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A Chemodosimetric Probe Based on a Conjugated Oxidized Bis-Indolyl System for Selective Naked-Eye Sensing of Cyanide Ions in Water

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Abstract: A new bis-indolyl-based colorimetric probe has been synthesized. This allows a Michael-type adduct formation for the detection of cyanide ions. The probe shows a remarkable color change from red to colorless upon addition of the cyanide ions in pure water. The cyanide ion reacts with the probe and removes the conjugation of the bis-indolyl moiety of the probe with that of the 4-substituted aromatic ring. This renders the probe colorless. The mechanism of the reaction of the probe with the cyanide ion was established by using ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and kinetic studies.

Keywords: bis-indolyl · chemodosimetry · cyanides · sensors · water

Introduction

Cyanide is among the most lethal anions.[1] The maximum permissible limit for cyanide ions in water is 0.2 ppm as specified by the United States Environmental Protection Agency (EPA).[2] The cyanide content detected in the blood of fire victims is found to be 23–26 μM.[3] Despite its extreme toxicity, cyanide is used in many industries such as gold mining, electroplating, metallurgy,[4] and so on, which produce nearly 140000 tons of cyanide per year worldwide.[5] This makes the selective detection of CN^- in water absolutely crucial.

On account of its high toxicity, many research groups have made efforts to make efficient cyanide-ion sensors. The main approaches that have been used for the anion detection involve tinkering with hydrogen-bonding motifs, donor–acceptor or electrostatic interactions, and so forth.[6] But for the detection of CN^- ion, most of the probes based on supramolecular approaches depend on the hydrogen-bonding motifs.[7] The main disadvantage of such an approach, however, is the lack of selectivity. Other anions—for example, F^-, acetate, and phosphate ions—often interfere with such assays. Some of the other ways to detect CN^- ions involve chemical reaction of cyanide with metal-coordinated sensors,[8] especially to copper-ion-complexed sensors, and also by the reaction of cyanide ion with CdSe quantum dots[9] or appropriate boronic acid derivatives.[10]

An alternative strategy used by some researchers for the detection of CN^- employs reaction-based indicators.[6a, 11] This generally provides improved selectivity toward CN^- detection due to the nucleophilic character of it. Reported reaction-based indicators of CN^- include probes based on oxazines,[12] cationic boranes,[13] acridinium salts,[14] benzil-based systems,[15] β-turn motifs,[16] α,β-unsaturated systems,[17] coumarins,[18] hydrazones,[19] aldehydes, and ketones.[20] But most of these probes suffer from limitations such as the requirements of high temperature, interference with other ions in the medium, and lack of visible changes in color. Most importantly for many of these, there is a serious lack of solubility in water. This limits the practical use of such probes for sensing the CN^- in water. Thus development of new reaction-based probes that work in water are absolutely necessary for detecting CN^- in water.

An ideal ion sensor or a probe should fulfill some important criteria such as 1) adequate sensitivity, 2) high selectivity towards the analyte, 3) fast response time, and 4) good signal-to-noise ratio. In addition, the probe must sense the ion in water, there should be no hysteresis, and it should have excellent long-term stability. Apart from these, a good sensor also needs to be robust, economic, simple, and reliable. Thus there is ongoing effort in search of new sensors that possess most if not all of these qualities.

Due to our continuing interest in the design of various small molecular sensors for different ions,[21] we have been involved in the search of new probes based on original chemistry. Many bis-indolyl-based probes have been reported for the detection of various ions,[22] but only one system

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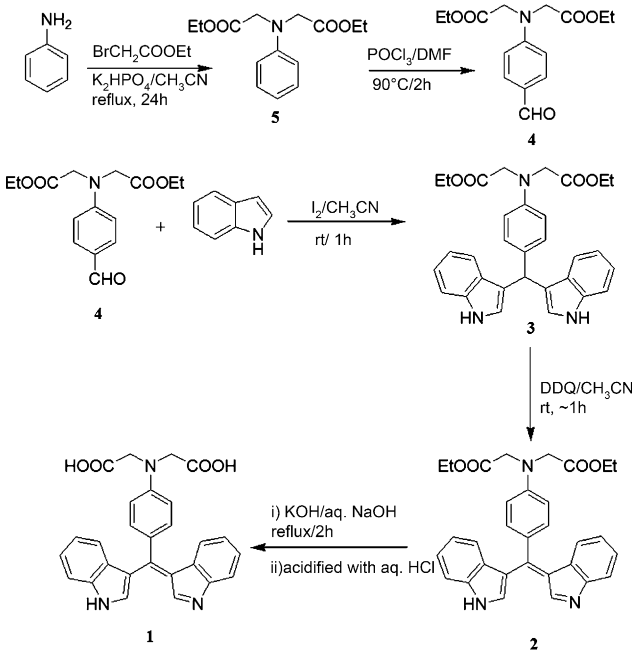
so far is known that reports the detection of cyanide ions in a 7:1 water/acetonitrile medium.[23] We report herein the synthesis of a new water-soluble oxidized bis-indolyl-based probe, **1**, which possesses two −COOH groups. This probe specifically reacts with the CN^- ion in pure water at ambient temperature and produces a remarkable change in color from red to colorless. The detection limit of the probe for the cyanide ion is below the ppm level, which is higher than the permitted limit of cyanide ions in water. The probe shows an immediate visible change in color from red to orange with the addition of cyanide, which becomes colorless with time. The presence of a through conjugation in **1** by means of its oxidized bis-indolyl moiety renders it highly colored. The added CN^- reacts with **1** in such a way that it cuts off the conjugation of the molecule, thereby resulting in the disappearance of its color. The mechanism of this process has been investigated by both NMR spectroscopy and mass spectrometry, and also by using kinetic studies.

