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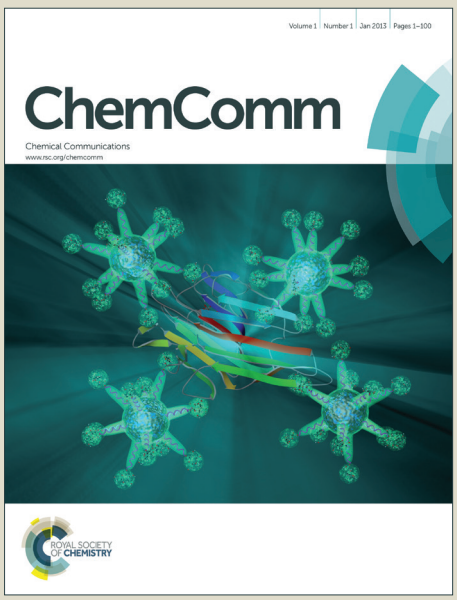

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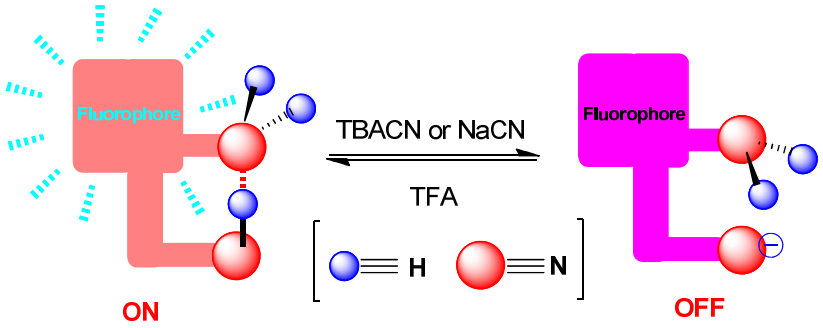
Reversible and selective chemosensor based on intramolecular $NH^{\cdots}NH_2$ hydrogen bonding for cyanide and pH detection

Chuanxiu Zhang, Kai Ji, Xinyu Wang, Hongwei Wu and Chuanxiang Liu*



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A highly selective and reversible chemosensor for cyanide and pH detection was developed based on intramolecular NH···NH_2 hydrogen bonding.

The cyanide ion (CN^-) is extremely toxic and plays crucial roles in health and environment.[1] CN^- can affect many normal functions in the human body such as the vascular, visual, central nervous, cardiac, endocrine, and metabolic systems.[2] Moreover, CN^- is widely used in many chemical processes including electroplating, plastics manufacturing, gold and silver extraction, tanning, and metallurgy.[3] Therefore, there is a growing interest in the development of artificial chemosensors with high selectivity for CN^-, particularly in water.[4] Optical chemosensors involving colorimetric and/or fluorescence changes before and after binding with CN^- have been investigated extensively over the past decade because of their simple, inexpensive, and rapid implementation.[5] However, the main challenge in sensing CN^- is the absence of chemosensors with the ability to successfully compete with water molecules, i.e., sensing features in pure water.[6]

The most reported strategy is mainly concentrated on the chemodosimeters for CN^- based on the nucleophilic addition of CN^- to activated carbonyl groups or double bonds.[7] This approach has positive advantages such as high selectivity and irreversible recognition; however, some of them have certain limitations such as delayed response, lack of reversibility and high detection limit.[8] Intramolecular hydrogen bonds (IHBs) have been used as the binding site and/or the active fragments in chemosensors to auxiliary binding with anion, with the usual optical response.[9] The most frequent use of IHBs is the N–H···O interaction involving the excited-state intramolecular proton transfer (ESIPT) mechanism.[10] To improve the sensitivity and operational ability of the chemosensor in an aqueous solution, a novel IHB fragment should be used to design the chemosensor. In this study, using the novel NH···NH_2 IHB as the binding site for the first time (Fig. 1), we developed a chemosensor that can detect tetrabutylammonium cyanide (TBACN) with comparable efficiency as that for NaCN even in 100% pure water.

