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# Strapped Calix[4]pyrroles Bearing a 1,3-Indanedione at a *β*-Pyrrolic Position: Chemodosimeters for the Cyanide Anion

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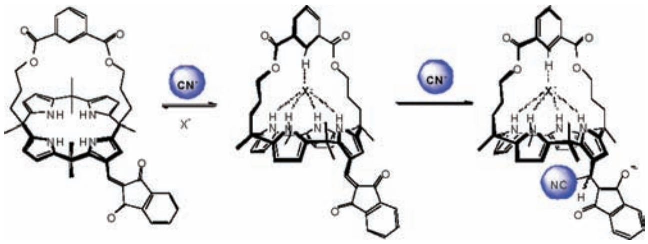
## ABSTRACT



**A strapped calix[4]pyrrole bearing a 1,3-indanedione group at a *β*-pyrrolic position has been synthesized and studied as a ratiometric cyanide-selective chemosensor. A concentration-dependent bleaching of the initial yellow color was observed upon addition of the cyanide anion. The bleaching, which was observed exclusively with the cyanide anion, occurred even in the presence of other anions. Spectroscopic studies provide support for a mechanistic interpretation wherein the cyanide anion forms a complex with the receptor ($K = 2.78 \times 10^4$ $M^{-1}$) through a fast equilibrium, which is followed by slow nucleophilic addition to the *β*-position of the 1,3-indanedione group. A minimum inhibitory effect from other anions was observed, a feature that could be beneficial in the selective sensing of the cyanide anion.**

The cyanide anion is well-known to be toxic to living animals. For instance, the cyanide anion binds to the ferric form of cytochrome *c* and inhibits electron transfer processes in man and numerous other animals.[1] Nevertheless, despite the risk it imposes, cyanide continues to be used in many industrial processes, including gold mining and electroplating. Needless to say, the widespread use of cyanide increases the risks of unwanted release into the environment. There is thus growing interest in the development of cyanide-selective receptors and species that can be used to detect its presence. These include so-called chemosensors ("sensors" for short) and indicators that produce reversible and nonreversible changes, respectively, in an easy-to-monitor signal in the presence of a cyanide anion. In recent years, a number of chemical-based detectors for cyanide anions have been reported. Most of these rely on changes in fluorescence intensity, produced upon cyanide anion binding, to generate the desired sensory effect; however, others take advantage of chemical reactions and associated color changes to reveal the presence of the cyanide anion.[2] Despite these recent advances, there are still relatively few examples of selective

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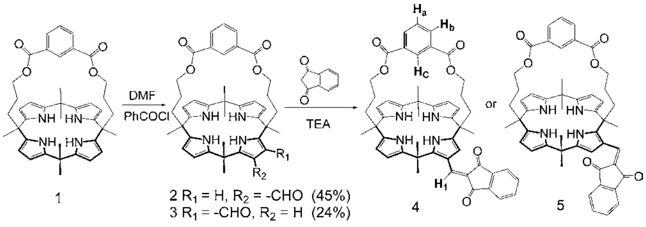
probes for the cyanide anion, particularly those that display limited interference in the co-presence of other anions. In this context it is worth noting that several ratiometric systems have been reported recently that are attractive because they allow monitoring at multiple wavelengths; these include systems based on squaraine,[3] acridinium salts,[4] oxazine,[5] trifluoroacetophenone derivatives,[6] and benzil derivatives,[7] many of which rely on the nucleophilic property of the cyanide anion to produce the observable physicochemical changes. However, even more useful would be receptors that display dual action, specifically, cyanide anion binding and cyanide-induced reactivity. To the extent they could be demonstrated as being fully dependent on the cyanide anion concentration, such dual mode systems might allow the effects of interfering anions, involved in, e.g., competing complexation with the receptor, to be effectively removed. They would also be expected to be fully ratiometric, in that the putative cyanide-dependent response could be monitored at several wavelengths or, in the limit, permit the use of analytical methods that complement those based on optical means.

With these considerations in mind, we have designed and wish to report here a cyanide-selective chemodosimeteric sensor system based on the strapped calix[4]pyrrole **1**.[8] This receptor, consisting of isomers **4** and **5**, produced and separated as a mixture during the early stages of synthesis, contains an anion-binding cavity as well as an electrophilic site on the periphery designed to permit reaction with the cyanide anion.

Targets **4** and **5** were prepared using a procedure developed by Anzenbacher et al. in the context of elaborating simple unsubstituted calix[4]pyrroles for use as anion sensors.[9] Specifically, the starting strapped system **1** was subjected first to Vilsmeier−Haack formylation according to the method of Bruckner.[10] This gave two different $\beta$-monoformylated regioisomers, which were readily separated to give **2** and **3** in 45% and 24% yield, respectively. Knoevenagel condensation with a 1,3-indanedione then gave the isomeric products **4** and **5**, as shown in Scheme 1. The regiochemistry of the two formylated products **2** and **3**, and thus by inference that of **4** and **5**, was unambiguously determined by carrying out a single crystal X-ray analysis of the dominant monoformylated product, regioisomer **2** (cf. Figure 1).

