

1,3-Indane-Based Chromogenic Calixpyrroles with Push–Pull Chromophores: Synthesis and Anion Sensing

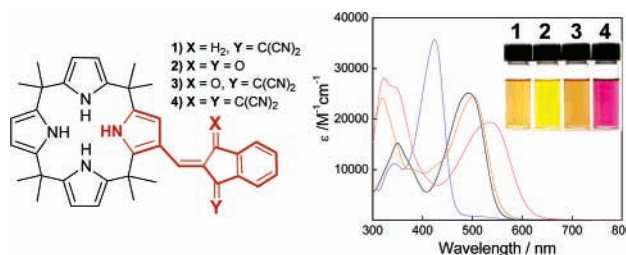
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ABSTRACT



Knoevenagel condensation of 2-formyl-octamethylcalix[4]pyrrole with selected 1,3-indanedione derivatives yields calix[4]pyrrole anion sensors with push–pull chromophores displaying strong intramolecular charge transfer. The push–pull feature results in augmented signal output as well as in dramatic changes in anion selectivity exemplified by a 50-fold increase in acetate vs chloride selectivity compared to the parent calix[4]pyrrole.

Anions play an important role in numerous biological processes and pathological events and are used as fertilizers and industrial raw materials, all of which necessitate the development of sensitive anion sensors.¹ Here, materials capable of reversible anion-induced changes in color are particularly attractive² as they require little or no instrumentation for practical use. Unfortunately, a few colorimetric anion sensors are able to differentiate selectively between anionic substrates of similar basicity and surface charge density or work in the presence of competing media such as water.² As part of the quest for simple yet reliable sensors with high substrate affinity and selectivity, new sensors are vigorously pursued.

A widely used approach to the synthesis of colorimetric anion sensors utilizes presynthesized chromophores (a sig-

naling unit) such as nitrophenyl,³ anthraquinone,⁴ and nitrobenzene azo groups⁵ and other electron-withdrawing moieties⁶ covalently attached to an anion receptor.^{2a}

In our recent efforts to develop chromogenic anion sensors for use in polyurethane sensor assays,^{6a} we realized the need for anion sensors with varying substrate selectivity and different colorimetric response patterns. Inspired by our sensor **1**, which showed dramatic changes in color in the presence of inorganic anions (Figures 4 and 5), we designed and synthesized sensors **2–4** utilizing indanone-ylidene malononitrile moieties (Figure 1) hoping that the highly

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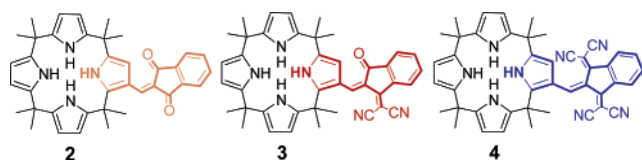
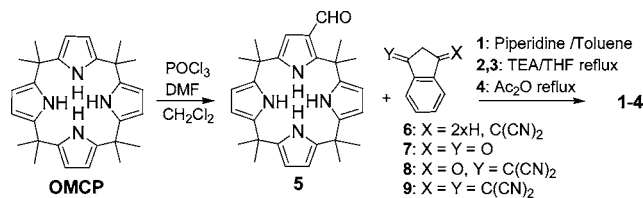


Figure 1. Structures of sensors 2–4 designed for tuning of anion affinity, selectivity, and also a degree of color response.

conjugated, push–pull chromophores would provide improved sensing performance (both binding and signaling) as well as insight into the photophysical and thermodynamic processes taking place in such materials.

