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Naked-Eye Detection of Anions in Dichloromethane: Colorimetric Anion Sensors Based on Calix[4]pyrrole**

Hidekazu Miyaji, Wataru Sato, and Jonathan L. Sessler*

The development of chemosensors for specific chemical species is emerging as a research area of considerable importance within the generalized field of supramolecular chemistry.[1] One of the more appealing approaches in this context involves the construction of optical sensors.[2–6] Such systems generally contain some combination of substrate-recognition functionality (receptor) and optical-signaling capacity (chromophore), either directly linked[2, 3, 5] or appropriately associated in a noncovalent manner,[4] and are designed to permit the detection of substrates by binding-induced changes in absorption or emission properties (termed colorimetric and fluorescent sensors, respectively). While the utility of these approaches are becoming increasingly appreciated in terms of both qualitative and quantitative analysis,[5] the number of colorimetric sensors available at present for anionic substrates remains quite limited.[6] Indeed, only a few systems are known that undergo color changes of sufficient magnitude that they can be used for the direct "naked-eye" sensing of anions.[4b, 6b, c] Here we report the synthesis of a new class of covalently linked calix[4]pyrrole–anthraquinone conjugates and show that they act as powerful naked-eye sensors for selected anions (namely, F^-, Cl^-, $H_2PO_4^-$) in dichloromethane.

The calix[4]pyrroles,[7] colorless macrocycles rich in pyrrole NH hydrogen bond donor functionality, are an easy-to-make class of uncharged anion receptors that show considerable promise in the area of anion sensing. In previous work we demonstrated that anion sensors could be generated from calix[4]pyrroles either by attaching a fluorescent reporter group to the basic tetrapyrrolic skeleton[7d] or through the use of a displacement process involving competition with *para*-nitrophenolate anions.[4b] Unfortunately, we were unable to produce inherently colored calix[4]pyrrole derivatives that functioned as naked-eye anion sensors. Recently, however, we discovered that calix[4]pyrroles functionalized at the β-pyrrolic positions[8] may be made using a modified Sonogashira coupling procedure.[9] By taking advantage of this approach as well as the current availability of the ethynyl-substituted calix[4]pyrrole **1**,[8] we have now succeeded in preparing (in 73% yield) an anthraquinone-functionalized system (**2**) that bears an appended chromophore directly

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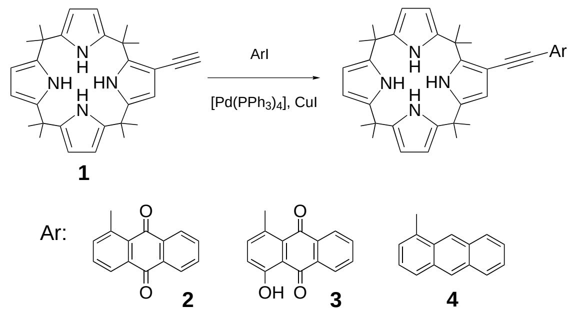
linked to the calix[4]pyrrole skeleton through a conjugating C–C triple bond (Scheme 1).[10]



Scheme 1.

The choice of anthraquinone as the chromophore reflected the thinking that it would act as an optically sensitive indicator of anion binding; being electron deficient, it could serve as a "sink" for vectorial charge-transfer processes involving bound anionic guests. The possibility of "color tuning" was also appreciated. Specifically, it was recognized that by using a modified anthraquinone molecule it might be possible to generate naked-eye anion sensors whose spectral characteristics differ from those of **2**. Accordingly, the hydroxyanthraquinone system **3** was also prepared (82% yield), as was the anthracene-containing control compound **4** (69% yield). In all cases, the necessary precursors, 1-iodoanthraquinone,[11] 1-iodo-4-hydroxyanthraquinone,[12] and 1-iodoanthracene,[13] were obtained readily using literature procedures.

