



Simple indole-based colorimetric sensors with electron-withdrawing chromophores: Tuning selectivity in anion sensing

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ABSTRACT

Three simple colorimetric anion sensors (**1**, **2**, and **3**) containing anthrone, 1,3-indanedione, and malononitrile as signaling chromophores and an indole binding site have been designed and synthesized. The introduction of electron-withdrawing groups can not only provide chromogenic signal output, but also tune the sensitivity and selectivity of indole-based anion sensors by electron push–pull features. Their anion binding and sensing properties were investigated in detail by dramatic color changes, UV–vis absorption, and ¹H NMR. As results revealed, sensor **1** showed high selectivity for F[−] over AcO[−] and H₂PO₄[−] with a distinct change in color due to the deprotonation of indole NH group. The excellent selectivity of **1** for F[−] can be attributed to the fitness in the acidity of its NH-group, which is tuned to be able to distinguish the subtle difference in the affinity of F[−], AcO[−], and H₂PO₄[−] to NH proton.

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1. Introduction

In view of crucial roles anions play in biological, pathological, and industrial processes, the development of simple and sensitive anion sensors continues to be a research area of considerable interest [1]. In this stance, artificial sensors capable of binding and sensing anions by an optical signal are being increasingly appreciated [2]. Of particular interest is the design of anion-induced colorimetric sensors, which allow direct naked-eye detection of anions with no equipment required [3]. Thus many synthetic anion sensors moieties have been widely reported, which can effectively respond anion-induced changes in color and optical spectra based on hydrogen bonds or deprotonation [4]. Unfortunately, a few colorimetric anion sensors are able to differentiate selectively between anionic substrates of similar basicity and surface charge density such as F[−], AcO[−], and H₂PO₄[−] [4,5].

In recent years, indoles, as an important class of building blocks for anion binding and sensing, have been integrated into a variety of anion sensors and sensors to detect specific anionic guests [6]. In our lab, we previously investigated indole-based derivatives as molecular sensors for special anionic species based on hydrogen bonds or deprotonation mechanism [7]. Generally, indole-based sensors were shown to bind anions with weak responses, which indicated the lower affinity of the indole NH as a hydrogen bond donor for anions. To improve their anion sensing abilities, a simple

and familiar method is to introduce an electron-withdrawing group into the skeleton of indole moieties. Thus, we adopted the nitro group to enhance the acidity of indole NH and obtained a positive effect on anion binding behaviors [8].

Herein, we have designed and synthesized three simple indole-based colorimetric anion sensors **1**, **2**, and **3** containing anthrone, 1,3-indanedione, and malononitrile as electron-withdrawing and chromogenic groups, respectively (Scheme 1). We found that the introduction of electron-withdrawing groups has a positive effect on anion binding behavior of indole, and the selectivity of indole derivatives for F[−], AcO[−], and H₂PO₄[−] is interrelated with the electron-withdrawing ability of chromophores. In this paper, we would like to present our studies on the anion binding properties of three indole-based colorimetric sensors.

2. Results and discussion

2.1. UV–vis absorption study

As shown in Fig. 1, the anion binding properties of **1**, **2**, and **3** were firstly studied by observing changes in color and UV–vis absorption in CH₃CN. The anions tested were added as tetrabutylammonium salts to the CH₃CN solutions of **1–3** (10 μM). In the presence of various anions (F[−], AcO[−], H₂PO₄[−], Cl[−], Br[−], I[−], ClO₄[−], and HSO₄[−]), **1** only responded to the most electronegative F[−] by significant color changes from pale yellow to light blue. In the case of **2** and **3**, moderate basic AcO[−] or H₂PO₄[−] could also produce the similar color changes to F[−] from pale yellow to golden and from colorless to pale yellow, respectively. This observation indicated

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that **2** and **3**, compared to **1**, showed more enhanced acidity of indole NH, which resulted from the stronger electron-withdrawing ability of 1,3-indanedione and malononitrile than that of anthrone moiety. In contrast, the addition of other anions tested resulted in no change in color. UV-vis spectroscopy experiments revealed