Results and Discussion

Probe **1** was synthesized in good overall yield (≈69%) by the synthetic route presented in Scheme 1 and was characterized by both NMR (^1H and ^{13}C) spectroscopy and mass spectrometry.



Scheme 1. Synthetic route to **1**.

The addition of CN^- to **1** in water resulted in an immediate change in color from red to orange, which progressively became colorless within approximately 2 h (Figure 1). This suggests that some reaction probably takes place between CN^- and **1**, which removes the conjugation of the molecule and renders it colorless.

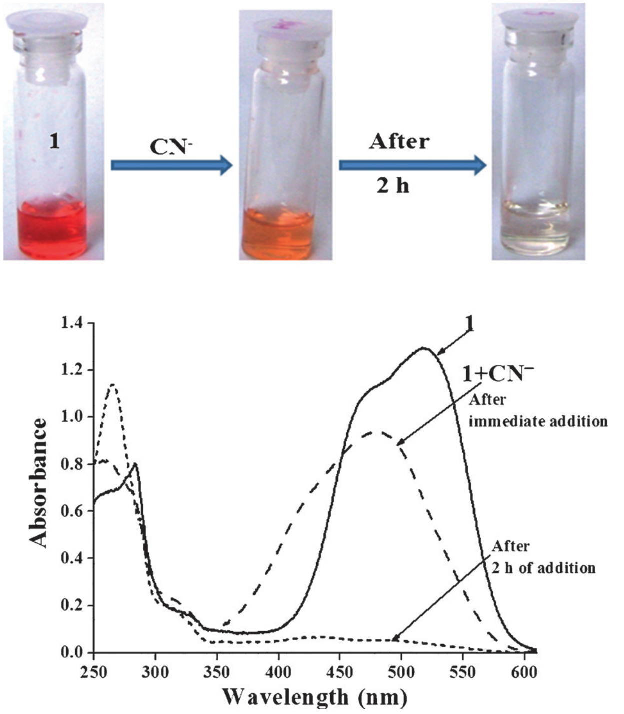


Figure 1. UV/Vis and colorimetric changes in **1** (50 μM) after immediate addition of CN^- (50 equiv) in water and after 2 h of addition.

The UV/Vis spectra showed a change in the absorption maximum (λ_{max}) from 530 to 488 nm immediately after the addition of cyanide ions (Figure 1). Then the band with $\lambda_{max}=488$ nm started decreasing progressively, and it completely vanished after approximately 2 h with a concomitant increase in the absorbance at 265 nm. The process maintained an isosbestic point at 291 nm, which suggests that there is equilibrium between the species involved. The selectivity of the probe was checked by the addition of a 50-fold excess amount of each of the various anions such as F^-, Cl^-, Br^-, I^-, AcO^-, SCN^-, $H_2PO_4^-$, N_3^-, and NO_3^- (all as potassium salts). None of the above anions showed any color change (Figure 2). The UV/Vis spectra did not show any change upon addition of any of these anions (Figure 2a). The immediate changes were observed both visibly and in the UV/Vis spectra upon the cyanide ion addition only.

The plot of changes in the absorbance at 413 nm upon the immediate addition of various anions clearly showed excellent selectivity of probe **1** towards the cyanide ion (Figure 2b).

Probe **1** showed an emission maximum at 590 nm upon excitation at 465 nm ($\lambda_{ex}=465$ nm). We checked the fluorescence responses of the emission band with the addition of various anions. Upon excitation of the probe at 465 nm, it could detect selective changes after the addition of the cyanide ion only. It showed a blueshift of approximately 20 nm immediately and selectively upon the addition of CN^- (Figure 3). None of the other added anions showed any shift in the emission maximum band under these conditions.