Figure 1 shows the changes in the absorption spectrum of receptor **2** (recorded in dichloromethane at a concentration of 5×10^{-5} M) observed upon the addition of tetrabutylammonium fluoride. In the absence of anions, the spectrum of compound **2** is characterized by the presence of two peaks at $\lambda_{max} = 357$ and 467 nm. Compared to anthraquinone itself ($\lambda_{max} = 327$ nm[14]) the position of this latter, longer wavelength absorption feature is red-shifted to the point where it appears in the visible region. This shifting, which has the effect of making compound **2** yellow, is ascribed to the presence of an extended π-conjugation network involving the anthraquinone moiety, the acetylene linker, and the pyrrole to which it is bound.

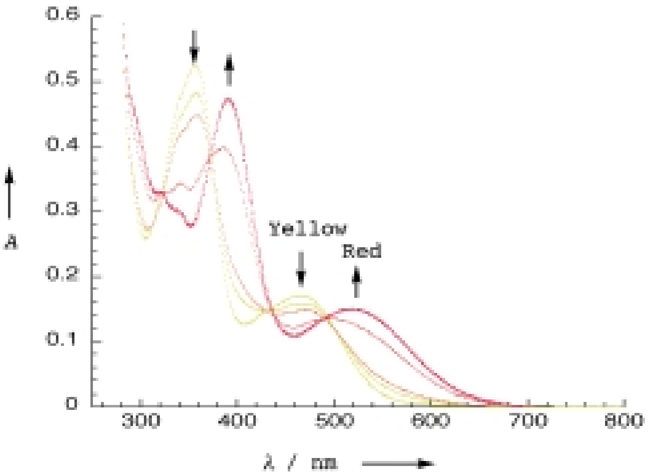


Figure 1. Absorption spectra of **2** recorded in CH_2Cl_2 (5.0×10^{-5} M) after the addition of 0, 1, 2, 4, 6, 8, and 10 equivalents of tetrabutylammonium fluoride.

As can be seen by inspection of Figure 1, upon the addition of fluoride anion, the peak at 467 nm decreases while a new peak appears at 518 nm. These changes, complete after the addition of only six equivalents of F^- ions, have the effect of changing the color of the solution from yellow to red (Figure 2).[15] The addition of either chloride or phosphate ions induced a color change that was less dramatic (that is, from yellow to reddish-orange) and required greater amounts of anion to effect a commensurate change (the absorption peak, originally at 467 nm, shifts to 501 and 497 nm upon the addition of 100 equivalents of tetrabutylammonium chloride and phosphate, respectively).[15] On the other hand, exposure to bromide, iodide, and sulfate anions, species that do not bind to calix[4]pyrroles appreciably,[7a] did not lead to any noticeable change in color (Figure 2).[15] This dramatic combination of anion-specific response/nonresponse makes this system an effective naked-eye-detectable anion sensor under these solution-phase conditions.

Figure 2. Color changes of **2** in CH_2Cl_2 (5.0×10^{-5} M) before and after the addition of 100 equivalents of representative anions (From left to right: **2**; **2** + F^-; **2** + Cl^-; **2** + Br^-; **2** + I^-; **2** + $H_2PO_4^-$; **2** + HSO_4^-).

Figure 3, which shows the color changes (if any) induced upon the addition of 100 equivalents of various anions to dilute (5×10^{-5} M) solutions of **3** in dichloromethane, serves to illustrate that the "color tuning" proposed for this system was indeed observed by experiment. Specifically, this particular calix[4]pyrrole derivative changes color from red to blue or purple upon the addition of anions, again with the effect being most dramatic and most pronounced in the case of fluoride ions.

Figure 3. Color changes of **3** in CH_2Cl_2 (5.0×10^{-5} M) before and after the addition of 100 equivalents of representative anions (From left to right: **3**; **3** + F^-; **3** – Cl^-; **3** + Br^-; **3** + I^-; **3** + $H_2PO_4^-$; **3** + HSO_4^-).

