by incorporating amido-urea based receptors, used in model compound **1**, into 1,3-disubstituted calix[4]arene in short and high yielding synthesis. We have demonstrated that these receptors can bind F^- in a 1:1 stoichiometry with concomitant colorimetric changes, where the binding occurs through hydrogen bonding and that no deprotonation of the receptors in either **1** or **2** occurs until high F^- concentrations are reached. We have also shown that a strong 1:1 binding is observed for $H_2PO_4^-$ and *pyr*, where the latter binding occurs by bridging the anion across the lower-rim cavity of the 1,3-functionalized calix[4]arene scaffold **2**. We are currently working towards developing other analogues of **2** with the aim of achieving a more selective anion sensing and the formation of anion template self-assembly structures.

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