Dipyrrolylquinoxalines: Efficient Sensors for Fluoride Anion in Organic Solution

Christopher B. Black, Bruno Andrioletti, Andrew C. Try, Cristina Ruiperez, and Jonathan L. Sessler*

Department of Chemistry and Biochemistry
The University of Texas at Austin
Austin, Texas 78712-1167

Received July 21, 1999
Revised Manuscript Received September 16, 1999

In recent decades, supramolecular chemists have devoted considerable effort to developing systems capable of recognizing, sensing, and transporting negatively charged species.[1] Among the range of biologically important anions, fluoride is of particular interest due to its established role in preventing dental caries.[2] Fluoride anion is also being explored extensively as a treatment for osteoporosis[3,4] and, on a less salubrious level, can lead to fluorosis,[5−7] a type of fluoride toxicity that generally manifests itself clinically in terms of increasing bone density. This diversity of function, both beneficial and otherwise, makes the problem of fluoride anion detection one of considerable current interest. While traditional methods of fluoride anion analysis such as ion selective electrodes and ^{19}F NMR spectroscopy remain important, there is mounting incentive to find alternative means of analysis, including those based on the use of specific chemosensors.[8] Particularly useful would be systems that can recognize fluoride anion in solution and signal its presence via an easy-to-detect optical signature.

In the past few years, we and others have proposed a wide range of anion sensors (sapphyrins,[9] calixpyrroles,[10,11] polyamines,[12−15] guanidinium,[16,17] etc.) that present varying degrees of affinity (and selectivity) toward anions such as F^-, Cl^-, $H_2PO_4^-$, and carboxylates. Unfortunately, and despite considerable effort, a need for good anion sensors remains. This is particularly true in the case of fluoride anion where few, if any, easy-to-use signaling agents exist.[18] Our recent experience with polypyrrole-based anion binding agents led us to consider that pyrrolic systems containing a built-in chromophore might give rise to useful anion sensors.

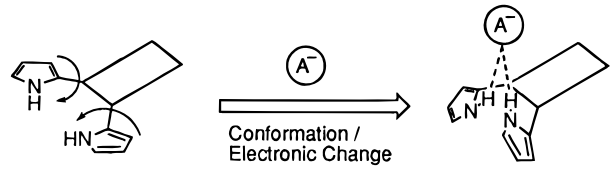
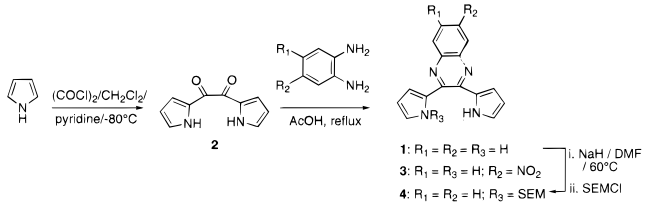


Figure 1. Proposed mode of anion binding and sensing. Recognition of, for instance, fluoride anion, is expected to perturb the orbital overlap between the pyrrole and quinoxaline subunits, thereby changing the optical characteristics of the latter.

Scheme 1



Our current investigations utilize the easy-to-prepare 2,3-dipyrrol-2′-ylquinoxaline **1**. While known in the literature since 1911,[19] to the best of our knowledge, this particular entity has never been considered as being a possible colorimetric anion sensor. It contains two pyrrole NH groups that could function as anion binding moeities and a built-in quinoxaline ring that might serve as a colorimetric reporter of any binding events. As illustrated in Figure 1, this putative sensing system is expected to operate through a combination of electronic and conformational effects.

The preparation of **1** involves condensing oxalyl chloride with pyrrole at −80 °C as described first by Oddo[19] and later refined by Behr.[20] Subsequent reaction between the resulting 2,3-dipyrrol-2′-ylethanedione **2** with *o*-phenylenediamine in acetic acid at reflux leads to 2,3-dipyrrol-2′-ylquinoxaline **1** in excellent yield (Scheme 1). By modifying this procedure and using other 1,2-diaminobenzenes, a wide range of 2,3-dipyrrol-2′-ylquinoxaline derivatives, possessing various electron-withdrawing or -donating groups, may, in principle, be prepared. In this paper we describe the synthesis of 2,3-dipyrrol-2′-yl-6-nitroquinoxaline **3** and the anion binding properties of it, its "parent" **1**, and the control systems, quinoxaline, 2,3-dipyrrol-2′-ylethanedione **2**, and the monotrimethylsilylethoxymethyl (SEM)-protected species **4**.