**Scheme 1.** Synthesis of Target Receptors **4** and **5**



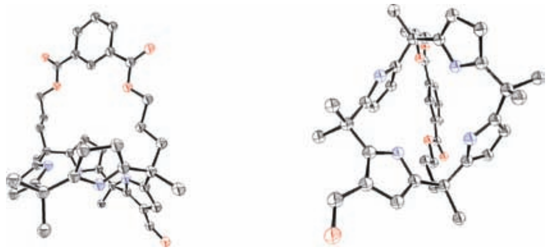


**Figure 1.** ORTEP diagram of **2** showing the site of formylation. Displacement ellipsoids are scaled to the 50% probability level. Hydrogen atoms have been omitted for clarity.

Unlike receptor **1**, the $\beta$-substituted receptors **2**−**5** possess inherent chirality. Thus, it is expected that the binding of an anion to the cavity would generate a enantiomeric pair of complexes. On the other hand, if the anion adds into the vinyl group, a diastereomeric mixture will be produced. It is expected that cyanide, and possibly other nucleophiles, can attack the $\alpha$-position of the vinyl group (i.e., the $\beta$-position of the 1,3-indanedione moiety) to generate stabilized anionic species. Such a nucleophilic attack is also expected to reduce the extent of conjugation, thus giving rise to a change in the spectroscopic features.

Unlike simple calix[4]pyrroles, and even the strapped "parent" **1**, isomers **4** and **5** are not transparent in the visible region. Rather, they are yellow, both in the solid state and in dichloromethane solution ($\lambda_{max} = \sim 430$ nm). Thus, anions that react with **4** or **5** via addition to the 1,3-indanedione subunit would be expected to lead to a loss in absorption intensity and, in the limit, produce colorless adducts. If the cyanide anion were the only nucleophile capable of inducing such changes, the result would be a promising anion-selective ratiometric sensor for the cyanide anion. The present study was designed to test this possibility. The fact that regioisomers **4** and **5** were obtained as individual products, rather than as an inseperable mixture, provides at least in principle a means to determine the effect of chromophore position.

Initial assessments of the interaction between receptor **4** and the test fluoride anion (as its tetrabutylammonium salt, TBAF) were carried out by monitoring the changes in the $^1$H NMR spectral features produced upon the addition of increasing quantities of TBAF (up to 2 molar equiv) in $CD_2Cl_2$ at room temperature (Supporting Information). The results provide support for the assumption that the fluoride

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anion binds to the cavity strongly. Specifically, the pyrrole N−H proton signals were found to shift to lower field and appear as four sets of distinctive doublets ($J = 46$ Hz) upon the addition of 1 equiv of TBAF. The vinylic proton ($H_1$), initially resonating at 8.14 ppm, was found to shift to 8.41 ppm upon the addition of fluoride anion. Similar spectral features were observed upon titration of receptor **5** with TBAF (likewise in $CD_3CN$/ DMSO-$d_6$ (30%) at 25 °C), and when both receptors were titrated with other typical anions, including $Cl^-$, $Br^-$, $AcO^-$, and $H_2PO_4^-$.

When receptor **4** was titrated with the cyanide anion, the $^1$H NMR spectral changes were observed that were completely different from those seen in the case of the simple test anions noted above. For instance, as can be seen from an inspection of Figure 2, the vinylic proton ($H_1$), originally resonating at 8.14 ppm, completely disappears upon the addition of ~3 equiv of the cyanide anion, while two new signals are seen to grow in at 5.13 and 5.19 ppm, respectively. These observations are consistent with the proposal that the cyanide anion adds to the $\beta$-position of the 1,3-indanedione moiety and that the new signals are those of the corresponding α-proton. The upfield shift of the $\beta$-pyrrolic protons is further consistent with cyanide anion binding within the cavity concurrent with nucleophilic addition to the indanedione vinyl group. Further, no signal corresponding to the α-proton of the 1,3-indanedione group was seen in the $^1$H NMR spectrum. This is as expected given the proposed formation of a stabilized enolate species (i.e., production of the anionic form of 2-hydroxyinden-4-one).