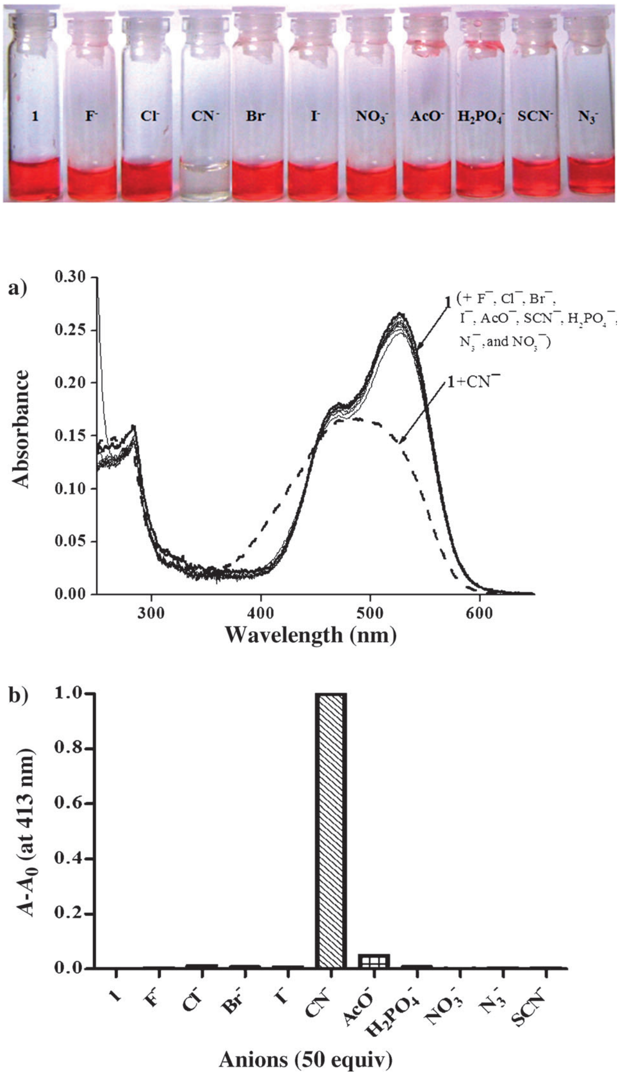


Figure 2. Top: Changes in color after addition of 50 equiv of various anions to **1** (50 μM) in water observed after 2 h. Bottom: a) Changes in the UV/Vis spectra of 10 μM of **1** after immediate addition of anions (50 equiv); b) normalized changes in the absorbance at 413 nm after immediate addition of each anion.

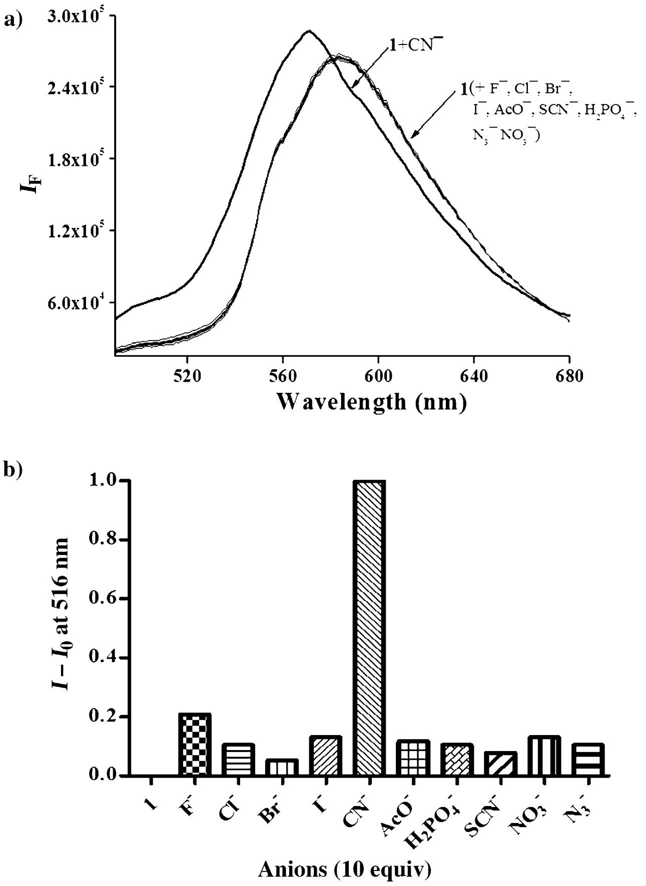


Figure 3. a) Fluorescence spectra of **1** (10 μM) (λ_{ex} = 465 nm) after immediate addition of various anions (10 equiv). b) Normalized change in fluorescence intensity at 516 nm of **1** (λ_{ex} = 465 nm) after addition of various anions (10 equiv).

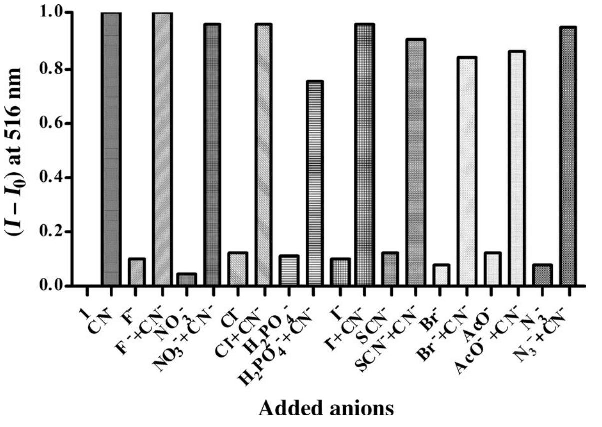


Figure 4. Normalized change in the emission intensity of **1** after addition of the CN⁻ ions (10 equiv) in the presence of an excess amount of other anions (25 equiv).

