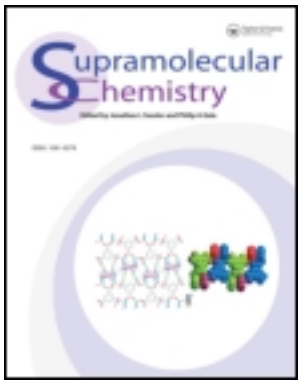

Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsch20

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Published online: 13 Aug 2012.

To cite this article: Keum-Hee Hong & Hae-Jo Kim (2013): Azo dye-based colorimetric chemodosimeter for cyanide in aqueous solution, Supramolecular Chemistry, 25:1, 24-27

To link to this article: http://dx.doi.org/10.1080/10610278.2012.712121

Supramolecular Chemistry
Vol. 25, No. 1, January 2013, 24–27

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Azo dye-based colorimetric chemodosimeter for cyanide in aqueous solution

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(*Received 11 June 2012; final version received 20 June 2012*)

Dedicated to Professor A. P. de Silva on the occasion of his 60th birthday

A latent colorimetric probe (**1**) was prepared through the Baylis–Hillman condensation reaction and applied to a Michael acceptor type of probe for cyanide in aqueous solution. The probe has shown a highly selective response to the cyanide anion over other various anions through 1,4-addition of cyanide to the α,β-unsaturated ketone unit of probe **1**. When cyanides were added, dramatic colour change of **1** was observable by the naked eye in aqueous buffer.

Keywords: Baylis–Hillman; colorimetric; cyanide; Michael acceptor; probe

Introduction

Cyanide ion is a highly toxic anion that does harm to organisms by absorption through the lungs, gastrointestinal tract and skin (*1*). The cyanide anion can strongly bind to the haem unit at cytochrome a_3, and can inhibit the electron transport chain in enzyme cytochrome oxidase at cytochrome a_3 (*2*). After binding of cyanide to cytochrome oxidase, the process of cellular oxygen metabolism is inhibited by the cyanide ion (*3*). As a result, the electron transport chain in mammals is disturbed, leading to death. Cyanide ions are also widely distributed in the environment and affect human beings. The cyanide ions have been found in many foods and plants. In addition, cyanide ions are used industrially in gold mining, electroplating and metallurgy (*4*). Humans are exposed to cyanides from food, industrial, environmental and other sources. Therefore, highly selective probes for the cyanide ion are of great interest. Despite much effort to develop efficient and selective probes for cyanide, a few chemosensors have been reported operating in aqueous environments due to the high solvation of the anions in water. To overcome the water desolvation energy during the cyanide–probe complexation, it is recently employed to take advantage of the nucleophilic nature of cyanide anion and to produce a chemodosimeter (*5*). Herein, we report an azo dye-based latent colorimetric chemodosimeter (**1**) possessing a masked phenol in the para position of an azo dye group, which exhibits a highly selective colorimetric response to cyanide over other anions in aqueous solution.

Results and discussion

Probe **1** was prepared through the Baylis–Hillman condensation reaction with 2-cyclopentenone from salicylaldehyde with an azo dye functional group (*6*). Probe (**1**) was expected to play a role of a Michael acceptor type of chemodosimeter for cyanide ions and to exhibit a dramatic colour change by the resulting free phenol group. As expected, probe **1** has shown selective response towards cyanide over various anions through 1,4-addition of cyanide to α,β-unsaturated ketone of the probe (Scheme 1).

The chemosensing behaviour of **1** was investigated by UV–vis spectroscopy. Time-dependent UV–vis spectra of **1** exhibited ratiometric changes when **1** (20 μM) was treated with CN^- (20 mM) in aqueous dimethylformamide (DMF) solution (DMF–HEPES 1:1, v/v, 0.10 M, pH 7.4). Upon the addition of cyanides to **1**, the absorbance of **1** at 380 nm decreased, whereas the absorbance at 500 nm gradually increased to afford a clear isosbestic point at 425 nm (Figure 1). The transformation of **1** to **1**-CN was completed within 6 h with the second-order rate constant $k_2 = 3.6 \times 10^{-2}\,M^{-1}\,s^{-1}$ at 25°C.