The above qualitative changes are reflected in more quantifiable terms in the corresponding absorption spectra

(Figure 4). Whereas 4-hydroxyanthraquinone itself is pale yellow and displays an absorption maximum at 405 nm in dichloromethane,[14] conjugation to calix[4]pyrrole through an alkyne spacer shifts the absorption maximum to the red region of the spectrum and produces a species with a lowest energy absorption maximum at 526 nm. Upon the addition of fluoride ions, the absorption maximum is shifted even further (to 613 nm) with the net result that the solution turns blue (approximately 20 equivalents are generally sufficient to effect near-complete color conversion). Similar, but less pronounced bathochromic shifts are seen upon the addition of excess chloride and dihydrogen phosphate ions, with the lowest energy maxima being observed at 567 and 549 nm, respectively. In these cases the colors of the solution change from red to purple and from red to dark purple, respectively. On the other hand, no significant color changes were observed upon the addition of bromide, iodide, or sulfate ions. These spectral results, as well as the corresponding visual changes, are thus completely consistent with the association constants recorded for **3**, namely $F^- > Cl^- > H_2PO_4^- \gg Br^- \sim I^- \sim HSO_4^-$.[15]

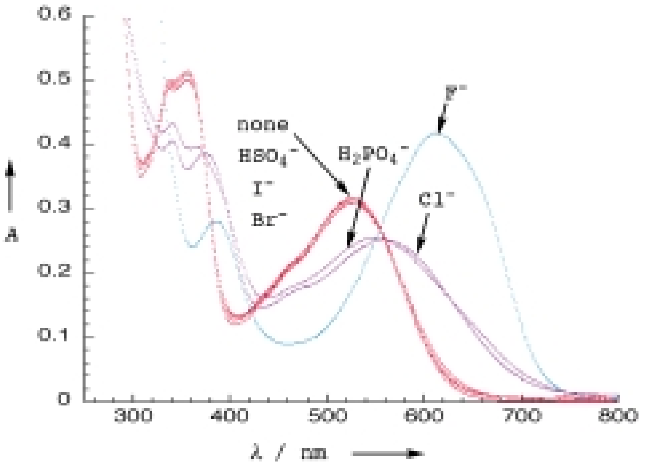


Figure 4. Absorption spectra of **3** recorded in CH_2Cl_2 (5.0×10^{-5} M) after the addition of 100 equivalents of representative anions.

While the origins of the dramatic color changes observed with chemosensors **2** and **3**, tentatively ascribed to charge-transfer interactions between the electron-rich, calix[4]pyrrole-bound anions and the electron-deficient anthraquinone moieties, remain the subject of current study, it is important to note that the anthracene-containing control compound **4**, a calix[4]pyrrole system bearing a more electron-rich appendage, does not act as a true naked-eye-detectable anion sensor. In this instance, addition of 100 equivalents of tetrabutylammonium fluoride to a 5×10^{-5} M solution in CH_2Cl_2 engendered only a slight bathochromic shift in the absorption maximum (λ_{max} shifts from 408 to 416 nm) along with a modest reduction in absorption intensity. Detailed ^1H NMR spectroscopic and fluorescence analyses revealed, however, that **4** nonetheless acts as an efficient receptor for F^-, Cl^-, and $H_2PO_4^-$ ions under these conditions.

The need for effective anion binding (as well as an appended chromophore) was supported by control studies carried out using unsubstituted anthraquinone. Even in the presence of a vast excess of tetrabutylammonium fluoride, no change in either the position or intensity of the absorption maximum at 327 nm was seen in dichloromethane. This finding is thus consistent with the earlier observations that even such electron-rich anions as bromide and iodide do not modify the color of sensors **2** or **3**; they are simply not bound to any appreciable extent in dichloromethane.

In conclusion, we have succeeded in preparing a new class of anion sensors that not only allow for the facile colorimetric detection of F^-, Cl^-, and $H_2PO_4^-$ ions but which are also amenable to "color tuning". To the best of our knowledge these systems are the first naked-eye-detectable chemosensors that permit discrimination between different anionic substrates as the result of disparate changes in color. Such systems are likely to be of particular benefit in situations where sophisticated instrumentation might be lacking (for example, in field tests). They could also prove useful in the development of multianalyte sensor arrays,[16] wherein a nonbinary signaling response is advantageous and apolar binding conditions often pertain.

