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Colorimetric Probes Based on Anthraimidazolediones for Selective Sensing of Fluoride and Cyanide Ion via Intramolecular Charge Transfer

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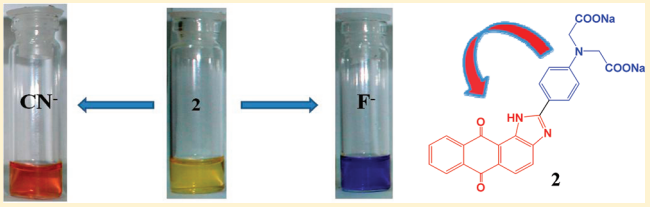
Supporting Information

ABSTRACT: Probes based on anthra[1,2-*d*]imidazole-6,11-dione were designed and synthesized for selective ion sensing. Each probe acted as strong colorimetric sensors for fluoride and cyanide ions and exhibited intramolecular charge transfer (ICT) band, which showed significant red-shifts after addition of either the F^- or CN^- ion. One of the probes (**2**) showed selective colorimetric sensing for both cyanide and fluoride ions. In organic medium, **2** showed selective color change with fluoride and cyanide, whereas in aqueous organic medium it showed a ratiometric response selectively for cyanide ion.



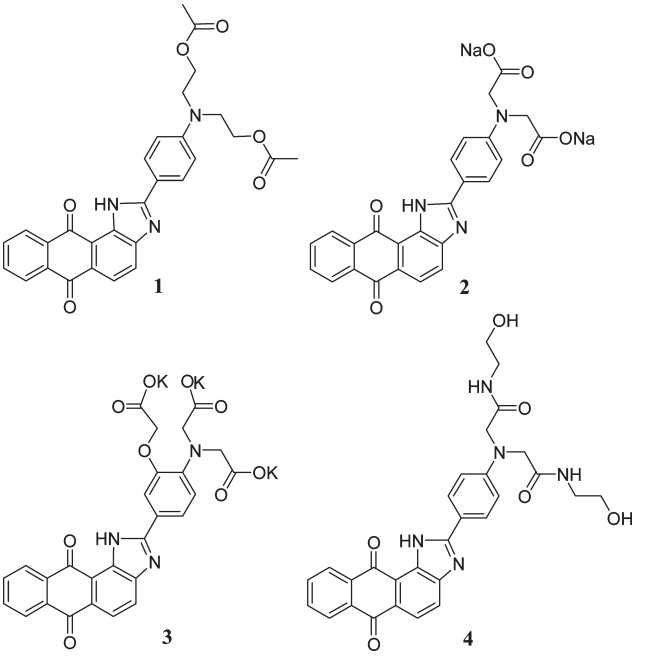
INTRODUCTION

Anions play a fundamental role in many biological and chemical processes.[1] Various anions have their different roles and importance. Thus, the design and synthesis for the molecular sensors that can detect the anions selectively are always of major interest. In current research, the anion-sensing using fluorescent and colorimetric sensors are important, as they do not require expensive instruments. The colorimetric sensors are even better as the signaling event can be detected by naked eye itself.

The fluoride ion is one of the most important anions because of to its role in dental care and in the treatment of osteoporosis.[2] Fluoride is also present in many anesthetic, hypnotic, and in psychiatric drugs. F^- ion sensors should also be useful in the detection of uranium enrichment via hydrolysis of UF_6 or in the detection of chemical warfare agent sarin, as F^- ion is released upon its hydrolysis.[3] Among various anions, cyanide is another important ion which needs to be detected at very low concentrations, since CN^- is one of the most toxic ions known to mankind.[4] It inhibits the cellular respiration in mammalian cells by interacting with the active site of cytochrome a_3, which makes even a small amount of cyanide very lethal to human beings.[5] Many reports have appeared in the literature describing the detection of either F^- or CN^- ion,[6] but examples of a sensor which can detect both anions are relatively less known.[7]

We have previously developed sensors and functional assemblies that are made up of peptide- or ligand-based frameworks.[8] Herein we introduce new anthraimidazoledione based sensors **1**−**4** (Chart 1) that can detect both F^- and CN^- ion via an intramolecular charge-transfer (ICT) process. ICT works on the "push−pull" effect of the donor (D) and the acceptor (A) moiety present in the sensor. So far, only a few sensors have been reported for the anion sensing which works via the ICT mechanism because the weak binding with anion results in a feeble spectroscopic signal.[9] The negatively charged analyte can bind with the electron-deficient acceptor site of a receptor. This can in turn alter the "D−A" to a "D−D" system and thereby reduce the charge-transfer character, weakening the signal.[10]

Chart 1. Molecular Structures of the Sensors



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The benzimidazole system is well-known to detect fluoride ion via deprotonation of its NH proton.[11] But none of the systems reported so far uses ICT for anion detection. ICT exerts a significant role on either a chromogenic or a fluorescent molecule, as it causes a shift in the absorption and fluorescene emission band, respectively. The shift of an absorption and/or emission band reflects the strength of the D−A interaction, and hence, this could be used for modulating the spectral properties of a molecule.[12] We report herein the interesting effect of variation of donor system on the ICT band. Toward this end, the "anthraquinone" part of the anthraimidazoledione is chosen for the first time as an electron-deficient acceptor to which different *N*-substituted aromatic units are linked in conjugation as donor sites. The receptors having electron-rich aromatic units containing the anionic moiety at the donor site show particularly pronounced red-shifted CT bands.