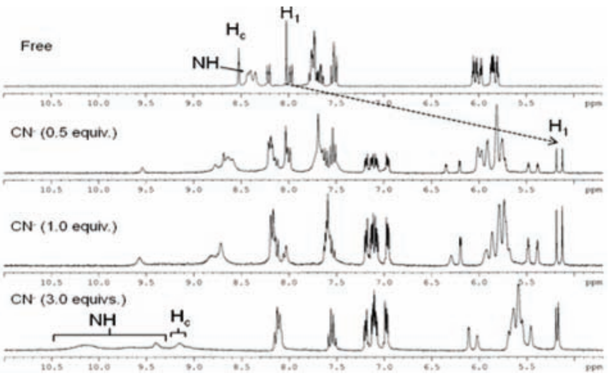

**Figure 2.** $^1$H NMR spectral changes observed upon the addition of cyanide anion (as its tetrabutylammonium salt) to receptor **4** (6.0 mM) in $CD_3CN$/DMSO-$d_6$ (30%) at 25 °C.

The fact that two distinctive signals for the $\beta$-protons (at 5.13 ppm and 5.19 ppm, respectively) are seen for the cyanide adduct, **4**•[CN] is fully consistent with the formation of two diastereomers. The addition of cyanide to the vinyl group produces a diastereomeric mixture of adducts, namely, (*S*)-**4**•[CN] and (*R*)-**4**•[CN] (Figure 3). The diastereomeric ratio ([(*S*)-**4**•[CN]]/[(*R*)-**4**•[CN]]), calculated from the integration of the α-protons, was 58:42.

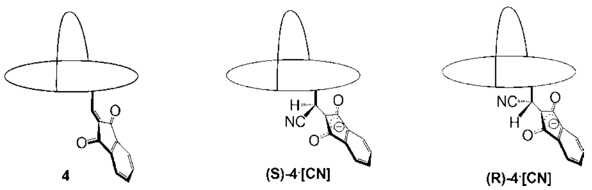

**Figure 3.** Schematic representation of receptor **4**•[$CN^-$] and its diastereomeric cyanide adducts.

Since anion binding to the receptor **4** is accompanied by conformational changes involving the calix[4]pyrrole moiety, namely, conversion from a 1,3-alternate to a cone conformation, it is expected that the diastereoselectivity could possibly vary depending on the specific conformation of the receptor. This is indeed appears to be the case. In particular, when the $F^-$-bound form of receptor **4** (produced by adding ~1.1 equiv of TBAF), a species known to adopt the limiting cone conformation, was titrated with the cyanide anion, the diastereomeric ratio was found to be 82:18. This stands in contrast to what was seen in the case of the initial calixpyrrole-bound cyanide complex, a species where full conversion to the cone conformation might not be expected. Consistent with this latter supposition, the diastereomeric ratios were found to vary depending on the initial cyanide anion concentration.

Figure 4a shows the typical UV−vis spectral changes produced upon titration of receptors **4** and **5** with fluoride anion. The spectral changes for other anions are all similar (Supporting Information). The binding constants obtained from both ITC and UV−vis spectroscopic analyses for both receptors **4** and **5** are given in Table 1. The anion affinities are comparable to those obtained in the case of other strapped calix[4]pyrrole systems.[8] However, receptor **4** and **5** exhibit exceptionally high affinities for the pyrophosphate anion. It should be noted that although a good match between these two independent measurements was seen in the case of most anions, in the case of fluoride and chloride anion a significant deviation was seen. While further effort will be required to

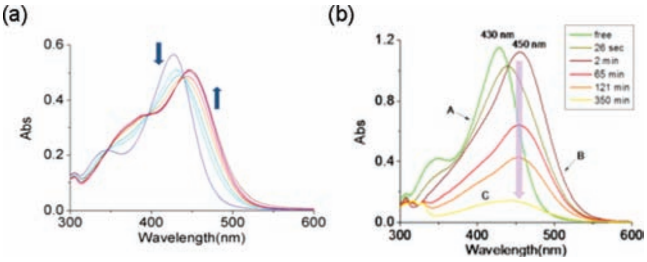

**Figure 4.** (a) UV−vis spectral change when the receptor **4** ($3.07 \times 10^{-5}$ M) is subject to titration with fluoride anion (as the tetrabutylammonium salt) in $CH_3CN$ (3% DMSO). (b) Time dependent, UV−vis spectral changes for receptor **4** ($3.92 \times 10^{-5}$ M in $CH_3CN$/3% DMSO) upon addition of the cyanide anion ($[CN^-] = 7.82 \times 10^{-4}$ M). A: free host **4**, B: cyanide complex, C: cyanide adduct.