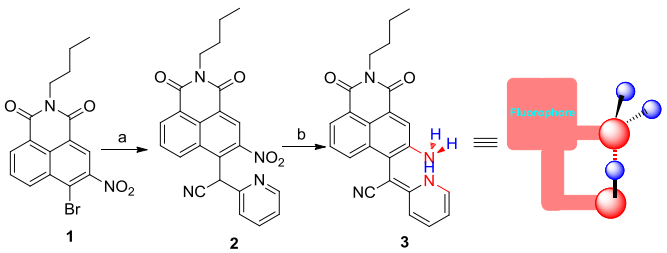

Fig. 1 Synthesis of chemosensor **3** and its cartoon-type representation; Reagents and conditions: (a) NaH, N_2, THF, 2-(cyanomethyl)pyridine, r.t., 70% yield; (b) $SnCl_2$, r.t., 79% yield.

As shown in Fig. 1, intermediate **2** was conveniently synthesized by the condensation of *N*-butyl-4-bromo-3-nitro-1,8-naphthalimide (**1**) with 2-(cyanomethyl)pyridine according to our recently reported procedure.[11] Intermediate **2** was reduced with stannous chloride to afford the target chemosensor **3**. To clarify the occurrence of the intramolecular pyridine NH···N (amino group), a reference compound, *N*-butyl-4-bromo-3-amino-1,8-naphthalimide (**4**), was also synthesized according to the reported procedure.[12] The structures of **2**–**4** were confirmed by ^{1}H NMR, ^{13}C NMR, HRMS, and IR spectroscopy (Fig. S1–S12). An NH signal (broad peak, δ 12.74 ppm) and the downfield shift of the amino NH_2 signal in chemosensor **3** (δ 6.87 ppm) compared to the free NH_2 signal (δ 6.34 ppm) in reference compound **4** indicate the presence of intramolecular NH···NH_2 bonding (Fig. S13). Solvent effect on the fluorescence spectra further confirmed that the maximum wavelength of the chemosensor can be red-shifted in polar solvents (Fig. S14). Moreover, a DFT calculation was performed to obtain the lowest energy state (Fig. S15), also indicating the occurrence of stable intramolecular NH···NH_2 hydrogen bonding.

Next, the selectivity of chemosensor **3** was first investigated in a DMSO/H_2O mixture (1:1, v/v) using various anions as their tetrabutylammonium (TBA) or sodium salt. Upon the addition of 4.0 equiv TBACN or NaCN, a slightly red-shifted peak (26 nm) was observed; then the color of the solution of chemosensor **3** turned from pink to violet as shown in Fig. S16a (inset, naked-eye detection). Importantly, the spectra of the other anions such as F^-, AcO^-, $H_2PO_4^-$, Cl^-, Br^-, I^-, NO_3^-, BF_4^-, and ClO_4^- (as their TBA salts) and the color of the solution of chemosensor **3** did not change. Further, the

spectrophotometric titration of chemosensor **3** (20 μmol L^{-1}) with TBACN was investigated in DMSO (Fig. S16b), DMSO/H_2O mixture (1:1, v/v, Fig. S16c), and pure water (100%, Fig. S16d); the addition of increasing concentrations of CN^- ions resulted in a dramatic color change from pink to violet, accompanied by the gradual red-shift of one new peak at 531, 526, and 517 nm, respectively, with a clear isosbestic point (524, 515, and 484 nm, respectively). This indicates a possible deprotonation of the pyridine NH group through hydrogen bonding (NH···CN^-) interactions, forming the intramolecular charge-transfer (ICT) state in the conjugated system of naphthalimide with 2-(cyanomethyl)pyridine.[13] The corresponding detection limits of chemosensor **3** in DMSO, DMSO/H_2O, and H_2O were determined to be 2.58, 7.98, and 17.61 μmol L^{-1}, respectively (Fig. S17–S19). Notably, chemosensor **3** is very soluble in water because of its NH···NH_2 IHB; further, the chemosensor worked well in 100% water for the selective sensing of CN^- ions without any interference caused by the other anions (Fig. S20–S21). The time-dependent behavior of the chemosensor in aqueous media for CN^- showed that the fluorescence of **3** was declined sharply within 0.1 s, indicating that **3** is quite sensitive to CN^- (Fig. S22).