RESULTS AND DISCUSSION

Synthesis. All the four receptors were synthesized as shown in Scheme 1. First, each aldehyde precursor was synthesized via Vilsmeier−Haack reaction, and then each aldehyde was oxidatively coupled with 1,2-diaminoanthraquinone in nitrobenzene to furnish the desired products.[13] All of the receptors were adequately characterized using ^{1}H and ^{13}C NMR and mass spectral methods.

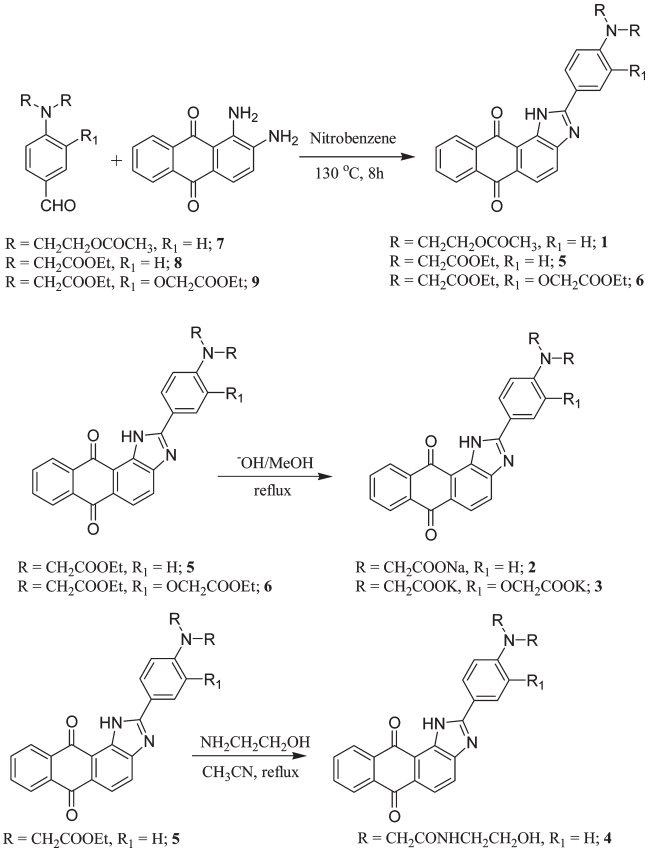
Colorimetric and UV−vis Spectral Response. Absorption spectra of **1**−**4** in acetonitrile showed the presence of an ICT band in each case. However, the maximum red-shift was shown by the receptor containing the anionic moiety at the donor site. Between the receptors that contain anionic moiety, i.e., **2** and **3**, the latter showed a more red-shifted CT band than the former in the absence of any added ion. However, after addition of fluoride ion, the maximum red-shift was found in the deprotonated (benzimidazole) species of **2**. The presence of electronegative oxygens at the ortho position of the donor site in **3** might have reduced the negative charge density on the donor site in this molecule. Thus, both the resonance (+R) as well as the inductive effect (−I) of the substituent on the aromatic unit appear to influence the ICT here.

Each compound showed colorimetric response upon addition of either F^- or CN^- ion in contrast to other anions. The anions were added in the form of their tetrabutyl ammonium salts in actonitrile−DMSO (95:5) mixure. After the addtion of either F^- or CN^- ion to each receptor, the ICT band was found to be red-shifted. Of these **2** showed a remarkable and selective color change from light yellow to dark blue upon the addition of F^- ion and from light yellow to red upon the addition of CN^- ion (Figure 1). The spectral responses were further investigated using UV−vis spectroscopy. Compound **2** (50 μM) showed bathochromic shifts ($\Delta\lambda_{max}$) of ∼120 nm and ∼81 nm in presence of F^- ion and CN^- ion, respectively (Figure 1). Other receptors also showed noticeable changes upon addition of either F^- or CN^- ion and only a very small change in presence of AcO^- and $H_2PO_4^-$ ion (Figure S2−S4, Supporting Information).

Selective Sensing of Fluoride Ion. Each receptor was found to be sensitive toward both the F^- as well as CN^- ion. Importantly, **2** and **3** were able to detect the F^- even in presence of CN^- ion in the medium (Figure 2). Other receptors, however, showed very little changes upon addition of F^- ion in presence of excess of CN^- ion in the medium (Figure S13 and S14, Supporting Information).

Effect of an Anionic Moiety on the Charge-Transfer Spectra. Among the four receptor molecules, only **2** and **3** showed maximum shifts upon addition of F^- ion. The common feature in both **2** and **3** is that the donor sites of the molecules have negative charges on them. To probe the effect of negative charge, we compared the

Scheme 1. Synthetic Routes to Compounds 1−4



UV−vis spectra of these two molecules with their neutral precursors, i.e., the ethyl esters of **2** and **3** (Figures 3 and S15, Supporting Information). The charge-transfer band of **2** has a maximum at 468 nm compared to 450 nm with its ethyl ester. This confirms that the negative charge on the donor site has a significant role on the CT band. The effect became more pronounced after the addition of F^- ion to it. The observed red-shift of the ester of **2** was only 40 nm compared to ∼120 nm shift in case of **2**. The comparison between **3** and its ethyl ester also showed similar results (Figure S15, Supporting Information). Thus, the build-up of negative charge on the molecule helps the formation of a more red-shifted CT band.

Job's plot involving each receptor confirmed its 1:1 stoichiometric interaction with either F^- or CN^- ion (Figures S16−S19, Supporting Information). This suggests an interaction of the added anion with the benzimidazole proton as this is the most labile proton in these compounds. The deprotonation of the benzimidazole upon addition of F^- ion was eventually confirmed by ^{1}H NMR titration as given below.