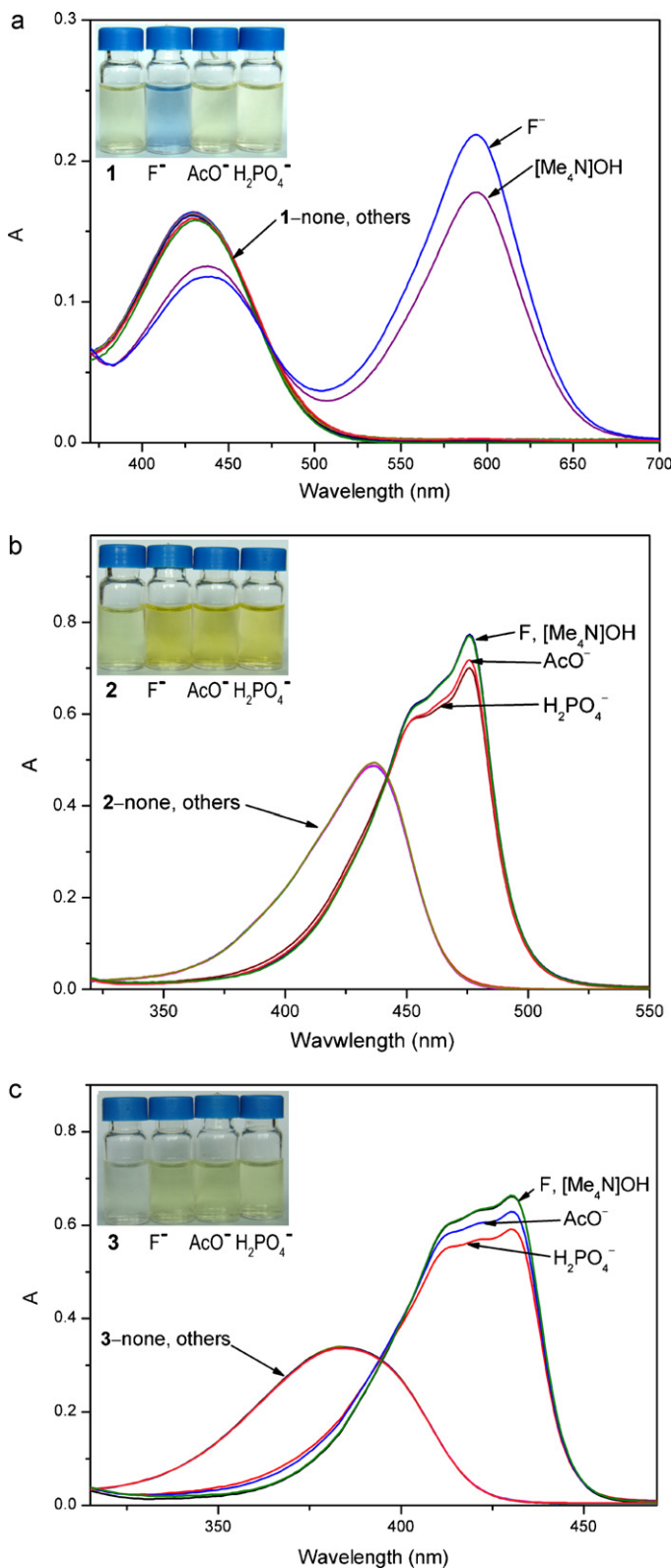


Fig. 1. UV-vis absorption spectra of sensors **1** (a), **2** (b), and **3** (c) (10 M, CH₃CN) in the presence of 30 equiv. of various anions. Inset: color changes of sensors **1** (a), **2** (b), and **3** (c) in the presence of 30 equiv. of F⁻, AcO⁻, and H₂PO₄⁻.

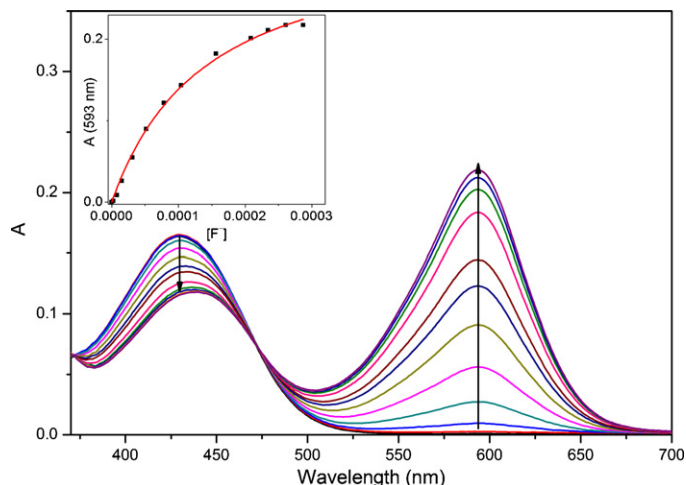


Fig. 2. The variations of UV-vis absorption spectra of sensor **1** (10 M, CH₃CN) after addition from 0 to 30 equiv. of F⁻. Inset: nonlinear curve fitting as a function of [F⁻].