The ability of the dipyrrole systems **1** and **3** to coordinate to F^-, Cl^-, and $H_2PO_4^-$ (as tetrabutylammonium salts) was inves-

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(21) UV/vis titrations: All stock solutions were prepared in dichloromethane. Spectra were collected on a Beckman DU-640 UV/vis spectrophotometer. Since **2** does not fluoresce significantly, yet maintains a relatively large extinction coefficient, anion binding titrations were carried out by monitoring changes in the UV band at 341 nm as a function of added anion concentration. The resulting decrease in intensity was fit using eq 1, as described by Connors.[23]

$$\Delta A/b = (Q_t K \Delta\epsilon[L])/(1 + K[L]) \quad (1)$$

Here, ΔA refers to the change in absorbance from the initial value, Q_t is the total concentration of **1**, K is the binding constant, $\Delta\epsilon$ is the change in extinction coefficient between the bound and unbound species, and L is the concentration of anion titrated.

10.1021/ja992579a CCC: $18.00
Published on Web 10/23/1999

Table 1. Anion Binding Constants (K_a) for Compounds **1**−**4**[a]

	1[b]	**3**	**4**	**2**[c]
F^-	18200 M^{-1}	118000 M^{-1}	120 M^{-1}	23000 M^{-1}
$H_2PO_4^-$	60 M^{-1}	80 M^{-1}	<50 M^{-1}	170 M^{-1}
Cl^-	50 M^{-1}	65 M^{-1}	<50 M^{-1}	<50 M^{-1}

[a] All errors are ±10%. All binding constants are reported as the average of 2−4 trials. [b] Binding constants determined by fluorescence quenching: For **1** λ_{max}(ex) = 412 nm, λ_{max}(em) = 490 nm; for **2** λ_{max}(ex) = 341 nm, λ_{max}(em) = 458 nm; for **3** λ_{max}(ex) = 450 nm, λ_{max}(em) = 600 nm; for **4** λ_{max}(ex) = 396 nm, λ_{max}(em) = 492 nm; Scan rate = 240 nm/min, emission slit width = 5 μm, excitation slit width = 5 μm. [c] Binding constants were determined from UV−vis absorbance titration measurements monitoring the spectral change occurring at 341 nm.

Figure 2. Color changes (if any) induced by he addition of anions. From left to right (dichloromethane solutions): **1**; **1** + Cl^-; **1** + F^-; **3**; **3** + Cl^-; **3** + F^-. All anions were used in the form of their tetrabutylammonium salts.

tigated using UV−visible absorption[21] and fluorescence emission[22] methods. The latter studies, which provided K_a values, were complemented by molar ratio analyses;[22] here, data consistent with a proposed 1:1 binding stoichiometry were obtained in each case. As summarized in Table 1, the compounds function as anion receptors. In fact, compound **3** undergoes a very dramatic yellow to purple fluoride anion-induced color change, as illustrated in Figure 2. Both systems also display fluorescence emission spectra that are to all extents and purposes quenched in the presence of F^- (cf. Supporting Information). The observed color changes also take place in DMSO. However, in both dichloromethane and DMSO the changes are reversed upon addition of water. Presumably this is because water competes for F^- at the pyrrolic NH hydrogen bond donating sites.

(22) Fluorescence titrations were carried out by adding stock dichloromethane solutions of the anions in question (as tetrabutylammonium salts) to solutions of the receptors in dichloromethane. Emission spectra were collected on a Perkin-Elmer LS-5. The fluorescence signal was measured as the area of the emission intensity between 420 and 750 nm. Fitting was carried out using eq 2, as described by Connors.[23]

$$F/F_o = (1 + (k_f/k_s)K[L])/(1 + K[L]) \quad (2)$$

Here, F refers to the fluorescence intensity, F_o is the fluorescence of the receptor in question, k_f is proportionality constant of the bound complex, k_s is the proportionality constant of the receptor, and K is the anion binding constant.

