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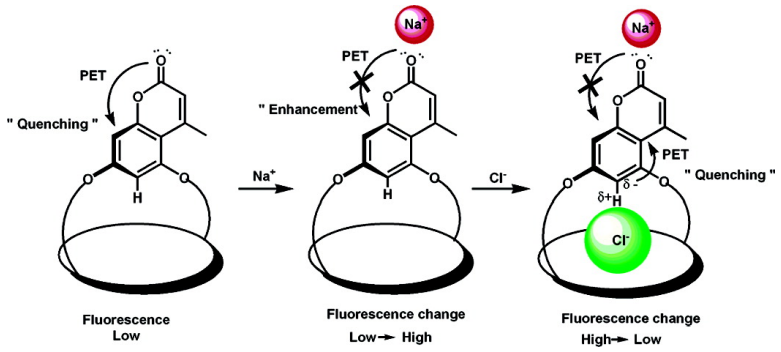

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Coumarin-Strapped Calix[4]pyrrole: A Fluorogenic Anion Receptor Modulated by Cation and Anion Binding

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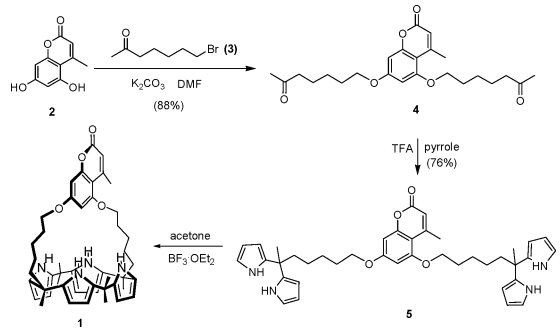
Receptors[1] and sensors[2] having strong affinity and selectivity for specific anions are a subject of great interest in supramolecular chemistry.[3] Among the various neutral receptor systems known, calix[4]pyrroles[4] have attracted particular attention because they display high affinity to halide anions. Size selectivity of strapped calixpyrroles toward anions has been demonstrated recently.[5] Introduction of diametrical bridging on one face of the calix[4]-pyrrole macrocycle also provides a convenient means of introducing functionalized groups at or near the binding domain. To date, several tunable systems have been reported.[5] However, more elaborate systems containing built-in chromogenic reporter groups have not hitherto been reported. Such systems would be potentially useful since they might allow the detection of analytes via direct optical or spectroscopic means.[6]

With these considerations in mind, we have prepared the strapped calix[4]pyrrole **1**, which contains a coumarin moiety as a potential fluorophore near the binding domian. This system was found to function as an INH logic gate,[7] wherein changes in cation and anion concentration serve as the input[8] and fluorescence intensity changes as the output. As shown in Scheme 1, the synthesis of target system **1** involves the reaction of 6-bromo-2-hexanone **3**[9] with 5,7-dihydroxy-4-methylcoumarin **2**. The resulting bisketone **4** was then condensed with pyrrole to afford dipyrromethane analogue **5**, which was successively condensed with acetone in the presence of a catalytic amount of $BF_3 \cdot Et_2O$ to afford receptor **1** in 14% yield. Preliminary fluorometric titration of **1** with various anions (studied in the form of their corresponding tetrabutylammonium salts) in dry acetonitrile[10] revealed behavior that was somewhat different from that of previous systems bearing fluorophores linked through a single bond.[6] For instance, no significant quenching of the fluorescence was observed when anions were added to dilute solutions of **1** in acetonitrile. On the other hand, the fluorescence intensity of **1** could be controlled by two different methods, i.e., "input parameters". In particular, upon the addition of water, an enhancement in the fluorescence intensity was observed that could then be reduced back to the original level via the subsequent addition of anions. As implied above, controlling the fluorescence intensity could be accomplished by addition of water. Indeed, the addition of water to an acetonitrile solution of **1** (1.0×10^{-6} M) causes the intensity of the fluorescence emission maximum at 396 nm to increase in a concentration-dependent manner (I/I_0) as the amount of water is increased to 3% (v/v) (see Supporting Information).