^{1}H NMR Titration Experiments. ^{1}H NMR titrations of each of the four receptors were performed in the DMSO-d_6 because of the limited solubility of such compounds in CD_3CN. With the addition of only 0.5 equiv of F^- ion, the peak due to the benzimidazole NH broadened, indicating a hydrogen-bonding interaction involving the fluoride with that of the N−H proton (Figure 4). After addition of 3 equiv of F^-, one triplet signal started developing at ∼16.3 ppm, which became quite prominent after addition of 5 equiv of F^- ion. Appearance of this triplet suggests the formation of HF_2^- ion and confirms the deprotonation of the benzimidazole N−H. This was also supported by the upfield shifts of the (c, d) protons of the anthraquinone nucleus (Figure 4).

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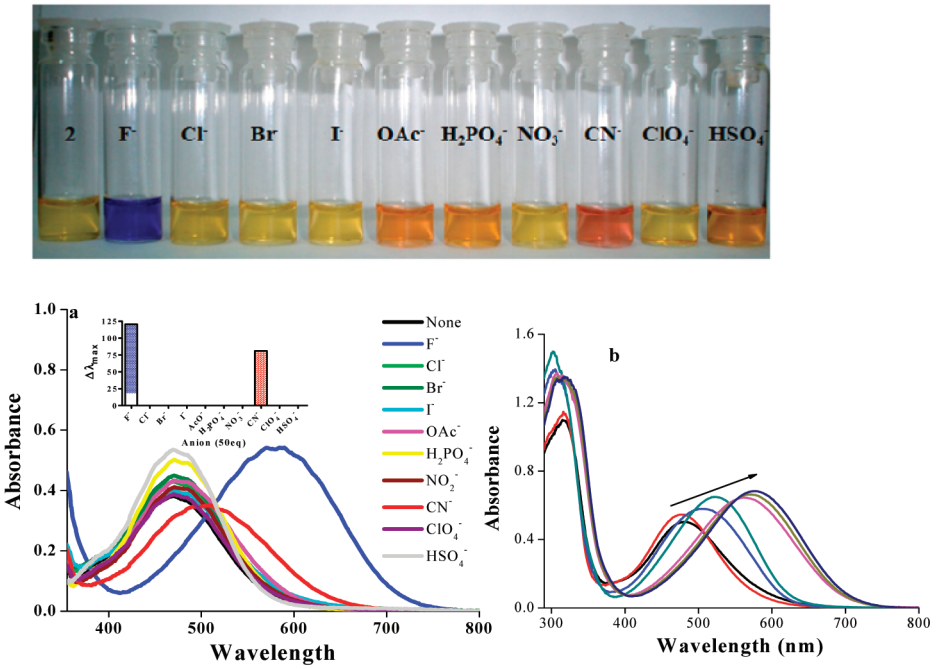

Figure 1. Colorimetric (above) and below (a) UV−vis spectral responses of **2** (50 μM) in CH_3CN (5% DMSO) after addition of 50 equiv of different anions (inset: Changes in $\Delta\lambda_{max}$ after addition of different anions). (b) UV−vis titration of **2** with fluoride ion.

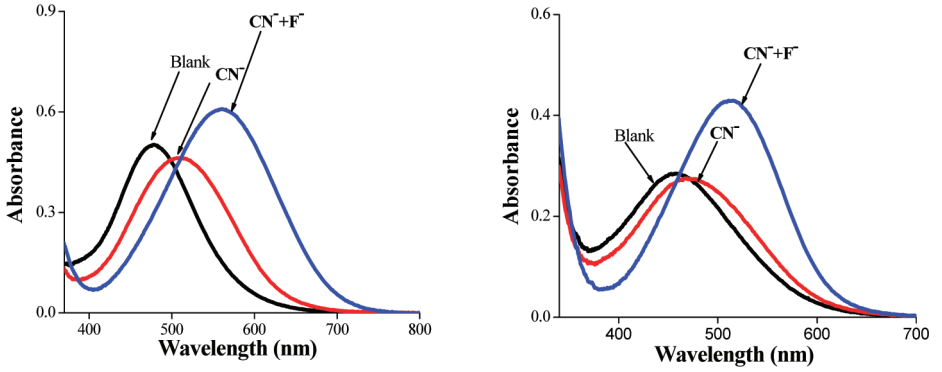

Figure 2. Changes in the UV−vis spectra of **2** and **3** (50 μM) upon addition of 2.5 mM CN^- first and then upon addition of 50 equiv of F^- ion in CH_3CN (5% DMSO).

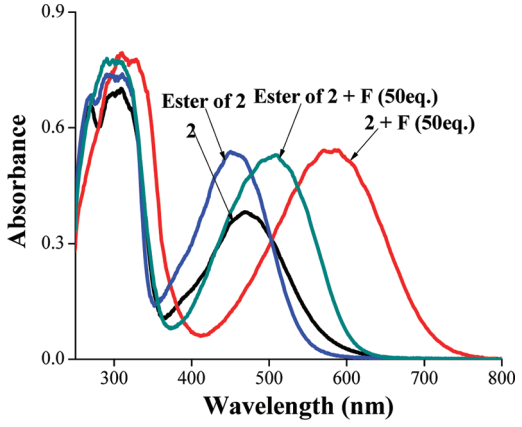

Figure 3. UV−vis spectra of **2** and its ester alone and after addition of 50 equiv of F^- ion in CH_3CN (5% DMSO).

