Highly activated Michael acceptor by an intramolecular hydrogen bond as a fluorescence turn-on probe for cyanide†

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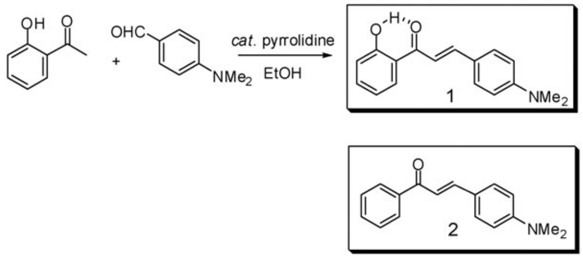
An activated Michael acceptor type of probe by an intramolecular hydrogen bond has shown a selective fluorescence turn-on response to cyanide through a conjugated addition of the nucleophilic anion to the enone probe with a 1300-fold increase in its fluorescence intensity.

The extreme toxicity of cyanide ions in physiological[1] as well as environmental[2] systems has led many researchers to develop optical probes[3] for the sensitive and selective detection of cyanide. Recently, fluorescent probes have attracted considerable interest owing to their simple and fast implementation as well as their high sensitivity.[4] Although a lot of fluorescence turn-on probes have been introduced by applying chemosensor,[5] displacement[6] or dosimeter approaches,[7] most of them have shown, however, a less than several tenths increase in their fluorescence intensity in the presence of cyanide and this therefore limits their resolution in the presence of other anions. Herein we report a fluorescent probe for the cyanide anions, which is activated by an intramolecular hydrogen bond and therefore easily reacts with cyanide to exhibit a fluorescence intensity increase of over one thousand-fold.

Recently, we have prepared optical probes with an *o*-hydroxy carbonyl group for effective intramolecular hydrogen bonding.[8] The hydrogen bonds activate the neighboring carbonyl oxygen for the fast sensing of cyanide anions. In this line of our research, we prepared a chalcone derivative having an *o*-hydroxy carbonyl group according to the literature procedure (Scheme 1).[9] The carbonyl group of **1** is plausibly being activated by the intramolecular hydrogen bond of the *o*-hydroxy group in order for the fast Michael addition of the cyanide ion. Probe **2** without a hydroxyl group was also prepared as a control compound.



Scheme 1 Synthesis of **1** and **2**.

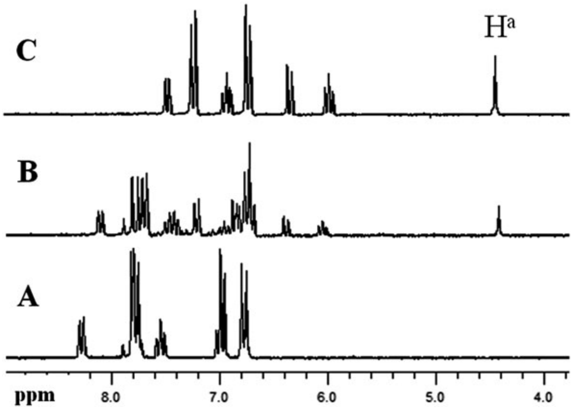


Fig. 1 Partial ^{1}H NMR spectra of **1** (20 mM) upon addition of NaCN (1 equiv.) in DMSO-d_6/D_2O (v/v, 100 : 1). (A) **1**; (B) **1** + NaCN, 0.5 h; (C) **1** + NaCN, 10 h.

To investigate the reaction pathway of **1** with cyanide, we monitored ^{1}H NMR spectra upon the addition of cyanide anions to **1** in D_2O/DMSO solvent (Fig. 1). A new peak at 4.4 ppm appeared while vinylic protons (8.3 and 7.5 ppm) disappeared and finally, a simple set of ^{1}H NMR spectra were obtained at rt after 10 h. The transformation was the Michael addition of the cyanide anions to the enone of **1** and corroboratively evidenced also by ^{13}C NMR and HRMS spectra. ^{13}C NMR spectrum showed two additional aliphatic peaks at around 44 and 31 ppm (Fig. S2, ESI†), and high resolution MS spectral analysis (Fig. S8, ESI†) indicated the presence of the Michael product at m/z 294.1363 ([M]$^+$, cal'd 294.1368).

Time-dependent UV-vis spectra of **1** showed the hypsochromic shift upon addition of cyanide in acetonitrile (Fig. 2). As the reaction proceeds, a new peak at λ_{max} 260 nm (ε = 2.8×10^4 M^{-1} cm^{-1}) increases whereas the original maximum peak at λ_{max} 430 nm (ε = 3.9×10^4 M^{-1} cm^{-1}) decreases with an isosbestic point at 272 nm. The kinetic analysis gave the rate constant $k = 8.2 \times 10^{-5}$ s^{-1} under the pseudo first-order reaction conditions.

The fluorescence of **1** is completely quenched due to the possible donor-excited photoinduced electron transfer from diethylamino-phenyl to the hydrogen bonded carbonyl group. However, the fluorescence intensity of **1** (10 μM in CH_3CN) becomes stronger upon addition of cyanide ions (100 equiv.) with a *ca.* 1300-fold intensity enhancement, the highest value ever known.[10] In contrast, other anions such as F^-, Cl^-, Br^-, I^-, N_3^-, $H_2PO_4^-$, HSO_4^-, and AcO^- have induced negligible fluorescence changes, therefore the solutions exhibited almost the same fluorescence intensities as that of **1** itself (Fig. 3). In addition, compound **2** without an intramolecular hydrogen

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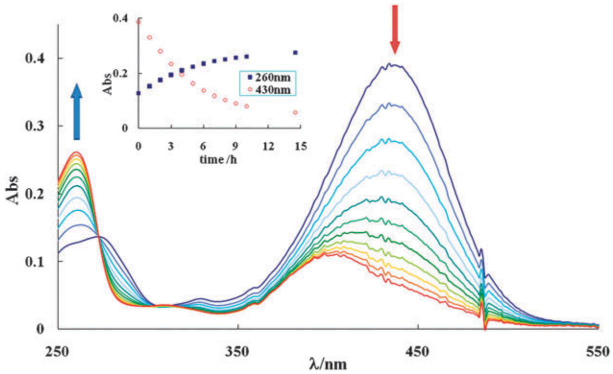

Fig. 2 Time-dependent UV-vis spectral changes upon addition of 100 equiv. of CN^- to **1** (10 μM in CH_3CN). Inset: its kinetics.

