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β -Vinyl substituted calix[4]pyrrole as a selective ratiometric sensor for cyanide anion†

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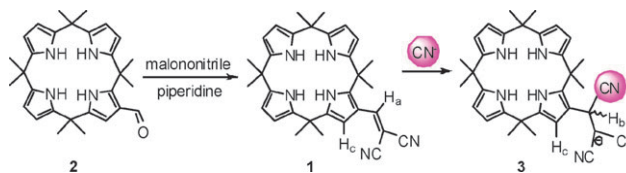
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A new calix[4]pyrrole-based, dual functional, chemodosimetric sensor was developed and studied as a cyanide selective indicator; complete color bleaching was observed even in the co-presence of an excess of other anions.

Cyanide anion is highly toxic to living animals; accordingly, any type of release into the environment can lead to serious problems. On the other hand, cyanide is used in various industrial processes, including gold mining and electroplating, enhancing the chance of unwanted release. Not surprisingly, therefore, there is growing interest associated with the development of cyanide selective receptors and sensors. Indeed, several sensor systems for cyanide anion detection have been reported to date¹ including utilization of the complexation of cyanide with metal ion,² with boronic acid,³ and with quantum dots.⁴ The majority of these rely on fluorescence changes, induced upon hydrogen bonding,⁵ to produce the sensor effect. However, in spite of these recent developments, there are still relatively few examples of selective probes for cyanide anion, especially those that display limited interference in the presence of other anions. More recently, several ratiometric systems have been reported and these systems to some extent overcome the limitations inherent in the earlier approaches. Many of these, including systems based on squaraine,^{1a} acridinium salts,⁶ oxazine,^{7,8} trifluoroacetophenone derivatives,⁹ and benzil,^{10,11} rely on the nucleophilic property of cyanide anion to effect chemical changes that give rise to the observed signals. Effective as these systems are, it would be more desirable to develop receptors that display both anion binding behavior and a selective ratiometric response to varying concentrations of the cyanide anion. Among other advantages, such a dual mode of action might allow the effects of interfering anions to be effectively removed from the system *via* pre-complexation with the receptor.

With these considerations in mind, we report a selective chemodosimetric sensor for cyanide anion, namely the functionalized calix[4]pyrrole **1**. This receptor contains a



Scheme 1

calix[4]pyrrole anion binding site and a dicyano-vinyl group as a putative cyanide-dependent reactive subunit.

Sensor **1** was synthesized from the condensation of β -monoformyl calix[4]pyrrole **2**¹² and malononitrile as shown in Scheme 1. As also shown in Scheme 1, it was expected that cyanide, and possibly other nucleophiles, could attack the α -position of the dicyano-vinyl group to generate stabilized anionic species **3**. Since this attack is expected to reduce the extent of conjugation, a spectral change should ensue. Unlike the parent β -unsubstituted calix[4]pyrrole, which is transparent in the visible region, receptor **1** is yellow in color ($\lambda_{\text{max}} = 374$ nm). Thus, nucleophilic addition of anions to the α -position of the vinyl group would be expected to produce a loss in color or at least in perceived brightness or intensity. If cyanide anion were the only nucleophile capable of inducing such changes, the result would be that receptor **1** would act as an anion-selective colorimetric sensor.

In order to evaluate the nature of the reaction of anions with receptor **1**, we monitored the ¹H NMR spectral changes produced *via* the addition of cyanide anion and chloride anion in CD₃CN (3% DMSO-*d*₆) at room temperature.

As shown in Fig. 1(a), the vinylic proton (H_a) shown at 8.14 ppm completely disappears upon the addition of ~1 equiv. of cyanide anion, while a new signal grows in at 4.85 ppm. These observations obviously indicate that the cyanide anion is added to the vinyl group. The newly appeared signal at 4.85 ppm corresponds to the α -proton (H_b). The upfield shift of the β -pyrrolic proton (H_c) is consistent with the binding cyanide anion within the cavity of the calix[4]pyrrole **1**. The affinity of cyanide anion with calix[4]pyrrole is rather small compared with other anions.¹³ Interestingly, no signal corresponding to the β -proton of the malononitrile group was seen in the ¹H NMR spectrum. This is possibly due to the formation of the stabilized anionic species **3** upon nucleophilic addition of cyanide anion.

