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A turn-on fluorescent probe for cyanide based on aggregation of terthienyl and its application for bioimaging

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ABSTRACT

A turn-on fluorescent probe based on terthienyl for CN^- has been constructed and CN^- was detected by taking advantage of aggregation-induced emission (AIE) behavior of terthienyl units in aqueous solutions. The probe displayed a high selectivity and sensitivity for CN^- against other analytes, and the detection limit was measured to be 0.1 μM. The aggregation behavior confirmed by DLS and SEM caused fluorescence enhancement in the sensing environment. A simple paper test strip system for the rapid monitoring of CN^- was developed. Moreover, the probe could be employed to detect CN^- in biological samples.

1. Introduction

As a raw material, cyanide anion (CN^-) plays a significant roles and is extensively utilized in many fields, such as electroplating, metallurgy, synthetic fibers and resins industry, as well as gold mining. The worldwide consumption of CN^- is estimated as much as 1.5 million tons per year [1,2]. However, CN^- is more famous for its toxicity. Although there is no endogenous CN^- in live cells, it is readily absorbed through lungs, gastrointestinal track and skin. CN^- can inhibit cellular respiration in mammals by inhibiting the cytochrome oxidase of the mitochondrial respiratory chain, leading to vomiting, convulsion, loss of consciousness, and eventual death [3–5]. The lethal dosage of CN^- for human is 0.5–3.5 mg in per kg of body [6]. According to the World Health Organization (WHO), only CN^- concentration in water lower than 1.9 μM is available to drink [7]. Therefore, efficient and simple methods for CN^- detection from the contaminant sources are highly required. For its high sensitivity, fast response, and easy operation, plenty of chemical-reaction based fluorescent probes for CN^- have been reported in vitro assay and in vivo imaging application over the past decade years [8–10]. However, most of these organic probes are poorly water-soluble, and some limitations, such as sensitivity, selectivity, longer wavelength emissions, and compatibility within 100% aqueous solutions are still attracted more attention [11].

A positively charged indolium or benzo[e]indolium-based probes, because of their long emission wavelengths, specific binding site, and satisfactory water solubility, are frequently used for detecting CN^- [12–18], HSO_4^- [19–21], and HS^- [22,23] in aqueous solutions. Most of these probes for analytes relied on disturbing the π-conjugation and blocking the intramolecular charge transfer (ICT) process, resulting fluorescence turn-on or ratio changes. Distinctively, Zhang et al. reported a fluorescence turn-on probe with a tetraphenylethylene (TPE) and an indolium, which could detect CN^- through the aggregation-induced emission (AIE) feature [13]. AIE, opposite to the aggregation-caused quenching (ACQ) effect, has attracted much attention as a novel mechanism for the fluorescent probe design. However, the fluorescent probes for CN^- based on AIE are really rare [13,24,25].

2,2′:5′,2″-Terthiophene-5-carbaldehyde (TTA) can be regarded as a α-aldehyde end-capped oligomer of thiophene with terthienyl units, and its AIE characteristic can be shown in solutions with appropriate water content [26]. The chain-typed TTA is commonly used as building block to construct light harvesting dyes, fluorescence chemosensor, and memory device, etc. [27–30]. Herein we report a new fluorescence turn-on probe **1** structured by terthienyl and indolium, which can be used for monitoring CN^- in 100% aqueous solution with fluorescence enhancement mainly caused by the AIE effect of **1**-CN (Scheme 1). The results reveal that **1** exhibits high sensitivity and selectivity toward CN^- in the sensing environment, and it can detect CN^- in biological samples.

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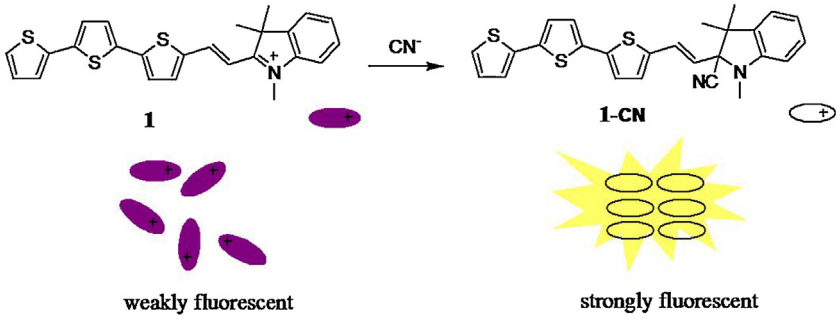

Scheme 1. Probe **1** and its sensing mechanism.

2. Experimental

2.1. Materials

All reagents and solvents were purchased from commercial source and used without further purification, if not stated. All reactions were carried out on the magnetic stirrers and their reaction process was monitored on thin layer chromatography (TLC). Stock solutions (100 mM) of CN^-, F^-, Cl^-, Br^-, I^-, HS^-, HSO_3^-, SO_4^{2-}, NO_3^-, NO_2^-, AcO^-, ClO_4^-, SCN^-, N_3^-, $H_2PO_4^-$, GSH, Cys, and Hcy were prepared by direct dissolution of proper amounts of sodium salts.