**Table 1.** Association Constants ($M^{-1}$) Obtained from UV−vis Spectroscopic Titrations and ITC Analyses of Receptors **4** and **5** and Various Anions[a]

| | **4** | | **5** | |
|---|---|---|---|---|
| | UV−vis | ITC | UV−vis | ITC |
| $F^-$ | $1.25 \times 10^6$ | $8.48 \times 10^5$ | $1.44 \times 10^6$ | N.D. |
| $Cl^-$ | $3.88 \times 10^5$ | $7.64 \times 10^5$ | $4.42 \times 10^5$ | $5.85 \times 10^5$ |
| $Br^-$ | $2.74 \times 10^2$ | $2.42 \times 10^2$ | $2.55 \times 10^2$ | $4.19 \times 10^2$ |
| $AcO^-$ | $4.07 \times 10^4$ | $4.58 \times 10^4$ | $2.95 \times 10^5$ | $1.59 \times 10^5$ |
| $H_2PO_4^-$ | $2.26 \times 10^3$ | N.D. | $2.60 \times 10^3$ | N.D. |
| $HP_2O_7^{3-}$ | $2.53 \times 10^6$ | N.D. | $2.45 \times 10^6$ | N.D. |

[a] Studied in the form of the corrsponding tetrabutylammonium salts, in 3% DMSO in $CH_3CN$ (v/v) at 25 °C. [**4**] = $3.07 \times 10^{-5}$ M (UV-vis), [**4**] = $4.86 \times 10^{-4}$ M (ITC), [**5**] = $3.62 \times 10^{-5}$ M (UV-vis), [**5**] = $3.62 \times 10^{-4}$ M (ITC). N.D. = not determined.

sort out this finding, we tentatively ascribe it to ion-pairing effects, which are expected to be subject to a concentration-dependent effect and hence exacerbated in the case of comparing measurements made at different concentrations (as in the case of ITC and UV−vis).

In contrast to what was observed for other anions, when receptor **4** (or **5**) was titrated with the cyanide anion, bleaching of the color was observed upon the addition of the cyanide anion. This bleaching process was found to be slow on the laboratory time scale. Further, the rate of bleaching was found to be dependent on the cyanide anion concentration.

As shown in Figure 4b, the initial spectral shift (from 430 to 450 nm) was observed in the presence of ~20 equiv of TBACN. This was followed by a loss in intensity of the resulting red-shifted absorption band. Since binding of anions to strapped calix[4]pyrroles is usually very fast on the laboratory time scale, the red-shift observed immediately after adding the cyanide anion is ascribed to such a complexation process. The slower bleaching is then thought to reflect nucleophilic addition of the cyanide anion to the vinyl subunit.

By analyzing the change in intensity of the latter feature as a function of time, a pseudo-first-order rate constant of $3.30 \times 10^{-4}\ s^{-1}$ could be calculated at $[CN^-] = 8.22 \times 10^{-4}$ M. This rate was considered reasonable for nucleophilic addition of the cyanide to the vinyl moiety. Consistent with such an interpretation, the pseudo-first-order rate constant for the cyanide-induced bleaching process was found to be virtually the same for the complex **4**·[$F^-$], formed by pretreating **4** with TBAF.

Evidence for initial binding of the cyanide anion within the receptor cavity in the absence of a competing anion comes from the observation that the addition of TBACN to **4** (or **5**) results in an upfield shift in the signals ascribed to the $\beta$-pyrrole protons. While not analyzed in a quantitative fashion, the fact that excess cyanide anion was required to effect these changes is consistent with the observation that the cyanide anion displays an affinity for simple strapped calix[4]pyrroles that is smaller than that seen for other test anions.

A critical finding made in the context of the present study is that the cyanide addition reaction is insensitive to the presence of other anions. For instance, in the case of **4**, the addition of 100 equiv of TBACN to a solution of the receptor (in 3% DMSO in acetonitrile (v/v), $4.10 \times 10^{-5}$ M) containing 100 equiv of $HP_2O_7^{3-}$, $F^-$, $H_2PO_4^-$, $AcO^-$, and $Cl^-$ gave rise to the same bleaching observed in the absence of these latter anions. We take this as further evidence that the cyanide anion interacts with these receptors via a mode that is very different from that of other anions, i.e., directed addition to the $\beta$-position of the 1,3-indanedione moiety.

Ideally, ratiometric sensors should work even in the presence of potential competing analytes. In the case of chemosensors for the cyanide anion, this means that producing a visible signal in mixtures containing of various other anions would be highly desirable, espceially since such species are expected to be present in samples taken from the field. In this regards, dual function receptors such as **4**−**5** that contain both a “classic” anion binding site and a separate, highly selective site of reactivity are particularly attractive.

In summary, we have demonstrated that strapped calix[4]-pyrroles bearing chromophores at the $\beta$-pyrrolic positions can act as dual functional, chemodosimetric sensors for the cyanide anion. The systems described here, compounds **4** and **5**, allow the cyanide anion to be detected selectively even when “hidden” within a mixture of other anions. This lack of competition from potential interferants is ascribed to the indandione-derived vinyl moiety that reacts selectively with the cyanide anion. This could make systems such as **4** and **5** useful as potential chemosensors for the detection of the cyanide anion under the exacting conditions relevant to use in the field.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for all compounds and single crystal X-ray data for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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