Each receptor showed similar results, and appearance of the triplet corresponding to the benzimidazole proton was observed (Figures S20−S23, Supporting Information). To investigate why receptor **2** showed maximum change among all the receptors, the ^{1}H NMR spectrum of each compound was compared. The only structural difference in each of the compounds was due to the variations in the *N*- or *O*-substituents on the substituted phenyl ring. We looked at the effect on the $-CH_2$ protons attached to the *N*-substituent of the ligand. The chemical shifts of the $-CH_2$ protons were different as they were attached to different functionality. The $-CH_2$ protons were shifted upfield upon addition of the F^- ion as a result of the deprotonation of the benzimidazole NH. But the extent of shift was different for each compound. The upfield shifts for **1** and **4** were found to be ~0.1 and ~0.2 ppm, respectively, having $-CH_2CO$ and $-CONH$ moieties next to the $-CH_2$ group.

It appears that the −I effects of these functional groups minimize the negative field generated on the $-CH_2$ protons after

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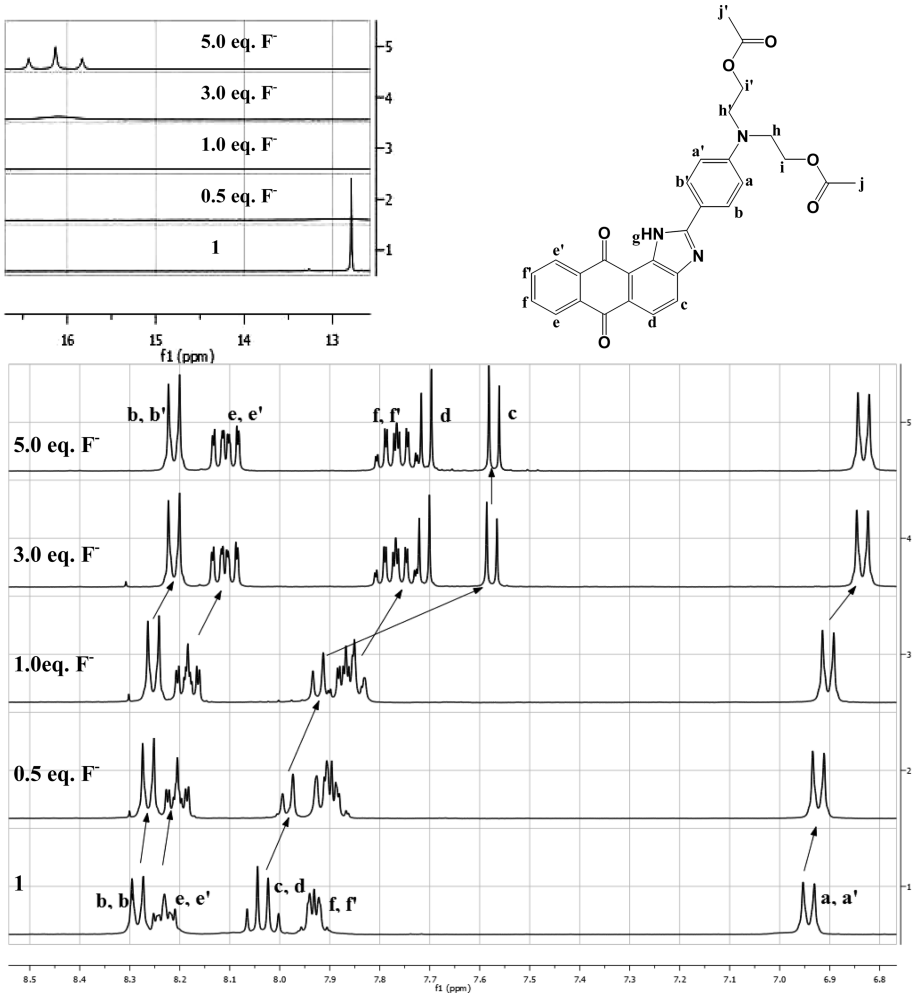

Figure 4. Partial ^{1}H NMR (400 MHz) spectra of receptor **1** in DMSO-d_6 in the absence and presence of 0.5, 1, 3, and 5 equiv of $[(n\text{-Bu})_4\text{N}]^+\text{F}^-$.

the deprotonation of the benzimidazole NH of **1** and **4**. A maximum upfield shift (>0.5 ppm) of $-CH_2$ protons was found in receptor **2** (Figure 5). It could be because the $-CH_2$ protons in **2** are attached to a COO^- group, which is already in possession of negative charge. So this could not stabilize the negative charge generated on the $-CH_2$ protons. In **3**, the upfield shift was only 0.2 ppm (Figure S22, Supporting Information). The difference between **2** and **3** lies in the presence of a $-OCH_2COO^-$ moiety on the substituted phenyl ring. Hence, an −I effect of the oxygen could be responsible for the charge stabilization. To explain the effect of CN^- addition, ^{1}H NMR titration of **3** was performed by adding CN^- ion. The anthraquinone protons shifted only by 0.1 ppm compared to ∼0.3 ppm shift observed with the fluoride addition. Also, no sign of deprotonation was visible even after the addition of 10 equiv of CN^- ion. The $-CH_2$ proton peaks at 4 ppm were broadened and shifted upfield by 0.1 ppm after addition of 10 equiv of CN^- (Figure S24, Supporting Information).

These results suggest that in receptor **2**, when F^- is added, maximum negative charge density is developed on the $-CH_2$ protons. Due to this, the red-shift of the CT band is maximum in case of **2** which results in a pronounced color change from yellow to intense blue. However, in other receptors, the color change was relatively modest, i.e., from yellow to red.