The above enhancement could be effectively "reversed" via the addition of anions. The ratio of the fluorescence intensity was found to be noticeably decreased upon the addition of only 1 equiv of TBACl. Further addition of TBACl served to effect a further

Scheme 1



decrease in the intensity. However, no fluorescence enhancement (or quenching) was observed in the absence of water. Although not a proof, these results are easily interpreted in terms of hydrogen bonding interactions between water molecule(s) and the carbonyl function of the coumarin moiety, as well as, perhaps, the phenoxy group, interactions that prevent the expected photoinduced electron transfer (PET) quenching process.[11]

To provide support for this supposition, a sodium cation source, $NaPF_6$, was added to a solution of receptor **1** in dry acetonitrile (H_2O < 10 ppm). $NaPF_6$ was chosen as a potential cation source to minimize interactions between host molecule and anion (PF_6^-). The cation (Na^+) was expected to interact with the oxygen atoms present in the receptor **1**, thereby inhibiting the PET quenching process. The experimental findings were found to be in accord with such predictions. Specifically, the fluorescence intensity ratio at $\lambda_{max} = 396$ nm (I/I_0) for **1** (concentration = 1.0×10^{-6} M) was observed to increase from 1 to 1.39 upon the addition of excess $NaPF_6$ (6×10^{-2} M) as illustrated in Figure 1. When the same solution was treated with tetrabutylammonium chloride (TBACl), the fluorescence intensity, with its maximum at 396 nm, was found to decrease upon the addition of 1 molar equiv of this salt (I/I_0 going from 1.39 to 1.08). A further decrease in I/I_0 to a value of 1.00 was observed upon the addition of 3 molar equiv of TBACl. These results indicate that the fluorescence intensity can be controlled by the dual "input parameters" of cation and anion; the added cation (Na^+) "switches on" the signal, generating a high intensity state, whereas the anion (Cl^-) "switches off" the signal, producing a low intensity state. Such competing ($\pm$) signaling effects are, to the best of our knowledge, unprecedented in a discrete chemical sensor system.

Proton NMR spectroscopic studies were carried out in acetonitrile-d_3 at 298 K in an attempt to elucidate the binding modes present within the complexes. The ^{1}H NMR spectrum of **1** (0.01 M), recorded before and after addition of $NaPF_6$ (saturated solution; concentration $\sim 1 \times 10^{-1}$ M), revealed that the signals for the four pyrrole NH protons of **1** (originally appearing at 8.21 and 8.14 ppm)

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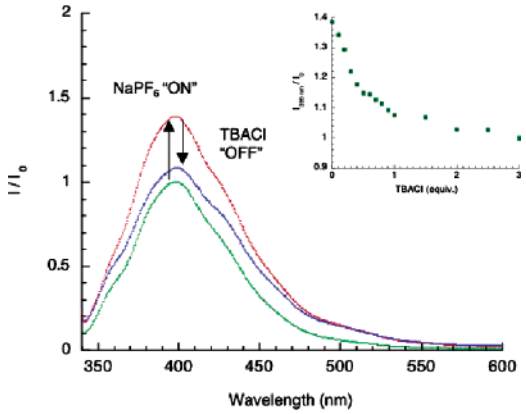

Figure 1. Fluorescence intensity changes of **1** before and after addition of excess $NaPF_6$ and further addition of 1 equiv of TBACl ([**1**] = 1.0×10^{-6} M in CH_3CN, λ_{ex} = 323 nm). Inset shows the intensity changes (in the presence of excess $NaPF_6$) at 396 nm that are seen upon the addition of TBACl.

were not shifted upon the addition of this salt. Since large downfield shifts are seen in the presence of anions, including fluoride, chloride, and carboxylates, this lack of guest-induced shifts in the spectrum is taken as an indication that no appreciable hydrogen bonding takes place between the calix[4]pyrrole and the PF_6^-. In other words, as implied above, this anion really is "innocent" as far as any putative molecular recognition events are concerned. Presumably, it resides outside the cavity generated by the strap, while the cation (Na^+), whose binding mode was not specifically determined, interacts with the coumarin moiety.