The interference was also checked in the presence of other anions, which showed that none of the other anions interfered with the CN^- ion detection (Figure 4). Furthermore, the titration studies with CN^- ions were performed upon excitation at 465 nm. The fluorescence intensity at 516 nm showed an incremental increase upon addition of cyanide (see the Supporting Information). The detection limit that was calculated from this titration showed a detection limit of approximately 0.38 ppm for the cyanide ion in water.[24] A gradual and complete change in color of **1** upon addition of the cyanide ion indicated a reaction-based change. To check this, we examined the time course of the reaction of **1** in the presence of an excess amount of cyanide ions (50-fold over **1**). The reaction followed a pseudo-first-order kinetic behavior in the presence of 50-fold excess amount of CN^- over **1** (Figure 5). The rate constant of the reaction was found to be $(1.658 \pm 0.003) \times 10^{-2}\,\text{min}^{-1}$ ($r^2 = 0.99994$) at 25 °C. This indicates that in approximately 40 min the absorption intensity at 480 nm almost halved upon the addition of CN^- ions.

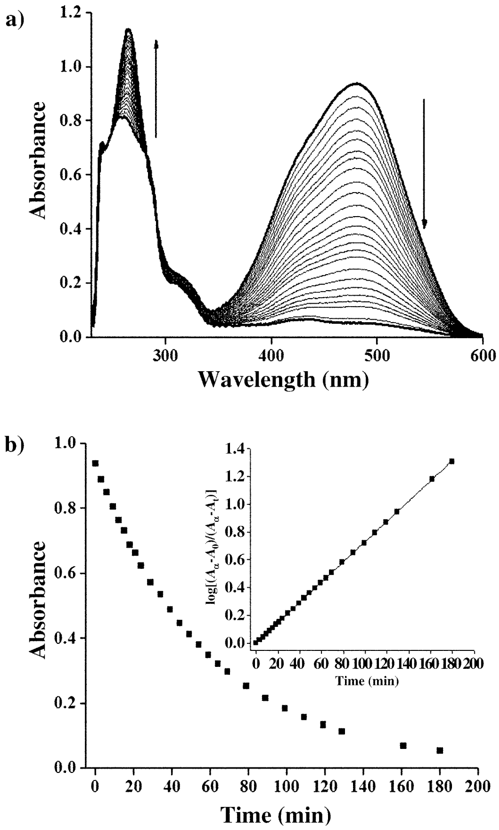


Figure 5. a) Changes in the UV/Vis spectra of **1** (50 μM) with time upon addition of CN^- ions (50 equiv). b) Changes in the $A_{480\,nm}$ were plotted against time. Inset: plot showing the first-order reaction.

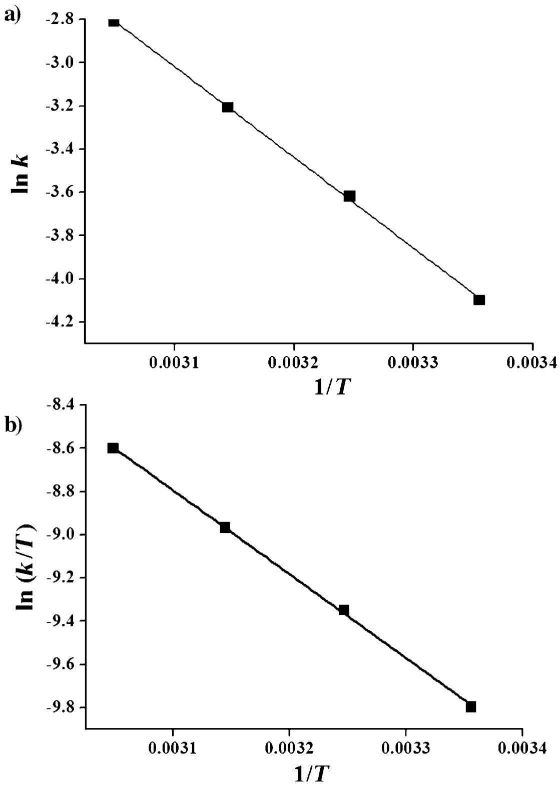


Figure 6. a) Arrhenius plot of the rate constants for cyanide complexation with **1**. b) Plot of $\ln(k/T)$ against $1/T$ (Eyring–Polanyi equation for calculating the activation free energy ($\Delta G^{\#}$), enthalpy ($\Delta H^{\#}$), and entropy ($\Delta S^{\#}$)) for the reaction of CN^- with **1**.

We further checked the changes in the rates of this reaction under pseudo-first-order kinetic conditions at various temperatures (see the Supporting Information). As expected, the rates increased as the temperature increased (Table 1), and at 55 °C, the absorbance halved in just approximately 11 min.

Table 1. Rates of reaction of cyanide ions with **1** in water at different temperatures.

T [°C]	Rate × 10^{-2} [min^{-1}]	r^2
25	1.658 ± 0.003	0.9999
35	2.682 ± 0.008	0.9998
45	4.049 ± 0.018	0.9997
55	6.032 ± 0.020	0.9994

From the rate constants measured at different temperatures, we determined the activation energy and frequency factor values on the basis of the Arrhenius rate equation [Eq. (1)] (Figure 6a). By using the Eyring–Polanyi equation [Eq. (2)], the activation parameters—for example, free energy ($\Delta G^{\#}$), enthalpy ($\Delta H^{\#}$), and entropy ($\Delta S^{\#}$)—of the reaction were calculated (Figure 6b, Table 2). A negative value of the activation entropy suggested the associative nature of the reaction.