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Photoacid-Induced Fluorescence Quenching: A New Strategy for Fluorescent Imaging in Polymer Films**

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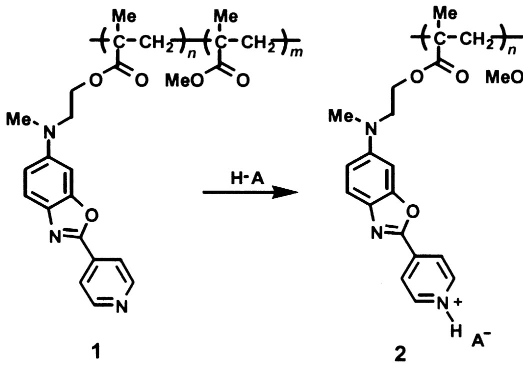
The generation of patterned images in polymer films has gained much attention in fundamental and applied research areas. The development of patterned functional images is also of great importance in the electronics industry. Recently, the generation of functional images by selective immobilization of organic dyes in polymer films has been reported.[1–3] The selective removal of labile acidic protecting groups by photo-induced chemical transformation followed by chemisorption of organic dyes from solution into the patterned polymer film afforded µm-scale functional images. Recently, we described finely resolved patterned fluorescent images with these transiently protected precursor molecules.[4, 5] As part of our efforts to produce functional images in polymer films we now report the synthesis of the novel copolymer **1**, which has pendant pyridylbenzoxazole groups, and its use in the generation of fluorescent images by photolithographic methods.



1 **2**

The strategy for the design of a molecule for fluorescent imaging is based on the following facts: in a conjugated aromatic system, the nature of fluorescence is often greatly affected by substituents. A strong fluorescence is, in general, observed when an aromatic compound has extended π conjugation and contains electron-donor substituents, such as hydroxy or amino groups, at both ends of this conjugated system. The fluorescence of the molecule, however, drastically decreases if one of the electron-donating substituents is replaced by an electron-withdrawing substituent, such as a nitro group. An electron-withdrawing effect, leading to fluorescence quenching, can also be induced when the fluorescent chromophore has a functional group which can interact with an acid. We have now designed the copolymer **1**, which has fluorescent pyridylbenzoxazole moieties as pendant groups. The benzoxazole chromophore of **1** has an electron-donating amino group at one end and an electron-rich pyridyl group at the other. However, the strongly fluorescent nature of **1** is expected to be affected when the electronic state of the benzoxazole chromophore is disturbed by interaction with an acid, as in **2**. If the acid-induced fluorescence quenching is significant, and occurs only in selected areas, then patterned fluorescent images will be obtained.

The preparation of the pyridylbenzoxazole monomer **8** is shown in Scheme 1. In general, benzoxazole derivatives are prepared by a prior formation of an *o*-hydroxy amide through the condensation of *o*-aminophenol with an acid chloride at low temperature, followed by thermal cycloaddition at high temperature.[6] In this cyclization step unwanted side reactions often occur. To avoid these we have developed a reaction with mild conditions for the formation of the benzoxazole ring. Thus, protection of the hydroxy group of 5-fluoro-2-nitrophenol (**3**) followed by aromatic substitution with (2-methylamino)ethanol provided the alcohol **5** in good yield, which was converted to pyridylbenzoxazole **7** in three steps. The removal of the protecting group and reduction of the nitro group by hydrogenation followed by treatment with 4-pyridinecarboxaldehyde gave the imine intermediate **6**. The oxidative cyclization of **6** with lead(IV) acetate, at room temperature, provided the benzoxazole chromophore **7** in high yield (80 % from **5**). Purification after the deprotection, imine formation, and cyclization steps was not necessary. The pyridylbenzoxazole **7** was converted into the desired monomer **8** (4PBZMA) by treatment with methacryloyl chloride.

Copolymerization of the monomer **8** with methyl methacrylate (MMA) was carried out with a 1:1 molar feed ratio in

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