Tetrahedron Letters 50 (2009) 4463–4466

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

1-(4-Nitrophenyl)-benzimidazolium-based ratiometric chromogenic probes for cyanide ion

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ARTICLE INFO

Article history:
Received 7 April 2009
Revised 11 May 2009
Accepted 16 May 2009
Available online 22 May 2009

ABSTRACT

1,3- and 1,4-bis-[1-(4-nitrophenyl)-benzimidazolium-3-methylene]benzene-based molecular probes interact selectively with cyanide ion to switch the absorbance from 270 nm to 376 nm and elaborate ratiometric chromogenic probes for the estimation of 1–270 μM cyanide ion—the desirable concentration range for practical applications.

Anion sensing is an area of immense contemporary investigations due to their significant role in many biological processes and in biological structures such as amino acids, neurotransmitters, enzyme substrates, co-factors, and nucleic acids.[1] Amongst anions, the cyanide is one of the most toxic anions and is lethal to humans at concentrations of 0.5–3.5 mg/Kg body weight.[2] In the blood of fire victims, the lethal cyanide ion concentration is 23–26 μM.[3] However, due to its wide applications in the production of organic chemicals and polymers[4] and its critical role in gold extraction process,[5] the effluents from these processes and affected soil and water samples always need to be tested for >1 μM concentrations of cyanide ion. This scenario has necessitated the development of the cyanide ion probes. The nucleophilic addition of the cyanide ion to oxazine,[6] pyrylium,[7] squarine,[8] and trifluoroacetophenone[9] derivatives that possess suitable signaling moieties has been used for developing such probes. These molecular probes act as chemodosimeters and in general, the strong affinity of cyanide ion toward the polarized sp^2-hybridized carbon plays key role.[10]

1,3-Dialkyl imidazolium and benzimidazolium salts due to their participation in both electrostatic and $[C–H]^+\cdots X^-$ interactions find generous applications as anion probes.[11] In all these molecular probes used for optical signaling, the fluorescent group is linked through sp^3 carbon spacer and has eluded the development of benzimidazolium-based ratiometric probes. Now we have designed new molecular probes, in which chromogenic nitrophenyl group is directly attached at one nitrogen of the benzimidazolium moiety and on interaction with an anion would result in the switching of absorbance wavelength through internal charge transfer, thus providing opportunities for ratiometric sensing.

The molecular probes **2b**, **3b**, and **4b** derived from 1-(4-nitrophenyl)benzimidazole (**1**) have been used for selective estimation of the cyanide ion in MeOH through the naked eye or UV–vis spectrophotometer. The switching of absorbance from 270 nm to 376 nm on addition of the cyanide ions provides opportunities for ratiometric estimation—which is useful for signal rationing and the estimation of concentration of an analyte independent of the concentration of the receptor. These molecular probes behave as chemodosimeters where the cyanide ion adds at the C-2 of benzimidazolium carbon to form adduct and thus releases the lone pair of electrons on the nitroaniline unit to regenerate its color. The benzimidazolium salt **5** has been used as a control compound which on addition of the cyanide ion did not show any discernible color change or the addition of the cyanide ion at its C-2 (^{1}H NMR) and points to the significance of 4-nitrophenyl unit.

1-(4-Nitrophenyl)-benzimidazole (**1**) on dry heating with dodecylbromide (10 equiv) at 80–90 °C gave **2a** (white solid, 60%). The methanolic solution of **2a** on treatment with NH_4PF_6 gave **2b**.[12] Similarly, **1** on heating with 1,4-bis-(bromomethyl)benzene (**6**) and 1,3-bis-(bromomethyl)-2,4,6-trimethylbenzene (**7**) in DMF at 110 °C gave **3a** (light yellow solid, 69%) and **4a** (light yellow solid, 75%), respectively. The methanolic solution of **3a/4a** on treatment with NH_4PF_6 gave the respective compounds **3b** and **4b**. Control compound **5** was synthesized by alkylation followed by the salt formation reaction of benzimidazole with dodecylbromide (Scheme 1).

Probe **2b** (20 μM, CH_3CN) exhibits the absorption band at λ_{max} 270 nm. On addition of AcO^-, F^-, CN^-, and $H_2PO_4^-$ ions (10 equiv) to the solution of **2b** (20 μM, CH_3CN), a new absorption band at 376 nm with varied intensities was observed (Fig. 1). During this addition of anions, the colorless solution changed to yellow one. However, the addition of NO_3^-, Cl^-, I^-, Br^-, ClO_4^-, SCN^-, and HSO_4^- anions (10 equiv) did not give any apparent color or spectral change. Similarly, the addition of AcO^-, F^-, CN^-, and $H_2PO_4^-$ anions to the solution of **3b** and **4b** (20 μM, CH_3CN) gave a new absorption band at 376 nm but in MeOH, the color/spectral change was observed with the cyanide ion only. The control compound **5** did not show any spectral or color change with these anions. Therefore, probes **2b**, **3b**, and **4b** in MeOH showed highly selective color and