2.2. Instruments

Absorption and fluorescence spectra were taken on a Shimadzu UV-1800 spectrophotometer and a Hitachi F-2700 fluorescence spectrometer, respectively. A pH meter (Mettler Toledo, Switzerland) was used to determine the pH values. ^{1}H NMR and ^{13}C NMR measurements were recorded at 600 and 150 MHz on a Brucker Avance 600-MHz spectrometer. $CDCl_3$ and Dimethyl sulfoxide (DMSO-d_6) were solvents and tetramethylsilane (TMS) was used as internal standard. HRMS (ESI) were taken on a Fourier transform ion cyclotron resonance mass spectrometry (Varian 7.0T). Dynamic light scattering (DLS) measurements were conducted on a Delsa PN A54412AB Nano Submicron Grain Particle Size Analyzer. The scanning electron microscopy (SEM) studies were performed using a Hitachi S-4800 scanning electron microscope. One drop of the solutions was placed on a silicon slice, which was then dried in air. An Olympus FV-1000 confocal fluorescence microscope and Hala cells were used in the in vivo experiment.

2.3. Preparation of probe *1*

2.3.1. 2,2′:5′,2″-Terthiophene-5-carbaldehyde (TTA)

TTA was synthesized according to the reported literature [26]. A solution of 2,2′:5′,2″-terthiophene (0.87 g, 3.50 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, then $POCl_3$ (0.76 g, 5.02 mmol) in dry DMF (0.39 mL, 5.02 mmol) and CH_2Cl_2 (15 mL) were added dropwise. After stirring the resulting mixture overnight at room temperature, the reaction mixture was added with 1 M sodium acetate (30 mL), and then stirred for about 5 h. The resulting solution was extracted with CH_2Cl_2, and the combined organic layer was washed with water, brine, sequentially, and dried on anhydrous $MgSO_4$. Solvents were removed by rotary evaporation and the residue was purified by silicon gel column chromatography to afford TTA as a yellow solid (0.80 g, yield: 82%). ^{1}H NMR (600 MHz, DMSO-d_6, ppm): δ = 9.84 (s, 1H), 7.65 (s, 1H), 7.26–7.11 (m, 4H), 7.10 (d, 1H), 7.03 (d, 1H).

2.3.2. Probe *1*

A solution of TTA (0.1 g, 0.36 mmol) and 1,2,3,3-tetramethyl indolium iodide (0.1 g, 0.36 mmol) in ethanol (10 mL) was refluxed overnight. After cooling down, the solid was collected by vacuum filtration, washed with cold ethanol. The crude product was recrystallized from ethanol to give a purple solid (0.12 g, yield: 60%). ^{1}H NMR (600 MHz, DMSO-d_6, ppm): δ = 8.63 (d, 1H), 8.14 (s, 1H), 7.84 (d, 2H), 7.69 (s, 1H), 7.64–7.55 (m, 4H), 7.48 (s, 1H), 7.43 (s, 1H), 7.23 (d, 1H), 7.14 (d, 1H), 4.07 (s, 3H), 1.77 (s, 6H). HRMS (ESI): calcd for $[M]^+$ 432.0909, found 432.0907 (Figs. S1 and S2).

2.4. Titration experiments of *1*

Deionized water was used as the solvent for titration experiment. The titrations were carried out in 10-mm quartz cuvettes at room temperature. Probe **1** was dissolved in DMSO (spectroscopic grade) to afford a concentration of 10 mM stock solution, and then diluted to 20 μM with deionized water. Anions (as their Na^+ salt, 10 mM and 100 mM) in deionized water were added to the diluted probe solution and used for the sensing behavior experiment. The excitation wavelength was 375 nm, and the PMT voltage was 400 V. The excitation and emission slit width were 10 nm and 10 nm, respectively.

2.5. ^{1}H NMR analysis experiments of *1*

The solution of probe **1** (3×10^{-3} M) in DMSO-d_6 (450 μL) was placed in the NMR tube, then equal mol of NaCN in D_2O (50 μL) was added.

2.6. Paper test of probe *1*

The neutral filter papers were dipped in the stock solution of **1** (10 mM) and dried. Then various solutions of anions (1 mM, 2.5 μL) were seriatim dropped.

2.7. Cell incubation and fluorescence imaging

Hala cells were seeded onto the cover slips and cultured in DMEM in an incubator (37 °C, 5% CO_2 and 20% O_2). After 24 h, the cover slips were washed three times with PBS to remove the media and then cultured in PBS for use. Ten microlitre of probe **1** was added to above cellular samples and incubated for 15 min, and then washed three times with PBS. In a further experiment, CN^- (10 μM) was added to the cells and the fluorescence change was observed under the confocal fluorescence microscope.