large red shifts of spectra of sensors **1–3** upon addition of anions corresponding to changes in color. Such large bathochromic shifts can be attributed to a charge transfer from the indole NH proton being interacted with anions to the electron-withdrawing chromophore [9]. The titration experiments were conducted to provide a further insight into sensor-anion interaction in detail.

As for **1** in Fig. 2, with stepwise addition of F⁻ to **1** (10 μM) in CH₃CN, the main absorption peak at 430 (ε = 16,380 M⁻¹ cm⁻¹) nm was gradually decreased and red-shifted to 440 nm (ε = 11,800 M⁻¹ cm⁻¹), while a new band at 593 nm (ε = 21,860 M⁻¹ cm⁻¹) evolved and reached its limiting value after the addition of 26 equiv. of F⁻. A clear isobestic point at 473 nm indicated the interaction between **1** and F⁻ in a 1:1 stoichiometry. Two F⁻-induced absorption bands at 440 nm and 593 nm may be assigned to the deprotonated form of anthrol tautomer (**1a** and **1b** Fig. 3) in the presence of the most electronegative F⁻ with delocalization of the negative charge from the nitrogen atom to the oxygen atom [10]. This was confirmed by the Brønsted acid–base reaction of **1** with a strong base [Me₄N]OH (Fig. 1). The equilibrium constant of **1** for F⁻ was calculated to be 7.28 × 10⁴ M⁻¹ according to Eq. (1), as shown in the inset of Fig. 2. The stoichiometry between **1** and F⁻ was proved by UV-vis Job plot, giving a sensor/fluoride stoichiometry of 1:1 (Fig. 4). The resulting bind curves were analyzed by nonlinear regression methods, and the association constants are listed in Table 1.

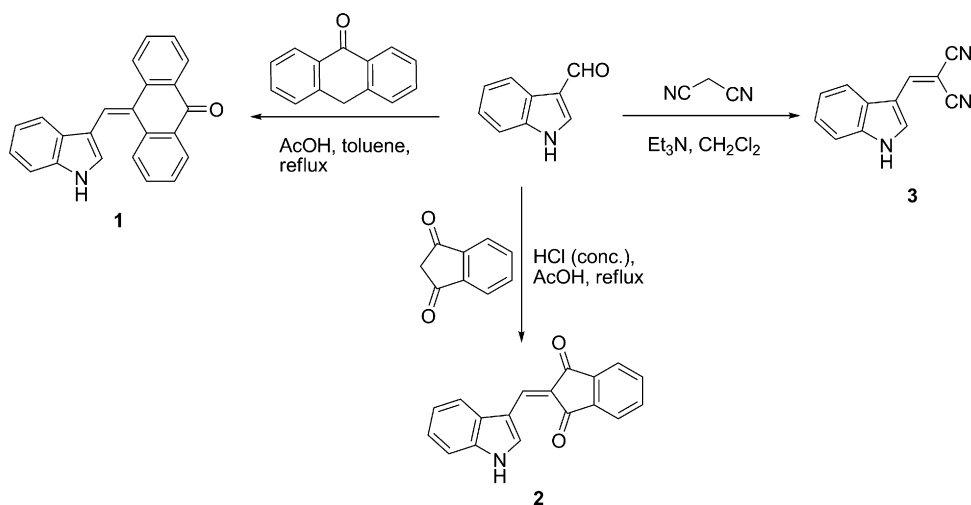
As expected, **2** and **3** displayed significant absorption responses not only for the most basic F⁻ (Figs. 5 and 6), but for moderate basic AcO⁻ and H₂PO₄⁻ (Figs. S1–S4). This is presumably due to the strong electron-withdrawing nature of 1,3-indandione and malononitrile groups, which increased the acidity of the indole NH proton. During the absorption titration of F⁻, AcO⁻, and H₂PO₄⁻ with a solution of **2**, the band at 437 nm (ε = 48,900 M⁻¹ cm⁻¹) disappeared and two new bands at 458 nm (ε = 56,600 M⁻¹ cm⁻¹)

Table 1
Equilibrium constants of sensors **1**, **2**, and **3** with F⁻, AcO⁻, and H₂PO₄⁻ in CH₃CN as determined from UV-vis absorption titrations.