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(24) Compared to **1**, **3**, and **4**, system **2** shows a relatively high (but still low absolute) affinity for inorganic phosphate. We speculate that the two carbonyl groups present in **2** may be involved in binding, stabilizing the complex via ancillary hydrogen bonding interactions involving the two HOP-phosphate protons.

The greater "success" of **3** relative to **1** is not really surprising considering that the greater electron deficiency of the mononitro derivative should lead to an increase in its hydrogen bond-donating character. Indeed, **3** displays an affinity constant (K_a) for F^- in dichloromethane (~1.2×10^5 M^{-1}), that is quite high compared to **1** ($K_a = 2 \times 10^4$ M^{-1}). Sensor **3** also shows a remarkable selectivity for fluoride anion ($K_aF/K_aCl > 1800$; $K_aF/K_aH_2PO_4^- > 1400$). Further evidence that compounds **1**−**3** bind fluoride anion in dichloromethane solution came from chemical ionization mass spectrometric analyses which revealed that in addition to the peaks corresponding to the anion-free receptors, unique peaks corresponding to the mono-TBAF adducts could be observed at *m*/*z* 521, 450, and 565 in the case of **1**, **2**, and **3**, respectively.

As a test of our proposed model of binding/sensing, the interaction of various anions with the three control system, namely quinoxaline, the mono-SEM-protected species **4,** and 2,3-dipyrrol-2′-ylethanedione **2** was investigated. The first of these, quinoxaline itself, is fluorescent but only faintly colored (i.e., it possess a low extinction coefficient for absorption in the visible spectral region). It also lacks the pyrrole NH hydrogen bonding donor functionality and displays no discernible changes in either its absorption or emission spectra in the presence of F^-, Cl^-, or $H_2PO_4^-$. The mono-SEM-protected systems **4** contains a fluorescent quinoxaline subunit. However, it too lacks a full complement of NH hydrogen bonding donor functionality and, like quinoxaline, displays little in the way of optical or spectroscopic changes when exposed to fluoride anion, even in a large excess (cf. Table 1). In contrast to the first two controls, diketone **2** displays a relatively large extinction coefficient but does not fluoresce. It is brightly colored in dichloromethane solution and, like **1**, undergoes a naked-eye detectable change in color, from yellow-green to orange, in the presence of F^-.[24] However, the lack of fluorescence displayed by this system leads us to suggest that the dipyrryldiones such as **2** are likely to be less useful as anion sensors than their quinoxaline-containing congeners such as **1** or **3**.

In conclusion, 2,3-dipyrrol-2′-ylquinoxalines provide a simple, hitherto unexplored class of anion receptors that, at least in dichloromethane and DMSO solution, allow for the detection of fluoride anion under both visual (i.e., naked-eye) and fluorescence emission conditions. Accordingly, it is possible to conceive the use of these systems in various sensing applications as well as in other situations, such as anion transport and purification, where the availability of cheap and easy-to-make anion receptors would be advantageous. We are currently exploring these possibilities and working to prepare more elaborate systems, including macrocyclic products that incorporate dipyrrylquinoxaline moieties.

Acknowledgment. Support for this work from the National Institutes of Health (Grant No. GM 58907 to J.L.S.), the National Science Foundation (CHE-9725399 to J.L.S.), the Texas ARP (Grant 003658-102 to J.L.S.) and an NIH Postdoctoral Fellowship to C.B.B. is gratefully acknowledged.

Supporting Information Available: Experimental details describing the syntheses of compounds **1**−**4**, UV−vis spectra of compounds **1** and **3** both free and in the presence of excess tetrabutylammonium fluoride, and fluorescence spectra of compounds **1** and **3** in the presence of F^-, Cl^-, and $H_2PO_4^-$ (as their tetrabutylammonium salts), and the ^1H NMR spectra from a titration experiment in which a tetrabutylammonium flouride is added to a DMSO-d_6 solution 6,7-dintro analogue of **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992579A