In order to get insight into the reaction, we monitored ^1H NMR spectrum after adding 0.5 equiv sodium cyanide to **1** and compared it with that of the probe itself (Figure 2). After the reaction was complete, its structure was elucidated by ^1H NMR spectral analysis. The prominent upfield shifts of vinylic proton (H^a) from 8.15 to 5.10 ppm and aromatic proton (H^b) from 7.21 to 6.23 ppm indicated that Michael addition reaction took place and significant electronic density was accumulated

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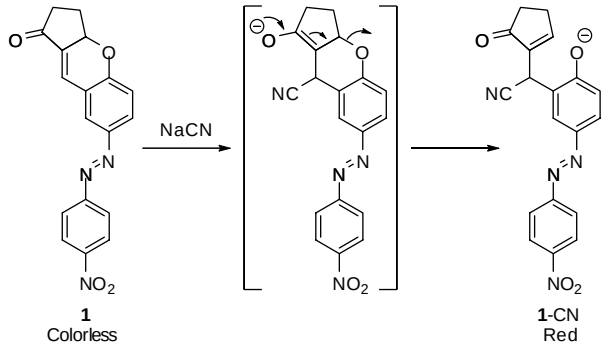
ISSN 1061-0278 print/ISSN 1029-0478 online

http://dx.doi.org/10.1080/10610278.2012.712121
http://www.tandfonline.com



Scheme 1. The Michael reaction of **1** with cyanide.

in the aromatic region of **1** owing to the free phenol formation upon the addition of cyanide anions as observed in a similar system (*7*).

The selective recognition of **1** towards CN^- could be monitored by UV–vis spectroscopy. The relative absorbance ratio (A_{500}/A_{380}) of **1** was significantly increased only by the cyanide ion, whereas other anions such as F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, HSO_4^-, AcO^- and N_3^- did not induce any detectable changes in the UV–vis spectra (Figure 3). Competitive anion assay was carried out by adding CN^- (20 mM) to **1** (20 μM) in the presence of other anions (20 mM) in 50% HEPES–DMF buffer (0.10 M, pH 7.4). It also showed a consistent result for the selectivity of

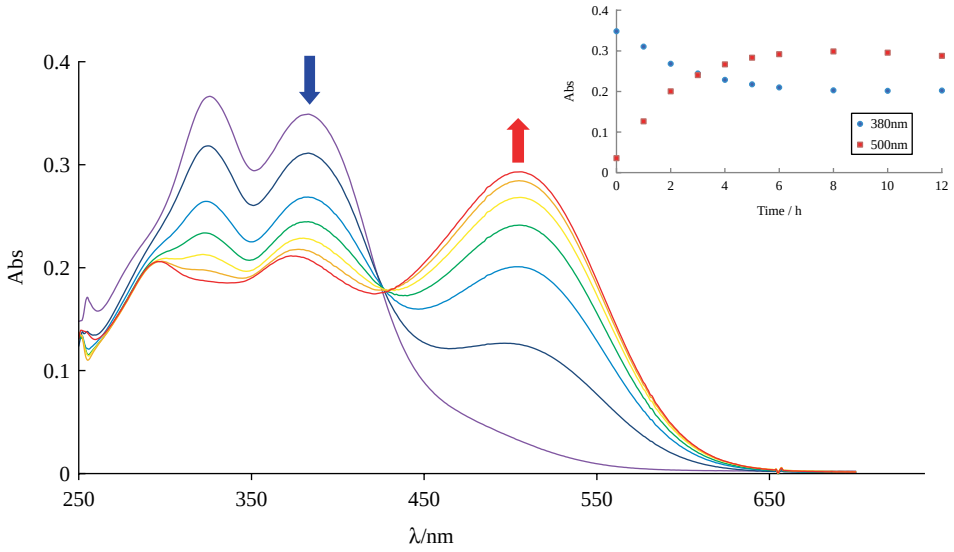


Figure 1. Time-dependent UV–vis spectra upon the addition of 1000 equiv of cyanides to **1** (20 μM, DMF–HEPES, 1:1, pH 7.4). Inset: its kinetics.