Thus, both UV−vis and ^{1}H NMR studies show first the association with the benzimidazole proton with 1 equiv of F^- ion

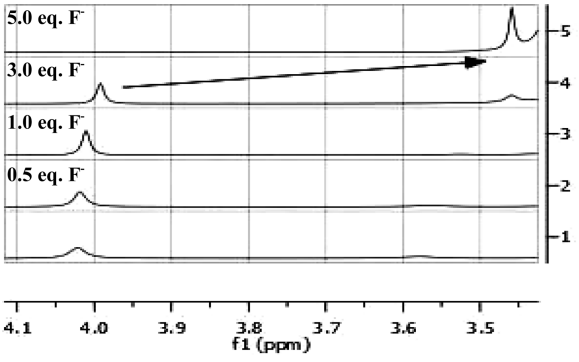

Figure 5. Partial ^{1}H NMR (400 MHz) spectra of **2** in DMSO-d_6 in the absence and presence of 0.5, 1, 3, and 5 equiv of $[(Bu)_4N^+]F^-$. (Arrow shows the shift of the CH_2 protons from ∼4 ppm to ∼3.4 ppm upon addition of F^-.)

followed by its deprotonation upon excess addition of F^-. To further prove this deprotonation phenomenon, we checked the interaction of the receptors with hydroxide ion in the same medium. With addition of 50 equiv of hydroxide ion, all the compounds showed red-shifts of ∼30−50 nm (Figure S25, Supporting Information). It confirms that the change in the absorbance, due to the addition of fluoride ion, occurs through the deprotonation process.

K_d from Absorption Spectra. The UV−vis and ^{1}H NMR titrations both indicated an involvement of a two-step mechanism in the above processes. This involves first the hydrogen bonding of the fluoride ion with the benzimidazole proton, and in the second step, deprotonation takes place upon addition of excess F^-. Such a two-step process has also been observed in the anion-induced urea deprotonation by Fabbrizzi et al.[14] The first equilibrium exists for the complexation of the ligand with the anion via hydrogen bonding, and then the ligand undergoes dissociation after addition of the anion in excess. A similar phenomenon was reported for the benzimidazole moiety also.[11] All four receptors follow a similar mechanism and show a dissociation induced by F^- ion as described in the scheme below.

$$LH + X^- \overset{K_a}{\rightleftarrows} [LH\cdots X]^- \quad (1)$$

$$[LH\cdots X]^- + X^- \overset{K_d}{\rightleftarrows} L^- + [HX_2]^- \quad (2)$$

Table 1. Proton Dissociation Constants of Each Receptor upon Interaction with Added F^- Anion

receptor	dissociation constant (log K_d)
1	4.38 ± 0.03
2	4.59 ± 0.02
3	4.52 ± 0.04
4	3.28 ± 0.07

The change in the charge-transfer band for the hydrogen-bonded complex with F^- anion was very small. Hence, the equilibrium constant (K_a) could not be determined reliably from the UV−vis spectral titrations. However, the dissociation of the benzimidazole proton caused a huge red-shift of the charge transfer maximum, and the corresponding equilibrium constant could be determined. The dissociation constants (K_d) of each sensor with fluoride ion are compiled in the Table 1. The K_d values represent the ground-state dissociation constants.[11] The higher log K_d values also demonstrate the selectivity of receptor **2** toward F^- over other receptors.

Responses in Aqueous Medium. We also checked the applicability of the above probes in aqueous medium. The introduction of water made the probes insensitive to the fluoride ion.

This is because the F^- ion is highly solvated in water and loses its basicity due to hydration. In aqueous medium, water competes with the sensors for the F^- ion.[15] But each probe showed changes due to CN^- addition in aqueous CH_3CN (9:1) medium. The comparatively lower hydration energy for the cyanide ion ($\Delta H_{hyd} = -67$ kJ/mol) than that of the fluoride ion ($\Delta H_{hyd} = -505$ kJ/mol) explains the selectivity of cyanide ion.[16] A maximum shift of 40 nm was observed with the probe **2** without any interference from other anions (Figure 6). The other probes showed only small changes upon CN^- addition (Figure S26, Supporting Information).

The titration with progressive addition of cyanide to the probe **2** showed decreases in the absorption band at 464 nm and increases at 504 nm (Figure 7a). The change in absorbance was complete with addition of just 5 equiv of cyanide. The plot of the

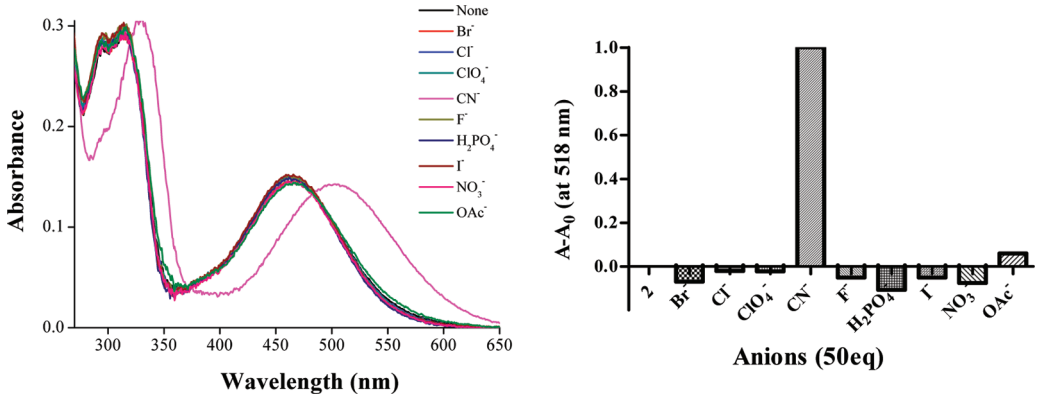

Figure 6. (a) UV−vis spectral responses of **2** (10 μM) in 9:1 CH_3CN−water (1% DMSO) after addition of 50 equiv of anions. (b) Normalized changes in absorbance at 518 nm after addition of anions.