Table 2. Activation parameters calculated by using the Eyring–Polanyi equation.[a]

E_a [$\mathrm{kcal\,mol^{-1}}$]	A [$\mathrm{min^{-1}}(\times 10^{22})$]	$\Delta H^{\#}$ [$\mathrm{kcal\,mol^{-1}}$]	$\Delta S^{\#}$ [$\mathrm{cal\,mol^{-1}\,K^{-1}}$]	$\Delta G^{\#}$ [$\mathrm{kcal\,mol^{-1}}$][a]
8.33	9.51	7.70	−40.76	21.08

[a] For the reaction carried out at 328 K.

$$\ln k = (-E_a/R)(1/T) + \ln A \qquad (1)$$

$$\ln(k/T) = (-\Delta H^{\#}/R)(1/T) + \ln(k_B/h) + \Delta S^{\#}/R \qquad (2)$$

in which k = rate constant, E_a = activation energy, R = universal gas constant, T = absolute temperature, A = pre-exponential factor, k_B = Boltzmann constant, and h = Planck's constant.

The reaction was also monitored by following the changes in the fluorescence emission spectra as a function of time upon the addition of an excess amount of cyanide. The fluorescence emission intensity increased at 500 nm with a concomitant decrease at 590 nm (Figure 7a). The changes in the fluorescence emission intensity were compared for each anion after 2 h of addition, and it showed an enhancement in the fluorescence intensity at 500 nm of approximately 10 times with CN^- specifically (Figure 7b).

The pH dependence of the probe in aqueous media was also checked by both UV/Vis and fluorescence emission

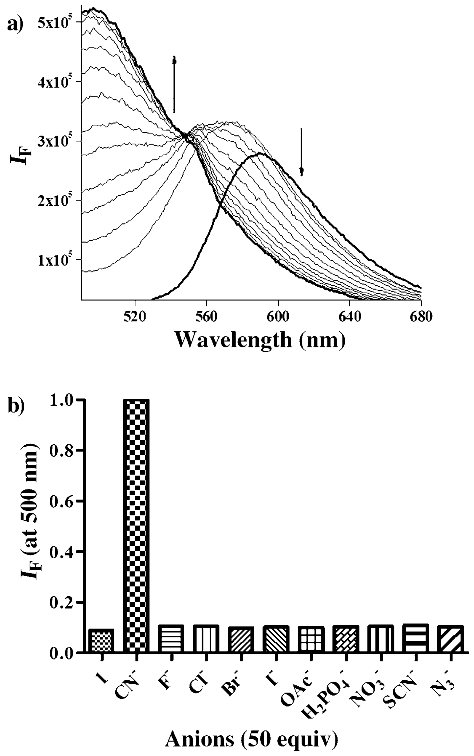


Figure 7. a) Changes in the fluorescence intensity ($\lambda_{ex} = 465$ nm) of **1** (10 μM) with time upon addition of CN^- (50 equiv). b) Normalized fluorescence intensity of **1** at 500 nm after 2 h addition of various anions.

spectroscopy. Cyanide ion was added to the buffered solution of the probe at different pH values. The results indicated that the binding of **1** with the CN^- only occurred effectively above pH 6 (Figure 8). Below pH 6, no change due to the addition of CN^- ion was observed in either the absorption or emission spectra.

The rates of change in both absorption as well as emission spectra upon the addition of 50 equivalents of CN^- were found to be faster at higher pH. But the rate of change in water was found to be much higher than in the buffered solution of pH 7. To investigate this, we checked the pH of the probe solution in water after adding 50 equivalents of KCN. The addition of an excess amount of KCN made the water basic (the pH changed from 6.8 to 8.5). This observation is consistent with literature.[25] This explains why a faster rate of reaction in water was observed. To ensure that the change in color was not due to a change in pH, we have checked the UV/Vis spectra of **1** in basic solution. In a medium of $pH > 9$ it showed only an initial blueshift of the absorption maximum but did not show any further change with time. Thus further change in the absorption spectrum appeared due to the cyanide ion addition, which indicated the reaction of CN^- ions with the probe.

To ensure that the change in color was not due to hydrolysis, we also checked the stability of compound in water by allowing the same solution to stand for 48 h. No change was observed in the solution of **1** after allowing it to stand for a longer time (see the Supporting Information).