Very different ^{1}H NMR spectroscopic behavior is seen after the addition of 1 equivalent of TBACl to receptor **1** (1×10^{-2} M in acetonitrile-d_3). Now, completely new signals for the pyrrole NH appear at 11.12 and 11.07 ppm. This observation provides support for the notion that the chloride anion is strongly associated with **1** and resides inside the central cavity.[5]

In the presence of both cation (Na^+) and anion (Cl^-), the signals for the pyrrole NH protons appear at low field (δ = 11.08 and 11.03 ppm). This is consistent with the fact that the chloride anion resides within the cavity even in the presence of 10 equiv of Na^+. However, a small percentage of the anion does appear to be dissociated from **1** under these conditions (cf. Supporting Information). As might be expected, the inner aromatic coumarin proton (i.e., the one located between the two ether groups) was seen to shift to 7.04 ppm from its original position at 6.37 ppm upon the addition of 1 equiv of chloride anion, while those of the other coumarin protons remained almost unchanged. This large downfield shift is consistent with the presence of a hydrogen bonding interaction between this inner aromatic proton and the chloride anion. Even in the presence of excess Na^+, this presumed coumarin−chloride anion interaction was maintained. On the basis of these findings, we propose that the incipient developing negative charge (δ^-) within the aromatic coumarin system ($H^{\delta+}-C^{\delta-}$) is largely responsible for the observed PET-like, anion-induced quenching process.

Because of the strong association of receptor **1** with chloride, as well as bromide and acetate, which were also specifically tested, it was not possible to determine accurate association constants (K_a) using ^{1}H NMR titration methods. Thus, the association constants (K_a) for the interaction of **1** with these three representative anions (studied as their respective tetrabutylammonium salts) were determined from fluorescence titrations[12] carried out at much lower concentrations ([**1**] = 1.0×10^{-6} M) in dry acetonitrile containing excess $NaPF_6$. Fits to the data were made using a standard curve-fitting program (see Supporting Information). The resulting association constants K_a values are shown in Table 1, along with association constants (K_a) obtained from ITC measurements that were carried out in the same solvent but at higher concentrations ([**1**] = 1.0×10^{-4} to 1.0×10^{-3} M).[5,13] The K_a values obtained from these two different measurement methods were found to be in good agreement within experimental error.

Table 1. Association Constants (K_a) of **1** with Anions in 3% H_2O/CH_3CN, $NaPF_6/CH_3CN$, and CH_3CN at 298 K

	K_a (M^{-1})		
anion source	3% H_2O/CH_3CN[a]	$NaPF_6/CH_3CN$[a]	CH_3CN[b]
TBA-Cl	1.9×10^6	2.3×10^6	3.6×10^6
TBA-Br	3.7×10^4	1.0×10^5	1.1×10^5
TBA-CH_3CO_2	8.9×10^5	1.3×10^6	1.9×10^6

[a] Determined by fluorescence emission. [b] Determined by ITC; average of 3 determinations at 2 concentrations.

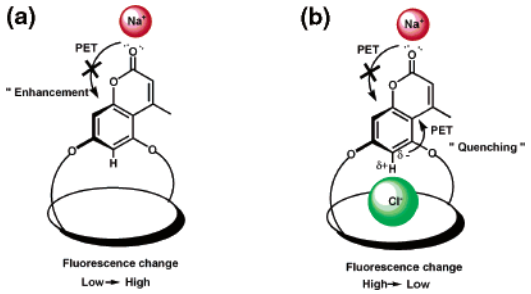

Figure 2. Schematic representation of the interactions of **1** with cation and anions. (a) Cation (Na^+) is thought to bind weakly to the oxygen lone pairs, which induces an enhancement in the fluorescence intensity. (b) The binding of an anion (Cl^-) activates a different PET mode and quenches the fluorescence signal.

The anion binding affinity of **1** in wet CH_3CN (3% v/v H_2O) was also studied by fluorescence titration, and again, the relevant K_a values are included in Table 1. As a general rule, the trend in K_a values was found to be $Cl^- > CH_3CO_2^- > Br^-$, with the magnitude of the values being a bit smaller than those of obtained in dry acetonitrile in the presence of $NaPF_6$. We interpret these results in terms of competing hydrogen bonding interactions between the water molecules and the pyrrole NH protons of receptor **1** that serve to weaken the association with anions. However, because of a greatly reduced electrostatic effect, the interaction between the pyrrole NH protons and the neutral species, water, is expected to be much smaller on a per mole basis than ones involving anions. Thus, even in 3% water the K_a values for anion binding remain appreciable.