All four sensors utilize octamethylcalix[4]pyrrole (OMCP) as an anion receptor⁷ as this material is easily synthesized by acid-catalyzed condensation of acetone and pyrrole and displays affinity for various anions, namely, halides, phosphates, and carboxylates.^{7b,c} Synthesis of 1–4 was performed in three steps according to Scheme 1. Although formyl-

Scheme 1. Synthesis of Sensors 1–4



OMCP 5 is known, its preparation via lithiation⁸ was found to be low yielding for practical applications. Thus, OMCP was converted to 5 by treatment with the Vilsmeier reagent in 44% yield. Compound 5 was then condensed with active methylene species previously used in the synthesis of push–pull chromophores.⁹ The push–pull nature of the chromophore serves here to amplify the signal process. Hence, the hydrogen bonding between an anion and the electron-rich pyrrole results in intramolecular charge transfer from pyrrole (push) to the electron-poor 1-indanylidene moiety, thus enhancing the color transitions (Figure 2). Also, the pyrrole NH becomes more acidic and more available for hydrogen

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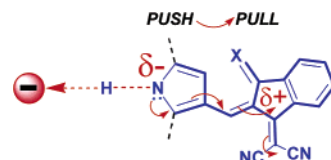


Figure 2. Anion–hydrogen bonding results in partial charge transfer from electron-rich pyrrole to electron-poor indanylidene.

bonding, which results in increased anion affinities. Potentially, the increased pyrrole NH acidity may result in pyrrole deprotonation but not binding. Here, by using ¹H NMR, we demonstrate that the anion binding is the prevalent process.

The Knoevenagel condensation with 1-indanylidene-malononitrile 6, 1,3-indanedione 7, 3-(dicyanomethylidene)-indan-1-one 8,^{10a} or 1,3-bis(dicyanomethylidene)indane 9^{10b} then gave sensors 1 (53%), 2 (52%), 3 (46%), and 4 (35%), respectively.

The X-ray structures of 1 and 2 (Figure 3) show that the 1-indanylidene moiety is coplanar with the attached methine bridge as well as the pyrrole, which supports the above theory of ketone/dicyanomethylidene benefitting from the internal charge-transfer process (Figure 2).

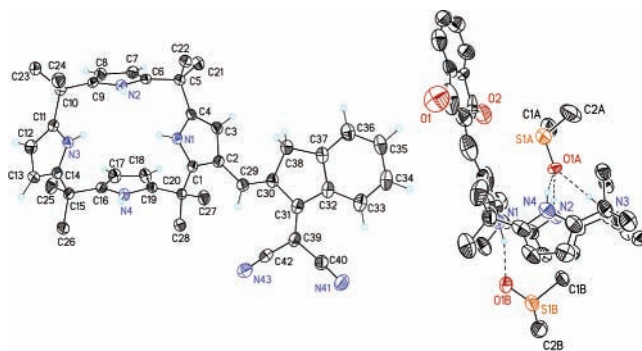


Figure 3. X-ray structures of sensors 1 (left) and 2 (2DMSO) (right) with an integrated calixpyrrole indan-1-ylidene chromophore.

Condensation of 5 with the indane precursors gave rise to a chromophore spanning a large part of the visible spectrum between 425 and 535 nm, showing yellow, orange, and pink color (Figure 4). Because of the 1:1 anion–sensor complex stoichiometry,² it is important that the color-defining maxima correspond to high extinction coefficients ($\epsilon \geq 20\,000\text{ L mol}^{-1}\text{ cm}^{-1}$), which allows for the observation of reasonably low anion concentrations (10–100 μM).

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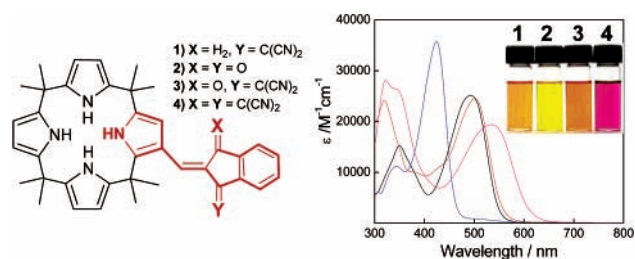


Figure 4. Structure and absorption spectra of sensors **1** (black line), **2** (blue line), **3** (orange line), and **4** (pink line) in CH_2Cl_2 ($50 \mu\text{M}$). Inset shows solutions.