Anion ^a	Sensor 1 (K ^a in M ⁻¹)	Sensor 2 (K ^a in M ⁻¹)	Sensor 3 (K ^a in M ⁻¹)
F ⁻	7.46 × 10 ³	2.67 × 10 ⁵	4.73 × 10 ⁵
AcO ⁻	^b	2.24 × 10 ⁵	3.99 × 10 ⁵
H ₂ PO ₄ ⁻	^b	3.44 × 10 ⁵	3.67 × 10 ⁵

^a Anions are used as their tetrabutylammonium salts.

^b The changes in the absorption spectra are too small to calculate the equilibrium constants precisely.



Scheme 1. The synthetic routes of sensors 1, 2, and 3.

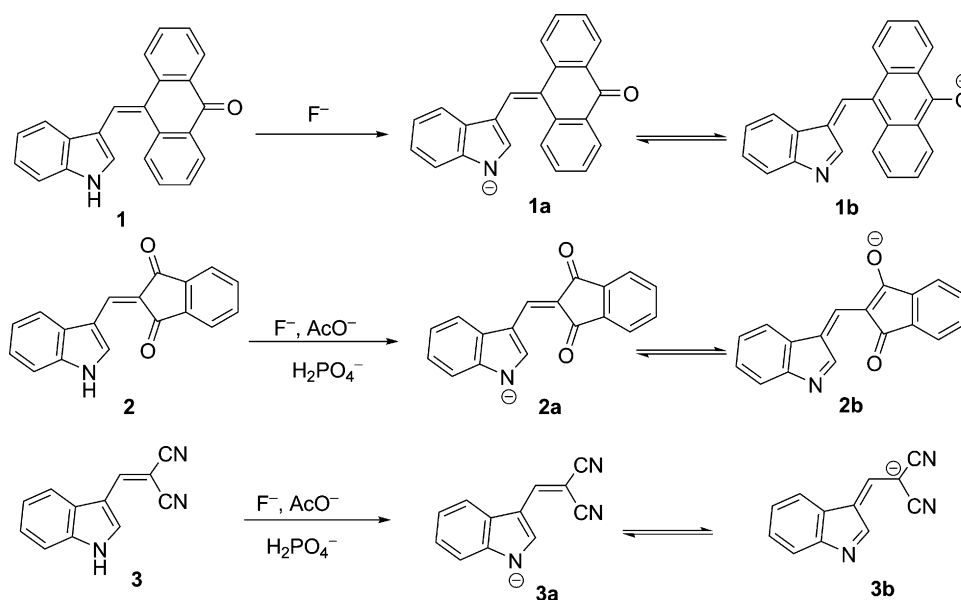


Fig. 3. The probably deprotonated structures of sensors 1, 2, and 3 after interaction with corresponding anions.

and 476 nm ($\epsilon = 77,400 \text{ M}^{-1} \text{ cm}^{-1}$) developed, which was responsible for simultaneous color changes. Similar results were also observed for 3 in the presence of putative anions, which demonstrated the existence of deprotonated forms of corresponding tautomers (Fig. 3). The addition of $[\text{Me}_4\text{N}]\text{OH}$, which definitely led to deprotonation, also induced the same color and spectral changes of both sensors as those observed with F^- , AcO^- , and H_2PO_4^- anions (Fig. 1). Moreover, equilibrium constants for 2 and 3 with F^- , AcO^- , and H_2PO_4^- were also given in Table 1 (Figs. 4 and 5 and S1–S4 inset). As described in Table 1, the order of F^- affinities of sensors is $1 < 2 \approx 3$, which is consistent with the electron-withdrawing nature of chromophores. These groups increase the acidity of indole NH proton, which, in turn, enhance the availability of NH moiety for deprotonation and affinity of sensors toward anions.