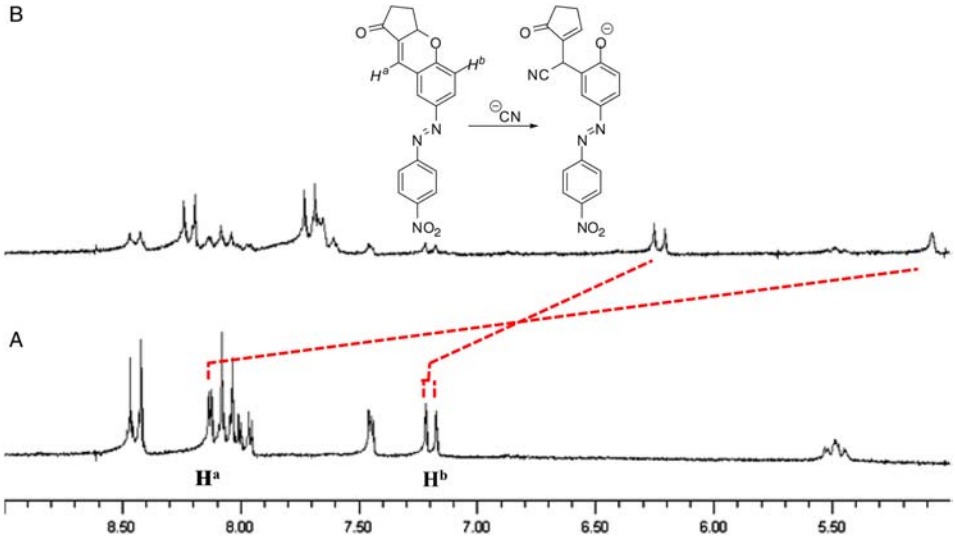


Figure 2. Partial ^{1}H NMR spectra of **1** (10 mM) upon the addition of NaCN (0.5 equiv) in DMSO-d_6–D_2O (v/v, 100:1). (A) **1**, (B) **1** + NaCN.

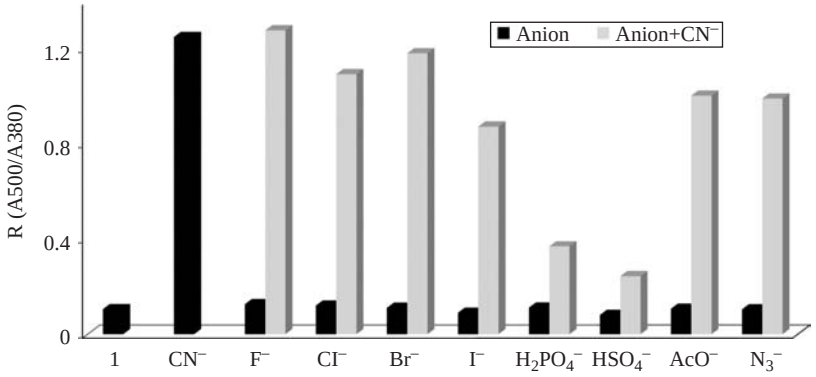


Figure 3. Ratiometric UV–vis absorbance of **1** (20 μM) in the presence of 1000 equiv anions in DMF–HEPES (1:1. v/v, 0.1 M, pH 7.4).

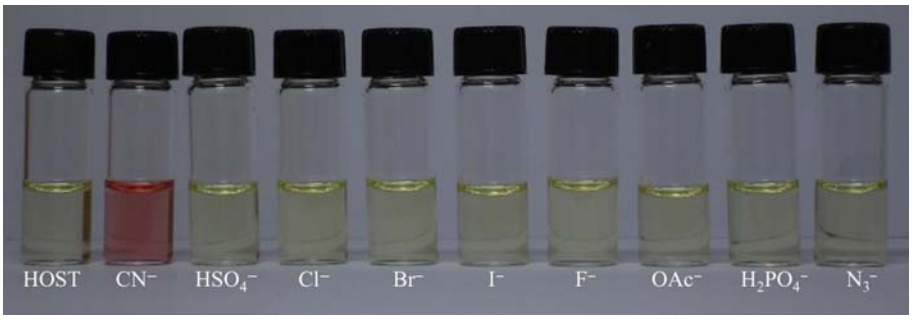


Figure 4. Naked-eye images of **1** in DMF–HEPES (1:1. v/v, 0.1 M, pH 7.4) upon the addition of various anions (1000 equiv).