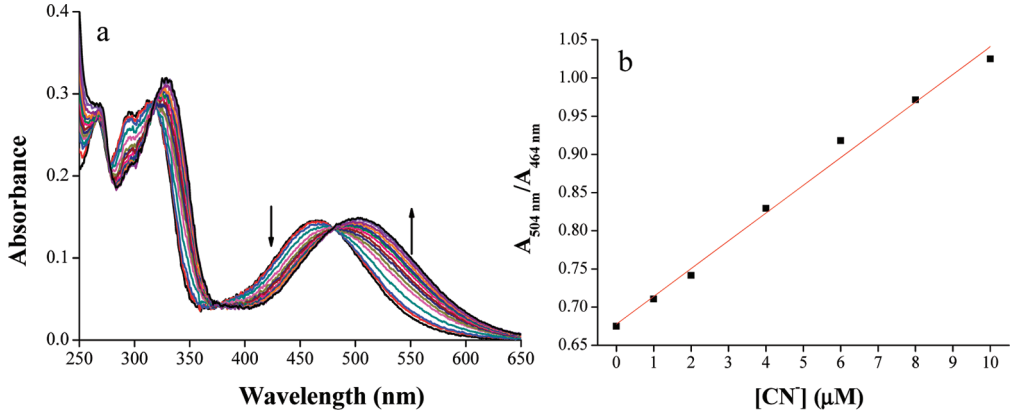

Figure 7. (a) UV−vis titration of **2** with cyanide ion (0−6 equiv). (b) Ratiometric response with added cyanide ion.

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ratio of the absorbance at 504 and 464 nm with the cyanide ion concentration showed a ratiometric response (Figure 7b). It indicated that cyanide ion can be detected using probe **2** even in aqueous medium at low concentration level selectively without any interference from other anions.

CONCLUSIONS

In summary, we have synthesized new colorimetric probes, which can detect both F^- as well as CN^- ions. F^- ions interact with the benzimidazole NH of the probe molecule, and the observed change in color is based on an intramolecular charge transfer. The anthraquinone part of each molecule has an acceptor moiety, whereas a substituted nitrogen-linked aromatic unit forms the donor site. Among the various donor moieties, the sites having negative charges on them were found to disperse greater electron density on them. Thus, the accumulation of negative charge density on the donor site leads to a red-shift in the CT band. Among the various anions, only F^- ion showed maximum red-shift because it was able to cause deprotonation of the benzimidazole NH due to its high electronegativity and basicity. Among the four receptors, **2** showed a maximum red-shift in the ICT band after the addition of F^- ion. Using this, one can detect both F^- and CN^- ion selectively as it changes to a distinctly different color with F^- ion (yellow to blue) and CN^- ion (yellow to red). Further, the probes showed selective detection of cyanide ion in aqueous medium too. Probe **2** showed a red-shift of 40 nm with the cyanide ion selectively in aqueous medium. It showed the ratiometric detection of the cyanide, which makes it a more reliable sensor in water as well.

EXPERIMENTAL SECTION

Synthesis. *General Procedure for the Synthesis of **1**, **5**, and **6**.* Each substituted benzaldehyde (**7** or **8** or **9**) (1.0 mmol) and 1,2-diaminoanthraquinone (1.0 mmol) was heated in nitrobenzene (4 mL) at 130 °C for ~8 h.[13] Then the reaction mixture was cooled to rt, and hexane was added to get a solid precipitate which was washed several times with hexane. The precipitate was finally purified by column chromatography (2−3% $CH_3OH/CHCl_3$) to get the desired product.

Compound 1: yield 80%; red solid; mp 186−187 °C; IR (KBr, cm^{-1}) 3418.0, 2956.0, 1732.2, 1721.9, 1660.7, 1607.3, 1593.7, 1488.3, 1296.5, 1244.4, 1044.2, 710.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.02 (s, 6H), 3.73 (t, J = 5.4 Hz, 4H), 4.23 (t, J = 5.6 Hz, 4H), 6.95 (d, J = 8.8 Hz, 2H), 7.93−7.95 (m, 2H), 8.01−8.07 (m, 2H), 8.21−8.30 (m, 4H), 12.83 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.6, 48.7, 60.9, 111.4, 116.1, 117.8, 120.9, 123.6, 126.1, 126.7, 126.9, 129.5, 133.0, 133.1, 133.2, 134.1, 134.3, 149.6, 149.9, 158.4, 170.3, 182.1, 183.2; HRMS m/z calcd for $C_{29}H_{26}N_3O_6$ $(M + H)^+$ 512.1821, found 512.1814.

Compound 5: yield 96%; red solid; mp 214−215 °C; IR (KBr, cm^{-1}) 3443.7,2978.9, 1751.7, 1739.4, 1661.1, 1606.3, 1487.9, 1441.3, 1290.0, 1203.3, 1179.3, 1006.6, 718.9; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 6H), 4.18- 4.28 (m, 8H), 6.73 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 6.9 Hz, 2H), 8.01 (d, J = 8.4 Hz, 3H), 8.13- 8.32 (m, 3H), 11.13 (br s., 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 53.3, 61.4, 112.5, 117.4, 118.0, 121.8, 124.6, 126.3, 127.4, 127.8, 128.6, 133.2, 133.4, 133.5, 133.9, 134.2, 149.8, 150.3, 157.1, 170.1, 182.5, 185.1; HRMS m/z calcd for $C_{29}H_{25}N_3O_6$ $(M + H)^+$ 512.1821, found 512.1818.