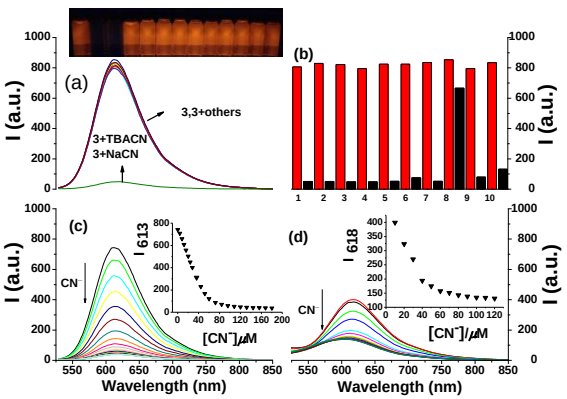

Fig. 2 (a) Fluorescence spectral changes of 2.0 × 10^{-5} mol L^{-1} solution of **3** in DMSO/H_2O (1:1) with various anions (Inset: from left to right: **3** only, NaCN, TBACN, F^-, AcO^-, $H_2PO_4^-$, Cl^-, Br^-, I^-, NO_3^-, BF_4^-, ClO_4^-); (b) Interference experiments of chemosensor **3** (2.0 × 10^{-5} mol L^{-1}) in DMSO/H_2O (1:1) for CN^- in the presence of other anions. The red bars represent the emission at 613 nm of **3** in the presence of 6.0 equiv of the anion of interest (from left to right: $H_2PO_4^-$, Cl^-, Br^-, I^-, NO_3^-, HSO_4^-, BF_4^-, AcO^-, ClO_4^-, F^-). The black bars indicate the change that occurs upon subsequent addition of 6.0 equiv of CN^- to the solution containing **3** and the anion of interest; (c) fluorescence spectral changes of **3** (λ_{ex} = 515 nm) in DMSO/H_2O (1:1) upon the titration with TBACN (0 to 6.0 equiv); and (d) fluorescence spectral changes of **3** (λ_{ex} = 515 nm) in H_2O (100%) upon the titration with TBACN (0 to 6.0 equiv).

In general, naphthalimide derivatives show excellent fluorescence property; [14] however, novel naphthalimide derivatives could not be obtained by the classical modification rather than the above mentioned synthesis routes. Therefore, we also used fluorescence spectroscopy to investigate the behavior of novel chemosensor **3** in the presence of CN^- ions. Upon the addition of CN^- ions (TBA^+ or Na^+ salts) to a solution of **3**, a significant decrease in the fluorescence intensity at 613 nm (λ_{ex} = 515 nm) was observed, and none of the other anions (F^-, AcO^-, $H_2PO_4^-$, Cl^-, Br^-, I^-, NO_3^-, BF_4^-, or ClO_4^-) induced any significant change in the fluorescence spectrum of chemosensor **3** (Fig. 2a). These results indicate that chemosensor **3** shows excellent selectivity for CN^- over other anions. This excellent selectivity was further highlighted by the interference experiments (Fig. 2b), in which a consistent turn-off fluorescence response was observed upon the addition of 6.0 equiv of CN^- ions to the solutions of **3** containing equal concentrations of potentially competing anions or other cations (Fig. S23). Moreover, a specific emission response to the CN^- in a DMSO/H_2O mixture (1:1, v/v) was observed (Fig. 2c). Upon the addition of CN^- ions to a solution of **3**, a significant decrease in the fluorescence intensity at 613 nm (λ_{ex} = 515 nm) was observed, indicating that the ICT state was affected by an increased electronic charge on the pyridine N atom and the coplanar geometry between 2-(cyanomethyl)pyridine with naphthalimide was destroyed by the CN^--induced deprotonation of the pyridine NH group.[15] Importantly, a linear fluorescence response to CN^- concentration in the range 0–56 μmol L^{-1} was established (Fig. S24), indicating that chemosensor **3** is potentially useful for the quantitative determination of CN^- ions. Although quenching of the fluorescence signal (on–off) occurred, the detection limits of chemosensor **3** in DMSO, DMSO/H_2O mixture (1:1, v/v), and pure 100% water (Fig. 2d) were determined by fluorescence spectroscopy to be almost the same, 0.034, 0.045, 0.18 μmol L^{-1}, respectively (Fig. S25–S27). [16]