1 towards CN^-. The addition of CN^- induced a significant ratiometric response in the mixture of **1** and other anions as much as that of **1**-CN solution. However, some protic anions such as $H_2PO_4^-$ and HSO_4^- interrupted the changes by decreasing the nucleophilic character of cyanide anions due to the possible hydrogen bonding between cyanide and the protic anions.

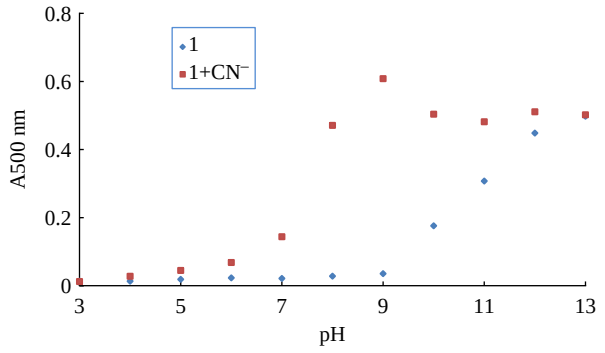


Figure 5. UV–vis absorbance change at 500 nm of **1** (20 μM) in the presence (square) and absence (diamond) of CN^- (1000 equiv) DMF–HEPES (1:1. v/v, 0.1 M, pH 7.4) as a function of pH.

The prominent bathochromic shift (>120 nm) was observable by the naked eye. The colour of **1** turned into red from colourless upon the addition of cyanide, whereas other anions did not induce any colour changes (Figure 4).

To investigate the effect of pH on the reaction of **1** to cyanide ion, the absorbance changes in **1** in the presence and absence of cyanide ions were measured at various pH (Figure 5). In the absence of CN^-, the colourless probe (**1**) showed no detectable UV–vis changes in a wide range of pH (pH 3–9). In the presence of CN^-, however, dramatic UV–vis changes were observed with concomitant colour changes into red at pH 7–9 with the maximal intensity observed at pH 9. This indicates that probe **1** can be used to detect cyanide ion around the biological pH condition.

Conclusion

We prepared a latent colorimetric probe (**1**) for cyanide. Upon addition of cyanides, probe **1** underwent a ring-opening reaction through the Michael addition of cyanide to give rise to a free phenol group, the signal of which was transduced into the azo dye unit to afford ratiometric UV–vis changes. The chemodosimeter exhibited a highly

selective and colorimetric response to cyanide ions over other anions in aqueous solution. The dramatic colour changes of **1** allowed us to detect toxic cyanide anions even by the naked eye in aqueous solvent.

Experimental

2-Cyclopenten-1-one and imidazole were purchased from Aldrich Chemical Co. and used without further purification. All solvents used for the measurements of UV–vis were purchased from Aldrich Chemical Co. as 'spectroscopic grade'. NMR measurements were carried out using 200 MHz spectrometer. All peaks were given as δ in ppm and were related to the signals of residual non-deuterated peaks. Mass spectra were recorded on a G6401A MS-spectrometer. thin layer chromatography (TLC) analyses were carried out on silica gel plates, and flash chromatography was conducted by using silica gel column packages purchased from Merck.

Synthesis of 1

2-Hydroxy-5-(4-nitrophenyldiazenylbenze)carboxaldehyde (271 mg, 1.00 mmol), 2-cyclopenten-1-one (167 µl, 2.00 mmol) and imidazole (68 mg, 1 mmol) were dissolved in tetrahydrofuran (3 ml) and water (2 ml). The reaction mixture was stirred at 66°C for 7 days, and then the final mixture was diluted with water and extracted with ethyl acetate. The mixture was purified by column chromatography using CH_2Cl_2 (R_f 0.57) to afford the desired product (**1**) as an orange solid (6.3 mg, yield 1.9%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.44 (d, $J = 9.2$ Hz, 2H), 8.13 (s, 1H); 8.06 (d, $J = 9.2$ Hz, 2H), 7.97 (m, 1H), 7.30 (s, 1H); 7.08 (d, $J = 8.6$ Hz, 1H), 5.41 (t, $J = 7.4$ Hz, 1H), 2.81–2.17 (m, 4H).

HRMS (FAB$^+$, *m*-NBA): *m/z* obsd 336.0981 ($[M + H]^+$, calcd 336.0984 for $C_{18}H_{14}N_3O_4$).

Acknowledgement

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea Government (MEST) (No. 2011-0028456).

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