Visual inspection of solutions of sensors **1–4** ($50 \mu\text{M}$ in CH_2Cl_2 or DMSO with 0.5% water) before and after the addition of anion salts¹¹ showed a dramatic change in color in the case of fluoride, acetate, and, to a lesser extent, dihydrogenphosphate, suggesting strong binding, whereas the addition of chloride, bromide, or nitrate resulted in weak or no changes in color (Figure 5). Quantitative absorption spectroscopy analyses essentially confirmed this trend.

The bathochromic shifts of spectra of sensors **1–4** upon the titration with anions (Figure 4, right panel) were used to calculate the binding constants (Table 1). The anion-mediated changes could be ascribed to a partial negative charge transfer in the anion–sensor complex.^{4b}

The anion binding studies revealed that all sensors **1–4** display augmented affinity toward anions compared to the parent OMCP. The order of anion affinities of sensors in the disubstituted indane series is $2 < 3 < 4$. **2–4** differ in the degree of ketone replacement by the dicyanomethylene moiety. The data in Table 1 indicate that the dicyanomethylene moiety in the chromophore enhances the binding ability of the receptor. This is presumably due to the electron-withdrawing nature of dicyanomethylene, which increases the acidity of the pyrrole NH proton. Interestingly, with increasing anion affinity in the series **2–4**, we also found that the relative sensor–anion selectivity changes. While the affinity for chloride increased ca. 5 times within the series **2–4**, the affinity for dihydrogen phosphate increased 35 times and that for acetate increased 390 times. These changes are expressed as ratios of binding constants ($K_{\text{AcO}^-}/K_{\text{Cl}^-}$) and ($K_{\text{AcO}^-}/K_{\text{H}_2\text{PO}_4^-}$) (Table 1). This is a remarkable change in substrate selectivity, particularly considering the remote location of the $\text{C}=\text{O}$ vs $\text{C}=\text{C}(\text{C}\equiv\text{N})_2$ effectors. The aspect of carboxylate–chloride selectivity is of crucial importance, as this feature may allow the sensing of carboxylate in the biological milieu such as blood plasma where chloride abounds in high concentrations.^{6a}

The increased acidity of pyrrole NH protons was also reflected by the chemical shifts of NH proton signals of sensors **2–4** in ^1H NMR. The chromophore–pyrrole NH proton signals in sensors **2–4** appeared at 7.36, 7.56, and

(11) Hydrated tetrabutylammonium (TBA) salts of the anions were used in this study: fluoride ($\times 6\text{H}_2\text{O}$), chloride, phosphate ($\times 2\text{H}_2\text{O}$), and pyrophosphate ($\times 2\text{H}_2\text{O}$). The degree of hydration was estimated from elemental analyses.