2.2. ^1H NMR spectra study

This trend in sensor-anion affinity, as reflected by the equilibrium constants, was also observed with the chemical shifts of NH proton signals of sensors 1–3 in ^1H NMR. The chromogenic

indole NH proton signals in 1–3 appeared at 11.67, 12.76, and 12.79 ppm in DMSO-d_6 , respectively (indole NH signals appeared at approximately 10.1 ppm). The observed order was consistent with the F^- binding affinities observed for sensors 1–3. As mentioned above, we concluded that the significant changes in color and absorption spectra might be resulted from the deprotonation of chromophore-modified indole NH. This deprotonation was also examined in the ^1H NMR titration spectra using sensor 1 with F^- anion in DMSO-d_6 . As depicted in Fig. 7, the signal of indole NH proton at 11.67 ppm disappeared after the addition of 0.4 equiv of F^- anion. With the gradual addition of F^- a new singlet signal developed at 16.10 ppm and then split into a 1:2:1 triplet signal. The appearance of new signals can be ascribed to the FHF^- dimer [11], which demonstrated the occurrence of the deprotonation of the NH group of the indole ring. With the deprotonation of 1, charge delocalized on the entire conjugated system, which shifted the vinyl CH and anthra rings upfield further. This deprotonation process indeed supported the conclusion from the UV–vis spectra changes observed in the presence of $[\text{Me}_4\text{N}]\text{OH}$.

Additionally, the reversibility of the deprotonation process was examined by adding water to the system of sensors and anions in

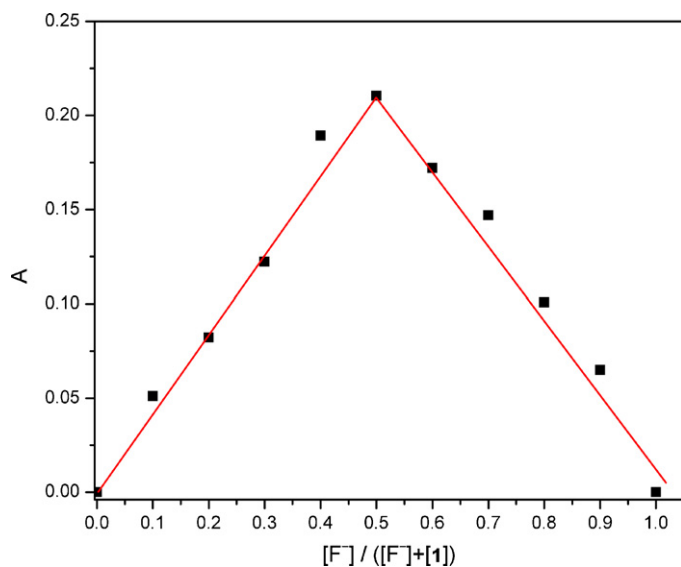


Fig. 4. A job plot of sensor **1** with F^- in CH_3CN , $[1] + [F^-] = 10$ (M).

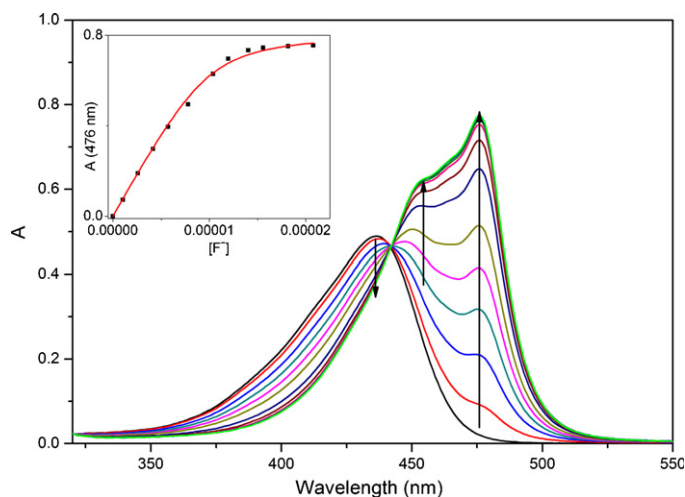


Fig. 5. The variations of UV–vis absorption spectra of sensor **2** (10 μ M, CH_3CN) after addition from 0 to 2.7 equiv. of F^- . Inset: nonlinear curve fitting as a function of $[F^-]$.