Figure 2 shows the proposed binding modes for the complexation of cations and anions by **1**. In the presence of an excess of $NaPF_6$, it is suggested that the Na^+ cation binds weakly to the carbonyl group (and/or other oxygen functionality) present in the coumarin moiety. This presumed association of the Na^+ with an oxygen lone pair serves to prevent the PET quenching process and thus serves to change the fluorescence intensity level from Low to High in accord with the switching model proposed above. Once an anion is introduced under these latter conditions, the build-up of negative charge acts to modulate the electronic nature of the coumarin moiety, resulting in a change in fluorescence intensity from High to Low.

As a control experiment, excess $NaPF_6$ was added directly to a solution of coumarin in dry acetonitrile. In accord with what would be expected based on the findings described above, under these conditions the fluorescence intensity of unfunctionalized coumarin was found to increase in intensity.[14] By contrast, no fluorescence

Table 2. Truth Table of Logic Responses of Receptor 1

inputs		output
cation (Na^+)	anion (Cl^-)	fluorescence (λ_{max} = 396 nm)
0	0	Low
0	1	Low
1	0	High
1	1	Low

quenching was observed upon the addition of TBACl (up to 3 equiv). Furthermore, little effect on the fluorescence was seen when excess tetrabutylammonium hexafluorophosphate ($TBAPF_6$) was added to a solution of coumarin in dry acetonitrile. Similar findings were obtained when these control experiments were carried out in wet CH_3CN (3% D_2O). Taken in concert, these results provide support for the postulated notion that it is the Na^+ cation that causes the fluorescence enhancement in **1** (as well as coumarin itself) and that it is the pyrrole NH-bound anion that serves to induce the observed fluorescence quenching. On the basis of the above findings, we suggest that the coumarin-strapped calix[4]pyrrole **1** works as a molecular logic gate.[7,8]

Table 2 shows the truth diagram for the logic responses seen for **1**. Here, the disparate inputs of cation and anion are represented as "0" = "absence", "1" = "presence". The fluorescence output is only observed at its High level when (Cation, Anion) = (1, 0). In the case of (Cation, Anion) = (1, 1), the output changes to the corresponding Low level. In the case of (Cation, Anion) = (0, 0), the output is also at a Low level. The addition of only the anion (Cation, Anion) = (0, 1) maintains this latter Low level. As a consequence, these logic responses are best described in terms of an INH logic gate.

The effect of cations other than Na^+ was also examined. When KPF_6 was used instead of $NaPF_6$, the enhancement in fluorescence of **1** was found to be minimal ($I/I_0 = 1.11$). In contrast, when $LiPF_6$ was applied a strong enhancement was observed ($I/I_0 = 1.96$). These observations are consistent with the Li^+ cation binding to the coumarin carbonyl group more strongly than Na^+, thus inhibiting the PET process more effectively. Doubly charged cations, such as Mg^{2+} ($I/I_0 = 5.99$) and Ca^{2+} ($I/I_0 = 5.70$), proved even more effective in terms of enhancing the fluorescence intensity (see Supporting Information). The fluorescence enhancement induced by these latter cations (e.g., Li^+ or Mg^{2+}) could be quenched via the addition of Cl^- anion (as its tetrabutylammonium salt). However, the efficiency of this quenching process proved less effective than in the case of Na^+.

In conclusion, we have succeeded in synthesizing a strapped calix[4]pyrrole−coumarin conjugate **1**. Association constants (K_a) corresponding to the interaction **1** with Cl^-, Br^-, and AcO^- anions were determined using fluorescence titrations carried out in the presence of Na^+ (or H_2O) and gave values concordant with those determined using ITC. The fluorescence emission properties of **1** were found to depend on the environment and could be specifically controlled via the addition of Na^+ (or H_2O) and anions. In acetonitrile, fluorescence quenching by anions is only observed in the presence of H_2O or cations, such as Na^+. These and other observations are consistent with the presumed PET process being controlled by both cation and anion recognition. We believe that our approach, involving the strapping of calix[4]pyrroles with fluorophores, will emerge as a powerful new approach to the design of "smart" molecular devices whose "logic" function can be controlled by ion or, in due course, neutral substrate recognition.

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Supporting Information Available: Details for synthesis, characterization, spectral data, and plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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