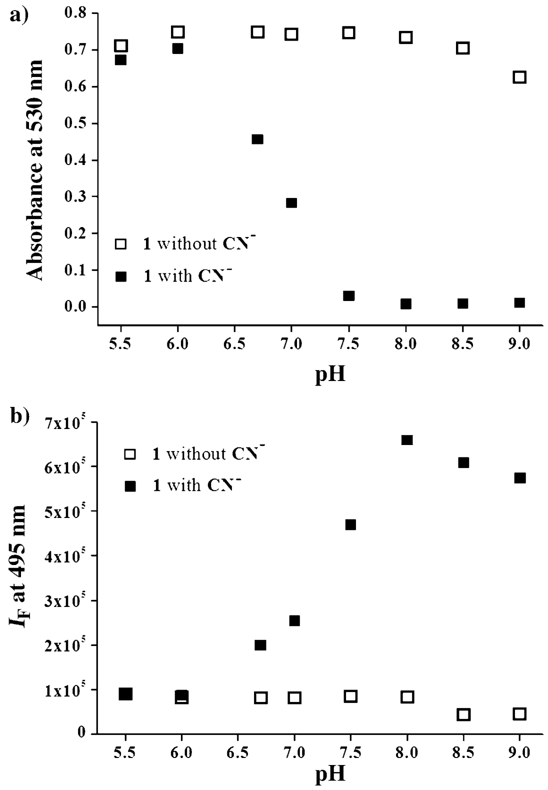


Figure 8. a) Plot of absorbance of **1** (50 μM) at 530 nm (observed after 4 h) after adding CN^- ions (50 equiv) at different pH. b) Plot of fluorescence intensity of **1** (10 μM) ($\lambda_{ex} = 465$ nm) at 500 nm (observed after 4 h) after adding CN^- ions (50 equiv) at different pH.

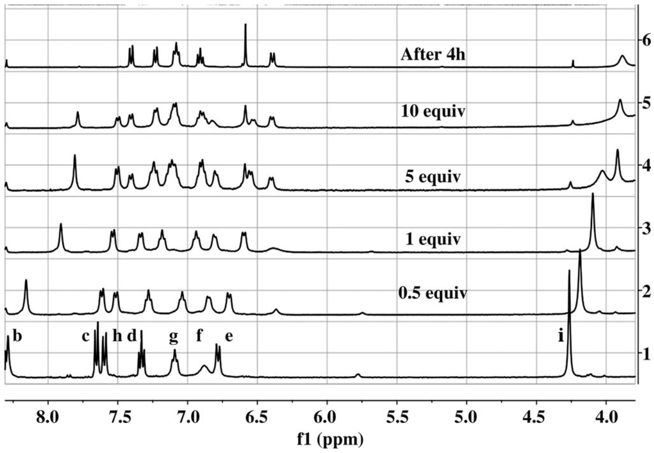
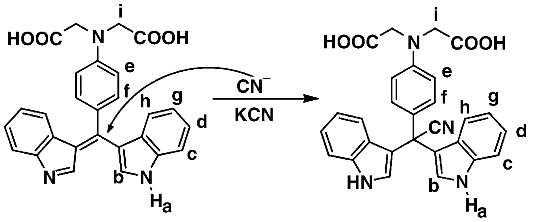


Figure 9. Partial ^1H NMR (400 MHz) spectra of **1** in [D$_6$]DMSO in the absence and presence of 0.5, 1, 5, and 10 equiv of KCN.

To further investigate the reaction, ^1H NMR spectroscopic titration of **1** was performed by adding KCN in [D$_6$]DMSO (Figure 9 and the Supporting Information).

All the protons of **1** shifted upfield upon addition of CN^-. After the addition of 1 equivalent of cyanide, new peaks started appearing, which indicated the formation of new species (see the Supporting Information). After the titration, when the ^1H NMR spectra were recorded after keeping the same solution for approximately 4 h, a completely new set of peaks emerged, which again supported the formation of new species.

A comparison between the ^{1}H NMR spectra of the unoxidized diester precursor of **1**, that is, **3**, and that of the oxidized diester **2** (Scheme 1) revealed that CN$^-$ ion formed an adduct with **1** under these conditions. Each proton of **3** showed ^{1}H NMR spectroscopic signals upfield relative to that of the oxidized **2**. It further indicates that the added cyanide ion attacks the C=C bond that maintains the conjugation of the 4-substituted aromatic ring with the bis-indolyl moiety (Scheme 2). Thus when the reaction is over, it completely cuts off the conjugation, which causes a pronounced change in color from red to colorless.



Scheme 2. Plausible mechanism of the cyanide adduct formation with **1**.

The actual mechanism of the reaction was probed by ^{13}C NMR spectroscopy, DEPT-135 (DEPT = distortionless enhancement by polarization transfer), and mass spectrometry. After recording the ^{13}C NMR spectra following the CN$^-$ addition reaction, the peak that corresponded to the formation of a tetrahedral carbon appeared at $\delta = 43.8$ ppm (see the Supporting Information). The peak at $\delta = 43.8$ ppm was also not observed in the DEPT spectrum, thereby confirming the reaction of cyanide to that of the α,β-unsaturated double bond (see the Supporting Information).

The formation of the **1**-CN$^-$ adduct was also evident from the detection of a mass spectral peak at 477.155 (*m/z* calcd 477.156), which might be assigned due to the formation of the cyanide addition product of **1** (see the Supporting Information).