Compound 6: yield 80%; red solid; mp 222−224 °C; IR (KBr, cm^{-1}) 3345.1, 2977.4, 1751.0, 1737.1, 1664.5, 1579.3, 1495.4, 1421.7, 1324.6, 1293.1, 1190.7, 1176.0, 1028.2, 716.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.28 (m, 9H), 4.13- 4.23 (m, 10H), 4.72 (s, 2H), 6.87 (d, J = 8.4 Hz, 2H), 7.55−7.75 (m, 4H), 7.98 (d, J = 8.4 Hz, 1H), 8.13−8.28 (m, 3H), 11.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 53.9, 60.9, 61.3, 66.1, 112.9, 117.7, 118.8, 121.3, 122.0, 125.0, 126.4, 127.5, 128.2, 133.3, 133.4, 133.7, 134.1, 134.3, 142.7, 149.3, 156.5, 168.2, 170.8, 182.6, 185.2; MS(ESI) m/z 636 $(M + Na)^+$; HRMS m/z calcd for $C_{33}H_{31}N_3O_9$ $(M + Na)^+$ 636.1958, found 636.1959.

Compounds 2 and 3. Compound **5** or **6** (0.5 mmol) was taken in MeOH (4.5 mL). and to it aq NaOH or KOH solution (0.3 mL, 3 M of NaOH for **5**; 0.4 mL, 5 M of KOH for **6**) was added dropwise at rt and the mixture refluxed for 2 h. After the mixture was cooled to rt, a solid separated out which was filtered. The solid was then washed with MeOH and dried until TLC indicated it to be pure.

Compound 2: yield 90%; red solid; mp >250 °C; IR (KBr, cm^{-1}) 3302.7, 1663.1, 1604.8, 1584.5, 1489.9, 1394.4, 1290.1, 1208.9, 717.1; ^{1}H NMR (400 MHz, D_2O) δ 3.95 (s, 4H), 6.51 (t, J = 7.6 Hz, 2H), 7.1 (s, 1H), 7.24 (s, 3H), 7.35 (s, 1H), 7.44 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, D_2O) δ 55.6, 111.4, 114.1, 121.5, 125.5, 125.9, 126.4, 128.9, 131.1, 131.5, 134.1, 134.4, 151.3, 157.7, 178.5, 182.7, 183.2; HRMS m/z calcd for $C_{25}H_{15}N_3Na_2O_6$ $(M + Na)^+$ 522.0654, found 522.0656.

Compound 3: yield 80%; red solid; m. >250 °C; IR (KBr, cm^{-1}) 3381.2, 3255.8, 1640.0, 1607.3, 1589.0, 1403.0, 1328.2, 1289.8, 1248.5, 1200.6, 720.9; ^{1}H NMR (400 MHz, D_2O): δ 3.94 (s, 4H), 4.44 (s, 2H), 6.68 (d, J = 8.4 Hz, 1H), 7.02 (s, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.37 (s, 3H), 7.52 (s, 2H), 7.64 (s, 1H); ^{13}C NMR (100 MHz, D_2O) δ 58.0, 69.4, 113.2, 117.9, 118.1, 119.2, 122.9, 124.3, 127.0, 127.7, 132.7, 132.9, 135.5, 135.8, 144.8, 149.0, 149.9, 158.6, 165.5, 178.1, 180.4, 184.2, 184.7; MS (ESI) m/z 644 $(M + H)^+$; HRMS m/z calcd for $C_{27}H_{16}K_3N_3O_9$ $(M + K)^+$ 681.9435, found 681.9439.

Compound 4. A mixture of **5** (0.15 g, 0.3 mmol) and 2-aminoethanol (3.75 mL) in CH_3CN (10 mL) was refluxed under N_2 for 2 h. The reaction mixture was cooled, and excess 2-aminoethanol was removed by evaporation. A solid started to appear after the residue was scratched using 1:1 EtOAc/MeOH. The resulting solution was filtered and dried: yield 80%; red solid; mp >250 °C; IR (KBr, cm^{-1}) 3439.9, 3397.6, 3303.4, 3071.9, 2920.1, 1661.8, 1638.5, 1614.9, 1488.5, 1325.8, 1291.2, 1241.4, 1060.0, 716.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.19−3.21 (m, 4H), 3.39−3.44 (m, 4H), 4.17(s, 4H), 4.67−4.70 (t, J = 5.2 Hz, 2H), 6.58−6.67 (m, 2H), 8.04−8.10 (m, 2H), 8.13 (d, J = 8.4 Hz, 2H), 8.23−8.30 (m, 2H), 8.91 (d, J = 5.2, 2H), 12.84 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.5, 56.0, 59.7, 111.2, 117.1, 117.9, 120.9, 123.8, 126.1, 126.7, 127, 129.4, 133.0, 133.1, 133.2, 134.1, 134.3, 149.5, 149.8, 158.3, 170.2, 182.2, 183.2; HRMS m/z calcd for $C_{29}H_{27}N_5O_6Na$ $(M + Na)^+$ 564.1859, found 564.1859.