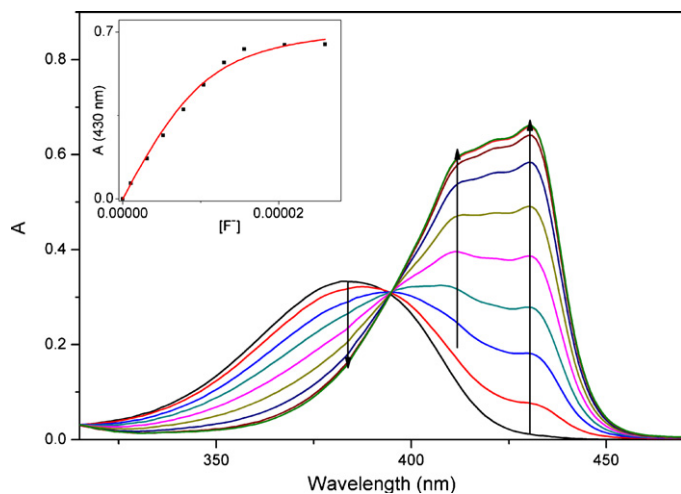


Fig. 6. The variations of UV–vis absorption spectra of sensor **3** (10 μ M, CH_3CN) after addition from 0 to 2.6 equiv. of F^- . Inset: nonlinear curve fitting as a function of $[F^-]$.

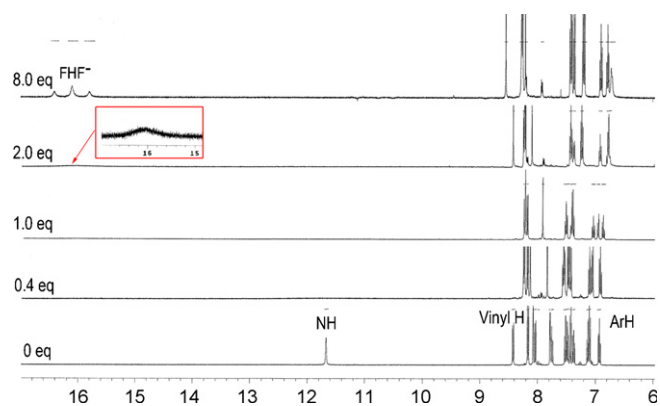


Fig. 7. Partial 1H NMR spectra of sensor **1** in the presence of 0, 0.4, 1.0, 2.0, and 8.0 equiv. of F^- .

UV–vis spectra (Fig. S5). We found that the absorption spectrum completely reverted to the original spectrum for **1** in CH_3CN containing 0.5% water, while **2** and **3** could tolerate trace water in the event of anion binding and sensing due to the strong acidity of their indole NH groups.

3. Conclusions

We herein have presented three simple indole-based colorimetric anion sensors using electron-pulling chromophores to tune the anion selectivity and the output signal. The selectivity and sensitivity of anion sensors is found to be interrelated with the electron-withdrawing ability of chromophores constituting the anion binding sites. Sensors **1–3** show increased affinities and enhanced binding constants for anions along with the increased electron-withdrawing nature of chromogenic groups. The push–pull feature renders the anion binding site indole NH more acidic and thus more available for hydrogen bonds or deprotonation. We believe that the introduction of reasonable chromophores allows the design of a variety of sensors for selective binding and sensing targeted substrates.

4. Experimental

4.1. Materials and methods

CH_3CN was HPLC grade and used directly, and other chemical materials were analytical pure and obtained from commercial companies. 1H NMR and ^{13}C NMR spectra were determined on a Varian INOVA 400 MHz spectrometer. ESI-MS studies were carried out using a Waters Micromass ZQ-4000 Spectrometer. UV–vis absorption spectra were recorded on a Perkin-Elmer Lambda 35 spectrometer. Elemental (C, H, N) analyses were made on a Vario-EL. The binding ability of sensors **1**, **2** and **3** for anions (as tetrabutylammonium salts) was investigated by UV–vis absorption spectroscopy in CH_3CN solution using a constant host concentration (10 μ M) and increasing concentrations of anions. The change in absorbance of three sensors was plotted against anion concentration and fitted by Formulae (1) as described by Connors [12].

$$X = X_0$$

$$+ 0.5\Delta\epsilon \left\{ c_H + c_G + \frac{1}{K_s} - \left[\left(c_H + c_G + \frac{1}{K_s} \right)^2 - 4c_Hc_G \right]^{1/2} \right\} \quad (1)$$

4.2. Synthesis of sensors

Sensors **1**, **2**, and **3** were prepared from the condensation of indolylaldehyde with anthrone, 1,3-indandione, and malonitrile, respectively, as depicted in Scheme 1 [13].