Conclusion

In conclusion, we have synthesized a new colorimetric probe for the effective detection of cyanide ions in water. The detection of CN$^-$ by using probe **1** was found to be totally free of interference from any other anions. The probe gives an immediate response to the cyanide ion both by visible color change as well as by spectroscopic means (UV/Vis and emission spectra). The cyanide ion can be detected below ppm level by using fluorescence emission spectroscopy. In contrast to other reported reaction-based probes for cyanide, the present system does not require any preoptimized conditions such as mixing of solvents, phase-transfer reagents, or high temperature. The mechanism of the reaction was investigated by various means. The time-course studies in the presence of an excess amount of CN$^-$ showed that the reaction follows an apparent first-order kinetic pathway. The activation entropy calculated by using the Eyring–Polanyi equation suggested the associative nature of the reaction. Furthermore, ^{1}H NMR spectroscopic titration and ^{13}C NMR spectroscopic studies confirmed the mode of reaction between probe **1** and CN$^-$ ion. This is further supported by the DEPT-135 spectrum and mass spectral analysis. Taken together, a plausible mechanism of the reaction is presented that is shown to operate by means of a Michael-type adduct formation under ambient conditions of pH and temperature in water.

Experimental Section

General

All solvents and reagents were purified and dried by means of the usual methods. All starting materials were obtained from the best known commercial suppliers and used as received. IR spectra were recorded using a Perkin–Elmer FTIR spectrum BX. ^{1}H and ^{13}C NMR spectra were measured using either a 300/75 MHz or a 400/100 MHz spectrometer. HRMS analyses were performed using an electron spray ionization (ESI) mass spectrometer (Q-TOF YA263 high-resolution instrument). UV/Vis absorption spectra were obtained using a Shimadzu UV-2100 spectrophotometer. Fluorescence spectra were recorded using a Fluorolog Horiba Jobin Yvon spectrofluorometer. The stock solution of the compound **1** was made in DMSO and the final concentration of DMSO in all the studies were less than 0.5 %

*Synthesis of **5***

Ethyl bromoacetate (4.67 g, 28.0 mmol) was added slowly to a mixture of aniline (0.931 g, 10.0 mmol) and K_2HPO_4 (5.22 g, 30.0 mmol) in CH_3CN (10 mL) at 0 °C and then allowed to stir at RT for 30 min. The reaction mixture was then heated to reflux for 24 h.[26] After evaporation of the excess amount of solvent under vacuum, water (5 mL) was added to it. A crude material was obtained after separation and extraction with EtOAc followed by evaporation of the organic solvent. The compound **5** was obtained after purification of the crude oil by column chromatography over silica gel (eluted at 5 % EtOAc/*n*-hexane). Yield 99 %, 2.62 g (pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 5.4$ Hz, 6 H), 4.18 (s, 4 H), 4.19–4.24 (q, 4 H), 6.63 (d, $J = 8.1$ Hz, 2 H), 6.80 (t, $J = 7.35$ Hz, 1 H), 7.21–7.26 ppm (m, 2 H); IR (neat): $\tilde{\nu}$2981.2, 1745.2, 1733.6, 1600.6, 1508.0, 1386.5, 1172.5, 1024.0, 748.2 cm^{-1}; 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.

*Synthesis of **4***

$POCl_3$ (3.54 g, 23.0 mmol) was added dropwise over a period of 10 min to cold *N*,*N*-dimethylformamide (DMF; 5.6 mL, 72.4 mmol), and then the mixture was allowed to mix under stirring for 30 min.[27] Compound **5** (5.52 g, 20.8 mmol) was added to this slowly under cold conditions and the solution was heated at 90 °C for 2 h. After completion of the reaction, the reaction mixture was cooled and poured over ice-cold water. This mixture was then neutralized to pH 7 by addition of solid sodium acetate. It was then extracted with EtOAc, washed successively with water and brine, and dried over anhydrous Na_2SO_4. Crude oily material was obtained after evaporation of the solvent. Compound **4** was obtained from this after purification by silica gel column (eluent: 20 % EtOAc/*n*-hexane) as a white solid. Yield 92 %, 5.6 g. M.p. 57–59 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.0$ Hz, 6 H), 4.17–4.25 (m, 8 H), 6.63 (d, $J = 8.4$ Hz, 2 H), 7.72 (d, $J = 8.4$ Hz, 2 H), 9.76 ppm (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 53.3, 61.5, 111.7, 127.3, 131.9, 152.5, 169.6, 190.4 ppm; IR (neat): $\tilde{\nu} = 3478.9$, 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 $\mathrm{cm^{-1}}$; MS (ESI): m/z: 294 $[M+\mathrm{H}]^+$, 316 $[M+\mathrm{Na}]^+$; HRMS: m/z: calcd for $\mathrm{C_{15}H_{19}NO_5Na}$ $[M+\mathrm{Na}]^+$: 316.1161; found: 316.1162.