Compound 7.[17] To a solution of *N*,*N*-bis[(hydroxyethyl)amino]benzene (4.23 g, 23.4 mmol) in CH_2Cl_2 (32 mL) were consecutively added Ac_2O (7.32 g, 71.8 mmol) and pyridine (5.3 g, 66.8 mmol) dropwise at 0 °C. Then the reaction mixture was stirred overnight at rt. The mixture was washed with water and dried. This was further purified by column chromatography (94:6 hexane/EtOAc) to obtain the intermediate as a pale yellow oil (5.7 g): yield 92%; IR (neat, cm^{-1}) 2958.8, 1739.7, 1599.4, 1505.9, 1379.9, 1232.3, 1036.7, 749.6; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (s, 6H), 3.55 (t, J = 6.15 Hz, 4H), 4.16 (t, J = 6.45 Hz, 4H), 6.62−6.69 (m, 3H), 7.16 (dd, J = 8.7, 1.8 Hz, 2H); MS(ESI) m/z 266 $(M + H)^+$, 288 $(M + Na)^+$.

The intermediate was then formylated using DMF (5.6 mL, 72.4 mmol) and $POCl_3$ (3.54 g, 23.0 mmol) upon stirring for 30 min at rt followed by heating at 90 °C for 2 h. Then the reaction was allowed to come to rt and ice−water was added. The mixture was neutralized to pH 7 by addition of solid sodium acetate. It was then extracted with EtOAc, washed with water, and dried. Final purification was done on a silica gel column (98:2 $CHCl_3/CH_3OH$): yield 90%; mp 57−58 °C; IR (neat, cm^{-1}) 2959.7, 2737.0, 1740.4, 1670.6, 1597.8, 1559.7, 1524.0, 1386.8, 1230.7, 1171.1, 1048.3, 819.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 6H), 3.68 (t, J = 6.15 Hz, 4H), 4.24 (t, J = 6.3 Hz, 4H), 6.78 (d, J = 9.3 Hz, 2H), 7.16 (dd, J = 9.3, 3.0 Hz, 2H), 9.72 (s, 1H); MS(ESI) m/z 294 $(M + H)^+$, 316 $(M + Na)^+$.

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Compound 8.[18] Synthesis of **8** was accomplished by substitution of aniline by ethyl bromoacetate followed by formylation as described in case of **7**. The crude intermediate was purified by column chromatography on silica gel (99:1 EtOAc/hexane): pale yellow oil (99% yield); IR (neat, cm^{-1}) 2981.2, 1745.2, 1733.6, 1600.6, 1508.0, 1386.5, 1172.5, 1024.0, 748.2; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 5.4 Hz, 6H), 4.18 (s, 4H), 4.19−4.24 (q, 4H), 6.63 (d, J = 8.1 Hz, 2H), 6.80 (t, J = 7.35 Hz, 1H), 7.21−7.26 (m, 2H); MS(ESI) m/z 266 $(M + H)^+$, 288 $(M + Na)^+$; HRMS m/z calcd for $C_{14}H_{19}NO_4Na$ $(M + Na)^+$ 288.1212, found 288.1213.

Purification of the product obtained upon formylation was carried out by chromatography on a silica gel column (98:2 $CHCl_3/CH_3OH$) to afford a solid (92% yield): mp 63−64 °C; IR (neat, cm^{-1}) 3478.9, 2919.2, 2829.0, 2749.7, 1742.3, 1672.0, 1596.1, 1525.5, 1385.9, 1320.5, 1167.0, 1020.5, 961.1, 812.6; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.0 Hz, 6H), 4.17−4.25 (m, 8H), 6.63 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 9.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 53.3, 61.5, 111.7, 127.3, 131.9, 152.5, 169.6, 190.4; MS(ESI) m/z 294 $(M + H)^+$, 316 $(M + Na)^+$; HRMS m/z calcd for $C_{15}H_{19}NO_5Na$ $(M + Na)^+$ 316.1161, found 316.1162.

Compound 9.[18] *o*-Aminophenol (0.89 g, 8.17 mmol) and bromoacetic acid (5.678 g, 40.85 mmol) were added to a solution of NaOH (2.29 g, 57.2 mmol) in 10 mL of H_2O and heated at 100 °C. Solid NaOH was then added slowly to maintain the pH at 10 and then it was heated for 1 h. The reaction mixture was cooled and dried. Absolute EtOH (29 mL) and H_2SO_4 (3.3 mL, 62.9 mmol) were added to the residue, and the mixture was refluxed for 3 days. The reaction mixture was cooled and filtered to leave a residue, which was dissolved in EtOAc and washed successively with 10% NaOH and brine. This afforded an oily material which was purified by chromatography on silica gel (hexane/EtOAc (5:95, v/v) as eluant): yield 40%; IR (neat, cm^{-1}) 2983.0, 1747.0, 1598.2, 1504.5, 1184.9, 1026.3, 749.4; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21−1.30 (m, 9H), 4.10−4.24 (m, 10H), 4.62 (s, 2H), 6.79−6.99 (m, 4H); MS(ESI) m/z 368 $(M + H)^+$, 390 $(M + Na)^+$.

Similarly, the intermediate was formylated by the procedure mentioned above: yield 40%; mp 55−56 °C; IR (neat, cm^{-1}) 1748.3, 1671.2; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25−1.31 (m, 9H), 4.19−4.27 (m, 10H), 4.65 (s, 2H), 6.80 (d, J = 8.1 Hz, 1H), 7.26 (s, 1H), 7.40 (d, J = 8.1 Hz, 1H); MS(ESI) m/z 390 $(M - C_2H_5 + Na)^+$.

■ ASSOCIATED CONTENT

Supporting Information. General experimental section, changes in color, absorption spectra upon addition of different anions, and titration study of **1**, **3**, and **4** described in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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