To test the potential mechanism involving the deprotonation of pyridine NH, ^{1}H-NMR titrations were further performed in DMSO-d_6 (Fig. S28). The addition of increasing concentrations of CN^- ions resulted in a significant upfield shift of the amino-NH_2 group signal and the disappearance of pyridine NH signal, indicating the NH deprotonation followed by the rupture of the NH···NH_2 IHB. When the concentration of CN^- was <1.0 equiv, the H_{A-D} signal of naphthalimide also slightly shifted to upfield; with further increase in the amount of CN^-, the signal straightly shifted to the downfield. This can be attributed to the competitive hydrogen bonding interactions between inter and intra IHB induced by the deprotonation of the NH group, probably because the rigid planarity of the probe was gradually destroyed. The deprotonation mechanism was further investigated by the titration of chemosensor **3** with TBAF, in which the remarkably FHF signal was observed when 10.0 equiv of F^- was introduced (Fig. S29).[17]

The reversibility and reusability of a chemosensor is very beneficial, particularly for the applications in real environment for the detection of CN^-.[18] A reversible CN^- chemosensor in water has rarely been reported, and some of the reported chemosensors showed a delayed response close to a few minutes.[19] To test the applicability of chemosensor **3**, systematic titration studies of **3**-CN^- complex (Fig. 3a) were performed by adding increasing amounts of trifluoroacetic acid (TFA) by fluorescence techniques. Upon the addition of increasing amounts of TFA to a solution of [**3**-CN^-] complex, the fluorescence emission gradually increased (Fig. 3b), and a 12-fold enhancement was observed on the addition of 6.0 equiv TFA. Thus, upon CN^- addition, the IHB and the coplanar rigid system constructed by the fluorophore with pyridine-2-acetonitrile were destroyed by the deprotonation of the NH group, causing the ICT quenching of the naphthalimide excited state. With further addition of TFA, the ICT quenching was prevented because of the protonation of the pyridine NH group, and the fluorescence properties were reverted. The reversible and reusable response of chemosensor **3** was demonstrated by carrying out six alternate cycles of the titration of chemosensor **3** with CN^-, followed by the addition of TFA (Fig. 3c). Moreover, the repeated demonstration of the OFF/ON fluorescence behavior and visual colour change from light

pink to violet and then back to light pink as shown in Fig. 3d (interval in ~30 s) demonstrate the sensitive reversibility and reusability of chemosensor **3**.

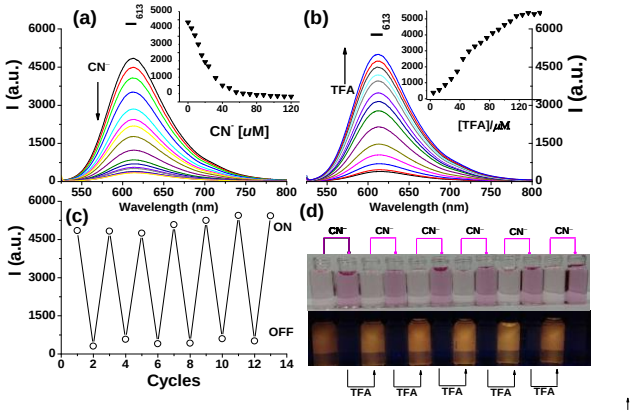

Fig. 3 (a) Fluorescence spectral changes of **3** (2.0×10^{-5} mol L^{-1}, λ_{ex} = 515 nm) upon the titration with TBACN (0 to 6.0 equiv) in DMSO/H_2O (1:1); (b) fluorescence spectral changes of **3**-CN^- (λ_{ex} = 515 nm) upon the titration with TFA (0 to 6.0 equiv) in DMSO/H_2O (1:1); (c) relative fluorescence intensity (λ_{max}= 613 nm) obtained during the titration of **3** with CN^- and H^+ (TFA) in DMSO/H_2O (1:1); (d) visual color and fluorescent changes after each sequential addition of CN^- and H^+ in DMSO/H_2O (1:1).