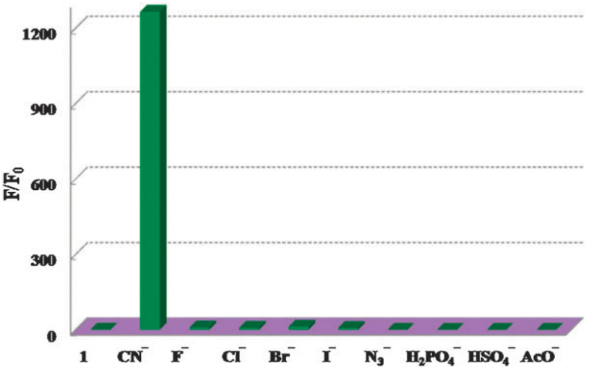

Fig. 3 Relative fluorescence intensities of **1** (10 μM in CH_3CN) in the presence of various anions (100 equiv.), where F_0 is the fluorescence intensity exerted by **1** only. λ_{ex} 272 nm, λ_{em} 469 nm.

bond, however, did not induce any significant chromophoric changes under the same condition as **1** (Fig. S4, ESI†). The higher selectivity of **1** for cyanide over other various anions may come from the hydrogen bonded enone of **1** as an activated electrophile as well as the nucleophilicity of cyanide. The competition reaction of **1** with the cyanide ion in the presence of other anions showed corroborative evidence for the selectivity of **1** toward cyanide (Fig. S5, ESI†).

The prominent changes of **1** were also observable by the naked eye (Fig. 4). Upon addition of cyanide anions, the solution color of **1** changed from yellow to colorless whereas other anions did not induce any color changes. The solution of **1**–cyanide adduct also displayed a strong blue fluorescence under a hand-gun UV spectroscopy.

To evaluate the detection limit of cyanide in solution, we measured the fluorescence changes by increasing the amount of cyanide. The lower limit of detection was *ca.* 1.7 μM with a signal-to-noise ratio of 3 in CH_3CN (Fig. S6, ESI†), meaning that probe **1** is operable well below the WHO cyanide standard in drinking water (1.9 μM)[11] and it is also useful for monitoring the lethal level of cyanide in fire victims (20 μM).[12] A Job's plot was carried out and the binding stoichiometry between **1** and CN^- was observed to be 1 : 1 (Fig. S7, ESI†).

From the spectroscopic evidence, we propose a plausible mechanism for the reaction of **1** with cyanide (Fig. 5). The activated α,β-unsaturated carbonyl group by the intramolecular hydrogen bond of *o*-hydroxyl group plays a crucial role of the Michael acceptor and reacts fast with the cyanide anion to afford an intermediate enol, which will tautomerize to the stable keto form to furnish the fluorescent phenolate **3**.[13]

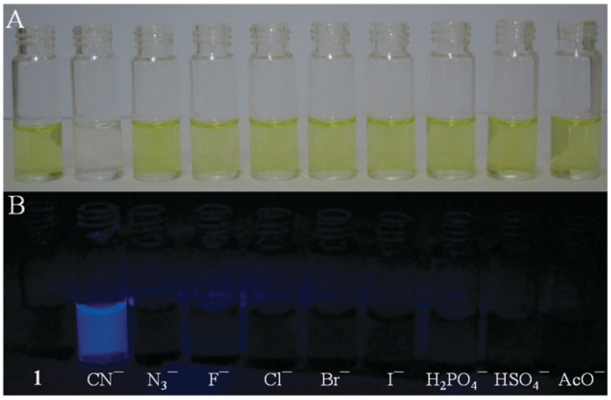

Fig. 4 Visible (A) and fluorescence (B, λ_{ex} 365 nm) images of **1** (10 μM) in the presence of 100 equiv. of anions (tetrabutylammonium salts) in CH_3CN.

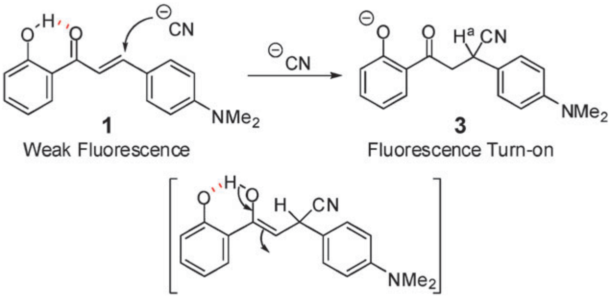

Fig. 5 Proposed reaction mechanism.

In summary, we have developed a simple chalcone derivative (**1**) having an *o*-hydroxy carbonyl group, which is highly activated by an intramolecular hydrogen bond. The Michael addition of cyanide to **1** showed a highly selective fluorescence turn-on response for the cyanide anion with a 1300-fold increase in the fluorescence intensity. A study of the fluorescence turn-on mechanism with a series of chalcone derivatives is on the way.

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