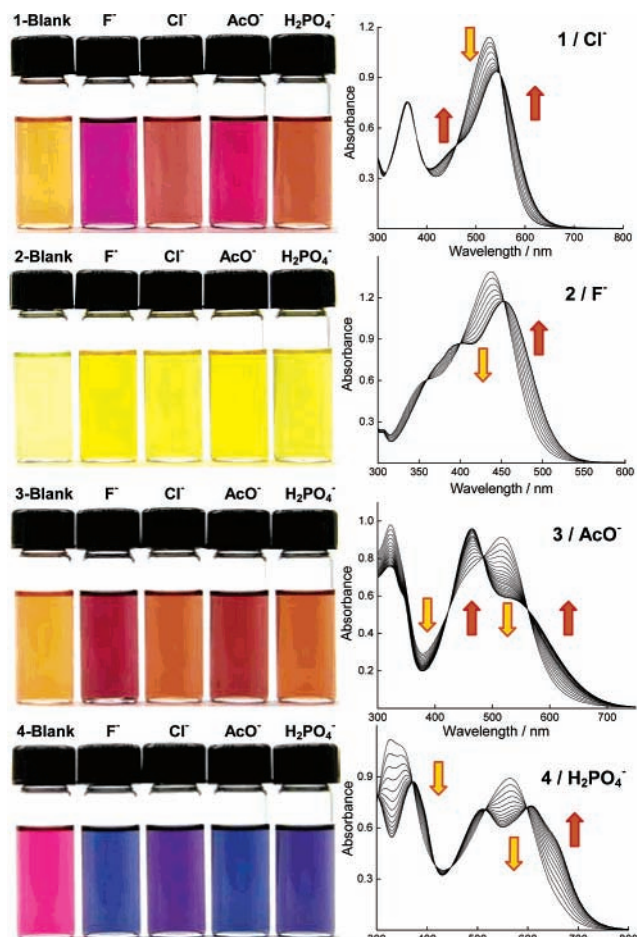


Figure 5. Left panel: solutions of sensors **1–4** ($50 \mu\text{M}$ in CH_2Cl_2) in the presence of anions (10 equiv excess). Right panel: examples of absorption spectroscopic titrations of sensors ($50 \mu\text{M}$ in DMSO) **1–4** (**1**/ Cl^- , **2**/ F^- , **3**/ AcO^- , and **4**/ H_2PO_4^-).

7.85 ppm in CDCl_3 , respectively (OMCP NH signals appeared at 7.01 ppm). The observed order in chemical shifts is consistent with the anion binding affinities observed for sensors **2–4**. We were concerned that the dramatic changes in color and the high binding constants might be caused by deprotonation of the acidic NH of the dye pyrrole rather than

Table 1. Affinity Constants (K_a)^a for OMCP, **2**, **3**, and **4** (M^{-1}) and Anionic Substrates in DMSO ($50 \mu\text{M}$, 0.5% Water at 22 °C)

anion	OMCP ^b	sensor 2	sensor 3	sensor 4
F^-	$> 10^4$	$> 10^6$	$> 10^6$	$> 10^6$
Cl^-	999	574	652	2840
AcO^-	6810	15700	125000	$> 10^6$
H_2PO_4^-	5670	4560	8050	160000
$K_{\text{AcO}^-}/K_{\text{Cl}^-}$	6.8	27	191	> 350
$K_{\text{AcO}^-}/K_{\text{H}_2\text{PO}_4^-}$	1.2	3.4	15.5	> 35

^a Determined from absorption spectroscopic titrations. Errors are $\pm 15\%$. 1:1 stoichiometry determined by Job plots. ^b Determined from ^1H NMR titrations. For isotherms and K_a calculations, see the Supporting Information.

by actual anion binding.^{3a,b,6,12} The ^1H NMR titrations, however, showed all four pyrrole NHs downfield shifted and split by interaction with the ^{19}F nucleus, a hallmark of strong binding (Figure 6).