We wondered whether chemosensor **3** would also work in the solid state.[20] The probe was adsorbed onto filter papers by immersing a filter paper in the DCM solution of chemosensor **3** (1.0 mmol L^{-1}) for 5 min and then drying it in air. Various concentrations of CN^- ions were applied on the paper using capillary tubes; the color of the points changed from pink to violet with increasing concentrations of CN^- (Fig. 4a). This demonstrates a prototype device using chemosensor **3** for detecting CN^- in real-world applications. Moreover, the test strips can detect CN^- at a low limit of ~10 μmol L^{-1}. The reversibility and reusability of chemosensor **3** were also investigated in the solid state for the detection of CN^-.[21] Upon the application of CN^- on the test strips, there was an evident violet "CN" marker on them, which could be observed by the naked eyes and a nonfluorescent marker under a hand-held fluorescent lamp. The "CN" marker on the test strips disappeared after the addition of TFA (Fig. 4b), indicating that chemosensor **3** can work well in both the solid state and solutions. Confocal microscopic images were also investigated, which show a fluorescent "turn–off" response upon addition of cyanide ions, indicating that the chemosensor could reacts with cyanide ions in living cells (Fig. S30).

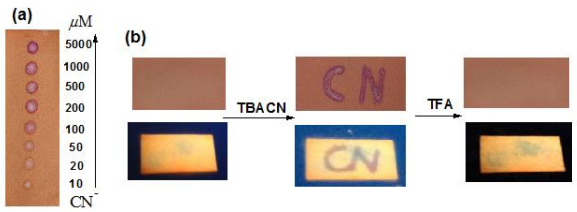

Fig. 4 Photograph of test strips painted with (a) various concentrations of cyanide ions (from top to bottom: 5000, 1000, 500, 200, 100, 50, 20, 10 μmol L^{-1}); (b) 5000 μmol L^{-1} cyanide followed by 5000 μmol L^{-1} TFA (top and bottom represents bright and fluorescence image, respectively; The test strips were irradiated with a hand-held UV lamp at 365 nm.)

We also wondered whether probe **3** would also be a sensitive pH chemosensor.[22] Its fluorescence changes in various pH values were also examined (Fig. S31). The pH dependence of probe **3** was first investigated in hydrochloric acid and sodium hydroxide solutions. When the pH values were increased from 1 to 4, the fluorescent intensity of probe **3** at 615 nm was progressively increased, indicating the formation of $NH^{\cdots}NH_2$ intramolecular hydrogen bonding. However, as the pH values were further increased from 5 to 10, the fluorescent intensity at 615 nm was decreasing linearly, which was resulted of the destruction of intramolecular hydrogen bonding (Fig. S31a, S31b). The detailed tiny changes of pH values were next achieved in sodium phosphate buffer solutions (5.8 – 8.0), and the fluorescent intensity decreased sharply ranging from 5.8 to 7.0, indicates that probe **3** is of high sensitivity within the above narrow pH range. Therefore, the compound **3** can be further used as a potential pH chemosensor (Fig. S31c, S31d). Further, the acidity constant of chemosensor **3** (pK_a = 2.77, Fig. S32) was calculated, and which is more acidic than that of those reported naphthalimide. [23]

In summary, we successfully demonstrated an approach involving the intramolecular $NH^{\cdots}NH_2$ hydrogen bonding to construct a novel chemosensor, with remarkable advantages such as high selectivity, reversibility, and detecting CN^- in 100% pure water. The sensitivity of the chemosensor in aqueous media for CN^- is quite short close to 0.1 second. A simple and inexpensive test strip can be prepared to determine the CN^- content of contaminants. Furthermore, the fluorescence of the chemosensor showed significant varying toward tiny pH changes and could be used as a potential pH chemosensor. The strategy involving intramolecular $NH^{\cdots}NH_2$ hydrogen bonding may pave the way for the development of novel water-soluble chemosensors. Efforts are underway in our laboratory to provide a potential CN^- detection device in concerned households.

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Notes and references

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† Electronic Supplementary Information (ESI) available: ^1H, ^{13}C NMR, IR and HRMS-ESI copies of compounds (**2**–**4**), and additional spectroscopic data.. See DOI: 10.1039/c000000x/

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