On the other hand, the vinylic resonance line shown at 8.14 ppm was unchanged upon the addition of chloride anion (Fig. 1(b)). Only typical spectral shifts corresponding to the anion binding with **1** were observed. All other added anions

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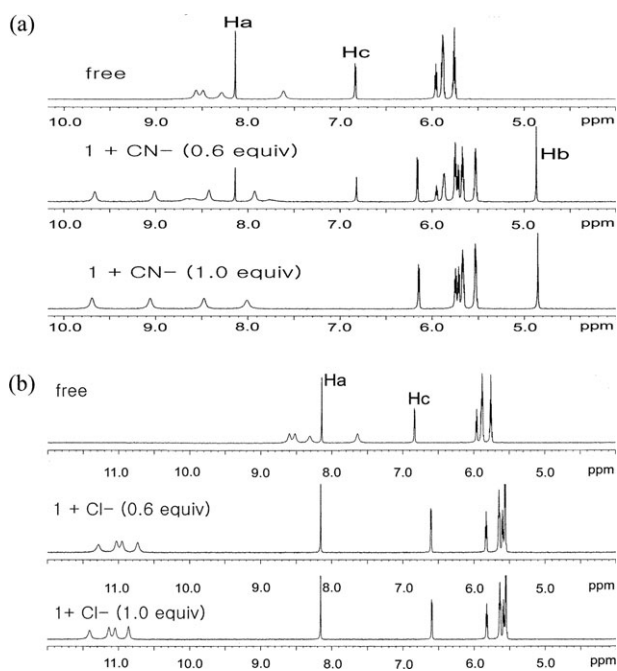


Fig. 1 (a) ^1H NMR spectral changes seen upon the addition of cyanide anion to receptor **1** (10.0 mM) and (b) chloride anion (as their tetrabutylammonium salts, respectively) in CD_3CN (3% $\text{DMSO}-d_6$) at 25°C .

including Cl^- , Br^- , NO_3^- , SCN^- , F^- , H_2PO_4^- and AcO^- displayed spectral changes similar to those of chloride anion addition. All the anions other than cyanide evidently bind to the calix[4]pyrrole cavity through “normal” N–H–anion hydrogen bonding interactions. Typical UV–Vis spectral changes were produced upon titration with other anions (as their tetrabutylammonium salts) in CH_3CN – DMSO (3%). A clear isosbestic point provides support for the proposed simple binding equilibrium; further, no additional spectral changes were observed upon letting the solution stand overnight (supporting information†).

In order to verify the competing pre-complexation of cyanide anion with host **1**, time-dependent absorption spectral changes in the presence of excess cyanide anion (20 equiv.) were monitored. As shown in Fig. 2, the initial complexation

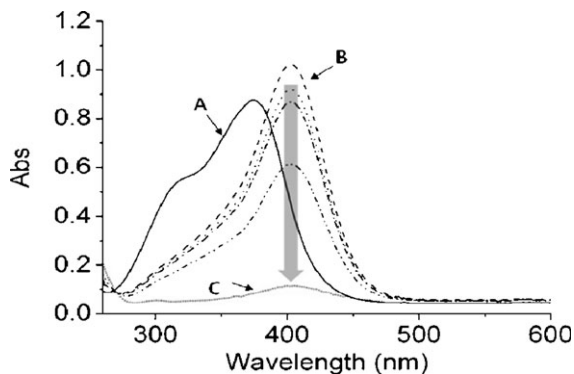


Fig. 2 Time-dependent UV–Vis spectral changes of host **1** (41.2 μM) seen upon the addition of 20 equiv. of cyanide anion in CH_3CN – DMSO (3%). (A) free host **1** only, (B) after 10 s upon addition of 20 equiv. of cyanide anion, (C) after 19 min upon addition of 20 equiv. of cyanide anion.

of cyanide anion was observed within 10 s of mixing and rather slow addition of cyanide anion to the double bond was followed. A large bathochromic shift from $\lambda_{\text{max}} = 374 \text{ nm}$ to $\lambda_{\text{max}} = 403 \text{ nm}$ was observed upon cyanide anion complexation. The calculated pseudo first order rate constant for cyanide addition was 5.35 s^{-1} . We also checked the cyanide binding behavior of 3-dicyanoethenylpyrrole in order to check the validity of the presence of the calix[4]pyrrole moiety. The UV–Vis spectrum of 3-dicyanoethenylpyrrole shows λ_{max} at 338 nm, that is colorless. So, the calix[4]pyrrole moiety seems to be important in colorimetric responses.

In order to evaluate further the cyanide-selective nature of the receptor **1**, absorption spectral changes upon addition of various anions including F^- , Cl^- , Br^- , NO_3^- , SCN^- , $\text{HP}_2\text{O}_7^{3-}$, H_2PO_4^- and AcO^- were studied (Fig. 3). 20 equiv. of each anion were added to a solution of **1** (41.2 μM) and incubated for 4 min at 25°C , before being subjected to spectral analysis. Characteristic spectral changes associated with anion binding were seen for all anions except cyanide anion. Complete bleaching of the color was observed with cyanide anion.

A more detailed analysis of the absorption changes produced upon the addition of cyanide anion is shown in Fig. 4. Upon addition of ~ 20 equiv. of cyanide anion, the absorbance of the solution bleached completely and the yellow solution became colorless. The bleaching was complete within 2–3 min after the addition of cyanide anion. The formation of adduct **3** has been verified by high resolution MALDI–TOF MS and proton NMR spectroscopy after acidic workup.