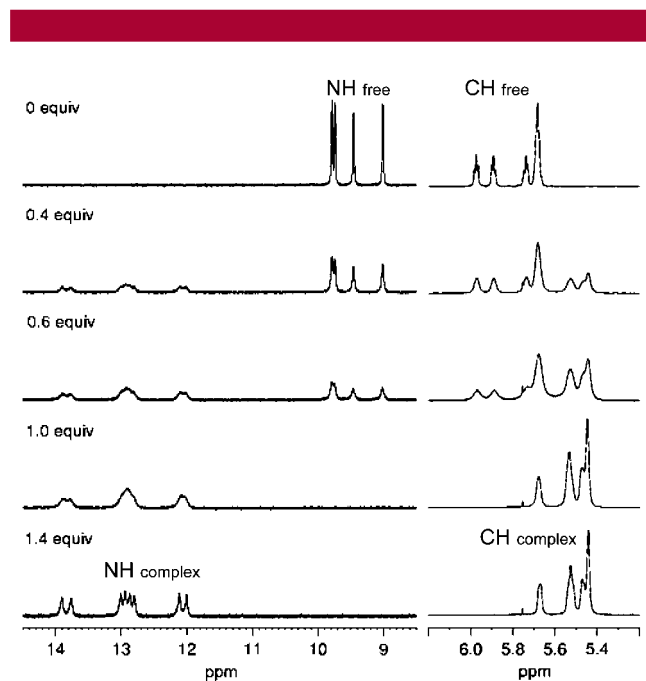


Figure 6. ^1H NMR spectra (selected regions) of sensor **2** (10 mM) in $\text{DMSO}-d_6$ titrated by fluoride. The NH and β -pyrrole CH proton resonances in free and complexed sensor **2** are labeled as follows: NH_{free} , CH_{free} , $\text{NH}_{\text{complex}}$, and $\text{CH}_{\text{complex}}$.

The issue of receptor deprotonation is, nevertheless, a complex one. At a very large excess of anions such as fluoride or acetate, a second event consistent with deprotonation is observed. For example, at 0–0.2 mM fluoride, sensor **3** shows only the effects corresponding to anion binding. Receptor deprotonation is then observed at a fluoride concentration between 0.2 and 0.7 mM (Figure 7). Hence, with sensors **1–4**, one can safely assume anion complexation is taking place at concentrations lower than 0.2 mM for all anion analytes tested.

The effective signaling, i.e., the sensitivity to anions as observed by a change in color, is attributed to the push–pull nature of the chromophore consisting of the electron-rich pyrrole connected to the electron-deficient indane moiety via a methine bridge. The interaction of an anion with pyrrole NH results in increased electron density on the pyrrole, from where it is distributed to the acceptor part of the chromophore, the indene ring. The higher number of dicyanomethylidene moieties on the “pull” end of the chromophore delivers a 2-fold benefit for the sensing process: First, it

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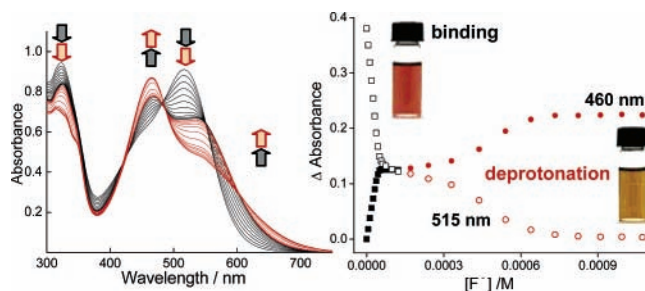


Figure 7. Absorption spectra of sensor **3** (50 μM in DMSO) titrated by fluoride. Absorption spectra (left) and binding isotherms derived from absorbance at 460 and 515 nm (right).

renders the pyrrole NHs more acidic and therefore more available for hydrogen bonding (while not being too acidic to undergo deprotonation). Second, the higher electronic density gradient between the “push” and “pull” moiety renders the intramolecular charge transfer responsible for the color change being more effective. This feature is obvious from Figure 5 which shows a yellow to deep yellow change in color for **2**, an orange to dark red color change for **3**, and a pink to blue color change for **4** when engaged in anion binding.

In summary, we have demonstrated not only that octamethylcalix[4]pyrrole-based anion sensors utilizing push–pull chromophores are good sensors but also that the push–pull feature may be used to tune sensor selectivity as well as the output signal. The depth of the color change was found to correspond to the degree of intramolecular charge transfer in the sensor chromophores. Sensors **1–4** show intensive color that changes in the presence of anions such as fluoride, acetate, and, to a lesser extent, phosphate. The sensors within the series show increasing affinity for anions and dramatically enhanced selectivity for acetate vs chloride (50 times compared to the parent OMCP). The increased anion affinity and carboxylate selectivity appear to be strongly augmented by the presence of the electron-withdrawing dicyanomethylidene moieties on the indane ring. We believe that the demonstrated changes in anion selectivity will be a welcome aid in the design of new sensors for selective binding and sensing of substrates of interest.

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Supporting Information Available: Experimental procedures and spectroscopic data for sensors **1–4**, UV–vis titration data, and Job plots. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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