4.2.1. 10-(Indol-3-yl)-methylene-anthrone-9 (1)

Indole-3-carboxaldehyde (0.73 g, 5 mmol) and anthrone (0.97 g, 5 mmol) were refluxed in a mixture of toluene (80 mL) and glacial acetic acid (0.5 mL). Any water formed during the reaction was removed azeotropically by heating in a Dean-Stark apparatus overnight. Solvents were evaporated under reduced pressure, and the crude product was purified by column chromatography with dichloromethane as an eluent to obtain **1** as a red solid (0.92 g, 57% yield). Mp: 247–248 °C. ESI-MS: m/z 322.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6), δ (ppm): 11.67 (s, 1H, NH), 8.42 (d, 1H, VinylH, $J = 8.00$ Hz), 8.16 (d, 2H, Ar_{anthra}H, $J = 7.20$ Hz), 8.07 (s, 1H, CHNH), 8.04 (d, 1H, Ar_{indolyl}H, $J = 7.20$ Hz), 7.76 (m, 2H, Ar_{anthra}H), 7.45 (m, 4H, Ar_{anthra}H), 7.11 (m, 2H, Ar_{indolyl}H), 6.93 (t, 1H, Ar_{indolyl}H, $J = 7.20$ Hz). ^{13}C NMR (100 MHz, DMSO- d_6), δ (ppm): 183.35, 140.66, 137.32, 136.52, 132.96, 131.59, 131.03, 129.39, 128.67, 128.14, 127.77, 126.81, 126.26, 126.10, 125.43, 124.16, 123.27, 122.07, 120.19, 119.81, 112.13, 112.06. Anal. Calcd. for sensor **1** (C₂₃H₁₅NO): C, 85.96; H, 4.70; N, 4.36. Found: C, 85.91; H, 4.69; N, 4.40.

4.2.2. 2-(Indol-3-yl)-methylene-indene-1,3-dione (2)

Indole-3-carboxaldehyde (0.73 g, 5 mmol) and 1,3-indandione (0.73 g, 5 mmol) were suspended in 15 mL of acetic acid and 3 drops of concentrated HCl were added under vigorous stirring. Then the solution was refluxed for 25 min and poured into 200 mL of water. The precipitate formed was filtered, dried, and purified by column chromatography with dichloromethane as an eluent to give **2** as an orange solid (1.09 g, 80% yield). Mp: 298–299 °C. ESI-MS: m/z 274.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6), δ (ppm): 12.76 (s, 1H, NH), 9.63 (s, 1H, VinylH), 8.17 (s, 1H, CHNH), 8.03 (m, 4H, Ar_{indolyl}H), 7.88 (m, 4H, Ar_{indandi}H). ^{13}C NMR (100 MHz, DMSO- d_6), δ (ppm): 190.22, 189.67, 141.36, 139.21, 138.42, 136.66, 135.29, 134.96, 134.73, 128.29, 123.71, 122.64, 122.27, 122.11, 121.11, 118.22, 113.16, 112.35. Anal. Calcd. for sensor **2** (C₁₈H₁₁NO₂): C, 79.11; H, 4.06; N, 5.13. Found: C, 79.16; H, 4.08; N, 5.09.

4.2.3. 2-(Indol-3-yl)-methylene-malononitrile (3)

Indole-3-carboxaldehyde (0.73 g, 5 mmol) was dissolved in a solution of malonitrile (0.33 g, 5 mmol) in dry dichloromethane (10 mL) and then 3 drops of triethylamine were added and the resulting solution was stirred overnight at room temperature. Precipitate formed was filtered and washed with cold dichloromethane (3 × 20 mL), then recrystallized with dichloromethane to afford **3** as a yellow solid (0.83 g, 86% yield). Mp: 223–224 °C. ESI-MS: m/z 192.2 $[M-H]^+$. 1H NMR (400 MHz, DMSO- d_6), δ (ppm): 12.79 (s, 1H, NH), 8.71 (s, 1H, VinylH), 8.53 (s, 1H, CHNH), 8.03 (dd, 1H, ArH, $J = 6.60$ Hz), 7.57 (dd, 1H, ArH, $J = 6.60$ Hz), 7.28 (m, 2H, ArH). ^{13}C NMR (100 MHz, DMSO- d_6), δ (ppm): 152.54, 136.27,

133.42, 126.73, 123.93, 122.56, 119.04, 115.97, 115.91, 113.08, 110.99, 69.06. Anal. Calcd. for sensor **3** (C₁₂H₇N₃): C, 74.60; H, 3.65; N, 21.75. Found: C, 74.62; H, 3.61; N, 21.72.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.08.001.

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