The initial lag phase up to addition of ~ 0.3 equiv. of cyanide anion was observed and this observation also corresponds to the fact that the cyanide anion interacts with the calix[4]pyrrole cavity. Since the real system usually contains a mixture of anions, dual functional receptors such as **1** bearing both the anion binding site and ratiometric anion addition site could be ideal sensor models for field application if the receptors possess anion selectivity. Consequently, the effective concentration of competitor or inhibitory anions with cyanide anion could be reduced upon pre-binding to the binding cavity. When chloride anion-saturated (~ 20 equiv.) receptor **1** was treated with cyanide anion, complete bleaching

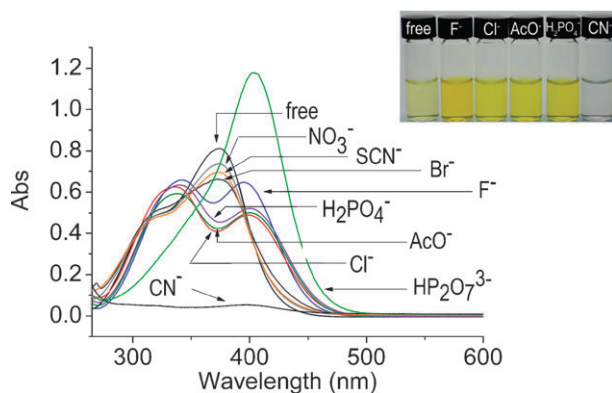


Fig. 3 UV–Vis spectral change of the free host **1** (41.2 μM) seen upon the addition of 20 equiv. of various anions in CH_3CN – DMSO (3%). Inset: Color changes of **1** (1.03 mM) seen in the presence of 20 equiv. of F^- , Cl^- , AcO^- , H_2PO_4^- and CN^- in CH_3CN – DMSO (3%).

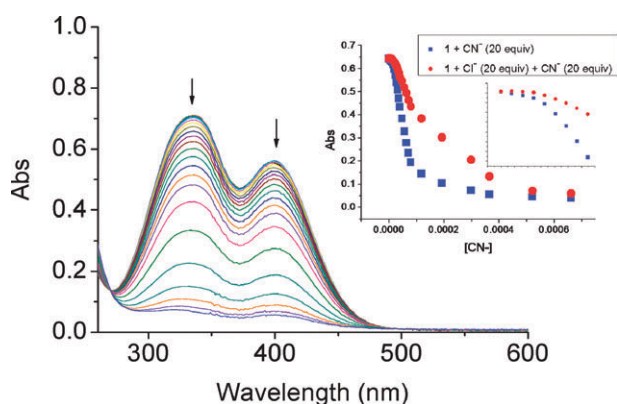


Fig. 4 UV-visible spectral changes seen for the mixture of **1** (41.2 μM) and Cl^- (20 equiv. as its tetrabutylammonium salt) upon addition of CN^- in CH_3CN –DMSO (3%). The inset shows the titration with cyanide anion only (blue dots) and titration with cyanide anion after pre-saturation with chloride anion (red dots) in CH_3CN (3% DMSO). $[\textbf{1}] = [41.2 \mu\text{M}]$.

Table 1 Affinity constants for receptor **1** for various anions calculated from the titration in 3% DMSO in CH_3CN at 25 $^\circ\text{C}$. $[\textbf{1}] = 41.2 \mu\text{M}$

Binding constant K_a/M^{-1}	
Anion	UV-Vis
F^-	6.24×10^5
Cl^-	9.75×10^4
Br^-	2.76×10^3
AcO^-	2.79×10^5
H_2PO_4^-	7.53×10^4
NO_3^-	N.D.
SCN^-	N.D.

of absorbance was also observed. On the other hand, the rate of bleaching was slower in the presence of the mixture of anions (F^- , Cl^- , AcO^- , and H_2PO_4^- , 20 equiv. each), possibly due to the increased ionic strength. These results indicate that the receptor **1** possesses high selectivity for cyanide anion and the presence of the other anions or cationic species did not cause any other side reactions. Job plot analysis for the complexation of receptor **1** with anions (F^- , Cl^- , AcO^- , NO_3^-) showed 1 : 1 binding stoichiometry (supporting information†). Table 1 summarizes the equilibrium association constants K_a , measured by UV-Vis spectroscopy for the binding of various anions to receptors **1** in acetonitrile–DMSO (3%). Close analysis of the table indicates that the binding affinities of receptor **1** with various anions are similar to values reported for octamethylcalix[4]pyrrole.¹³

In summary, we have demonstrated that the calix[4]pyrrole-based, dual functional, chemodosimetric sensor **1**

can be synthesized and that such systems, as currently produced, are selective for the cyanide anion; the latter can be selectively detected when “hidden” within a mixture of other anions. The binding affinities for a variety of other anions were calculated from the absorption changes produced in the presence of various anions and were found to be similar to those of octamethylcalix[4]pyrrole. The present system displays fast color bleaching only with cyanide anion even in the presence of a large amount of other anions, including chloride anion. The anion binding sites present in the current system could play a role in reducing the effective concentration of inhibitory anions during the ratiometric detection of cyanide anion. Design and synthesis of more sensitive systems are in progress.

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