*Synthesis of **3***

A mixture of **4** (293 mg, 1.0 mmol), indole (234 mg, 2.0 mmol), and a catalytic amount of iodine (approximately 13 mg, 0.2 mmol) in acetonitrile (10 mL) was stirred at room temperature for approximately 1 h. After completion of the reaction, the mixture was quenched with aqueous $\mathrm{Na_2S_2O_3}$ solution (5 %, 10 mL) and the aqueous phase was extracted with ethyl acetate (3×5 mL). The organic phase was dried over anhydrous $\mathrm{Na_2SO_4}$, and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel to afford **3** (eluent: ≈20 % EtOAc in *n*-hexane). Yield 94 %, 478 mg (white solid). M.p. 146–147 °C; TLC: $R_\mathrm{f}=0.2$ (30 % EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): $\delta=1.23$ (t, $J=6.9$ Hz, 6 H), 4.08 (s, 4 H), 4.17 (q, $J=7.1$ Hz, 4 H), 5.75 (s, 1 H), 6.47–6.57 (m, 4 H), 6.96 (t, $J=7.3$ Hz, 2 H), 7.10–7.14 (m, 4 H), 7.29–7.37 (m, 4 H), 7.87 ppm (s, 2 H); ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): $\delta=14.1$, 38.9, 53.4, 61.0, 110.9, 112.3, 118.9, 119.9, 121.6, 123.6, 127.0, 129.3, 133.8, 136.6, 146.0, 171.2 ppm; IR (KBr): $\tilde{\nu}=$ 3451.9, 3353.6, 2981.4, 1725.9, 1610.2, 1517.7, 1455.9, 1415.4, 1336.4, 1193.7, 1095.3, 1025.9, 736.7 $\mathrm{cm^{-1}}$; MS (ESI): m/z: 508 $[M+\mathrm{H}]^+$, 510 $[M+\mathrm{H}]^+$, 532 $[M+\mathrm{Na}]^+$; HRMS: m/z: calcd. for $\mathrm{C_{31}H_{31}N_3O_4Na}$ $[M+\mathrm{Na}]^+$: 532.2212; found: 532.2212.

*Synthesis of **2***

A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 227 mg, 1.0 mmol) in acetonitrile was added dropwise to a solution of **3** (510 mg, 1.0 mmol) in acetonitrile at room temperature. Upon addition of the first few drops of DDQ solution, the initial color turned to dark red immediately. After stirring at room temperature for 2 h, a dark red solid precipitated, which was filtered, washed thoroughly with $\mathrm{CH_3CN}$, and dried under vacuum. Yield 90 %, 457 mg (green solid). M.p. 204–205 °C; ^{1}H NMR (400 MHz, $[\mathrm{D_6}]$DMSO): $\delta=1.22$ (t, $J=6.8$ Hz, 6 H), 4.16 (q, $J=6.8$ Hz, 4 H), 4.48 (s, 4 H), 6.90 (d, $J=7.6$ Hz, 4 H), 7.11 (s, 2 H), 7.35 (t, $J=7.2$ Hz, 2 H), 7.58 (s, 2 H), 7.66 (d, $J=8.0$ Hz, 2 H), 8.34 (s, 2 H), 13.4 ppm (s, 1 H); ^{13}C NMR (100 MHz, $[\mathrm{D_6}]$DMSO): $\delta=14.0$, 52.5, 60.8, 112.6, 113.9, 120.0, 120.6, 123.4, 125.0, 139.0, 144.6, 154.2, 169.1 ppm; IR (KBr): $\tilde{\nu}=3149.8$, 2987.5, 2217.9, 1741.2, 1598.7, 1512.0, 1477.9, 1411.9, 1186.7, 1123.8, 747.6 $\mathrm{cm^{-1}}$; MS (ESI): m/z: 508 $[M[+\mathrm{H}]^+$; HRMS: m/z: calcd for $\mathrm{C_{31}H_{30}N_3O_4}$ $[M+\mathrm{H}]^+$: 508.2236; found: 508.2257.

*Synthesis of **1***

Aqueous KOH (39 mg, 0.68 mmol) was added dropwise at RT to a solution of **2** (86 mg, 0.17 mmol) in MeOH (0.2 mL), and then the mixture was heated to reflux for 2 h.[27] After cooling to RT, the reaction mixture was acidified to pH ≈2.0 by dropwise addition of diluted HCl. A solid was precipitated out, which was then filtered. The solid was then washed with $\mathrm{MeOH/H_2O}$ (1:1) and dried under vacuum. Yield 90 %, 69 mg (red solid). M.p. >250 °C; ^{1}H NMR (400 MHz, $[\mathrm{D_6}]$DMSO): $\delta=4.28$ (s, 4 H), 6.80 (d, $J=8.4$ Hz, 2 H), 6.89 (s, 2 H), 7.11 (d, $J=6.4$ Hz, 2 H), 7.34 (t, $J=7.6$ Hz, 2 H), 7.61 (d, $J=8.4$ Hz, 2 H), 7.66 (d, $J=8.0$ Hz, 2 H), 8.30 (s, 2 H), 13.43 ppm (br s, 2 H); ^{13}C NMR (100 MHz, $[\mathrm{D_6}]$DMSO): $\delta=55.9$, 112.3, 113.9, 119.9, 120.8, 123.3, 124.9, 126.7, 138.0, 139.1, 144.2, 154.0, 171.6 ppm; IR (KBr): $\tilde{\nu}=3114.3$, 2226.7, 1721.6, 1600.2, 1496.2, 1412.1, 1387.1, 1317.0, 1212.9, 1187.6, 1129.9, 965.6, 749.0 $\mathrm{cm^{-1}}$; MS (ESI): m/z: 452 $[M+\mathrm{H}]^+$; HRMS: m/z: calcd for $\mathrm{C_{27}H_{22}N_3O_4}$ $[M+\mathrm{H}]^+$: 452.1601; found: 452.1610.

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