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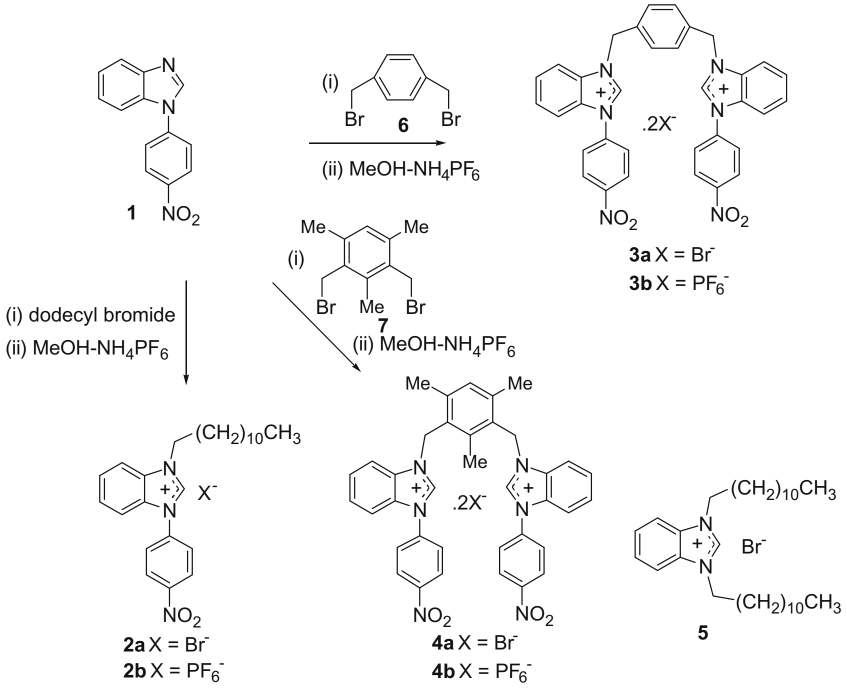
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.05.047



Scheme 1.

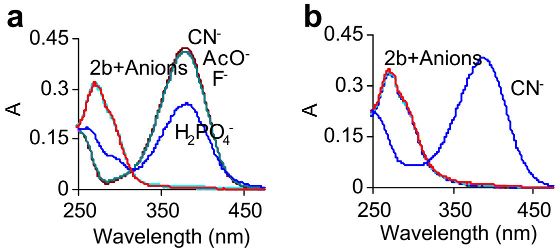


Figure 1. Effect of anions on UV–vis spectrum of **2b** (20 μM) (a) in CH_3CN and (b) in MeOH.

spectral changes with the cyanide ion and so can be developed as molecular probes for selective estimation of cyanide anion. This selectivity toward CN^- in MeOH could be attributed to the larger solvation of F^-, AcO^-, and $H_2PO_4^-$ anions and higher nucleophilicity of cyanide ion under protic conditions. On gradual addition of TBA CN to the solution of **2b** (20 μM, MeOH), the absorbance at 270 nm (ε 19,300 l mol^{-1} cm^{-1}) underwent gradual decrease in intensity with a concomitant increase at 376 nm (ε 22,400 l mol^{-1} cm^{-1}) (Fig. 2). Therefore, **2b** can be used as a probe for selective estimation of the CN^- ions using MeOH as solvent. In order to study the effect of water, the estimation of cyanide ions was studied using MeOH–H_2O (1:1) as the solvent. The analysis of spectral data obtained by titration of **2b** with TBA CN in MeOH–H_2O (1:1) revealed similar sensitivity to cyanide ions as observed in pure MeOH. The presence of water did not affect the estimation of cyanide ion.

The switching 'OFF–ON' behavior at 270 nm and 376 nm on addition of CN^- ions to the solution of **2b** provides a dual absorption channel for elaborating a ratiometric approach (Fig. 3). The ratio of the absorption of **2b** (20 μM, MeOH) varies from 0.02 to 2.44 on gradual addition of cyanide ions and can be used to estimate CN^- ions between 60 μM and 500 μM.

Further to evaluate the cooperative effect of two benzimidazolium units linked through 1,4-bis-(methylene)benzene or 1,3-bis-(methylene)-2,4,6-trimethylbenzene as spacer, the probes **3b** and **4b** were studied. The presence of two benzimidazolium units in probes **3b** (λ_{max} 270 nm, ε 34,600 l mol^{-1} cm^{-1}) and **4b** (λ_{max} 270 nm, ε 30,400 l mol^{-1} cm^{-1}) did not have any effect on λ_{max} val-

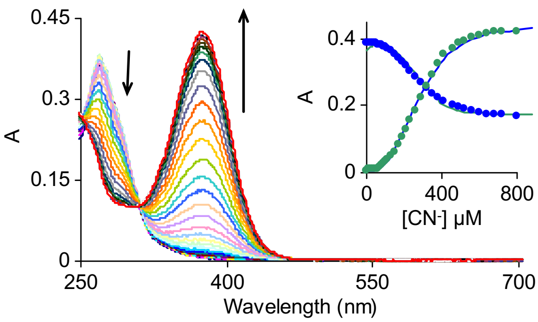


Figure 2. Changes in UV–vis spectrum of **2b** (20 μM, MeOH) on gradual addition of TBA CN.

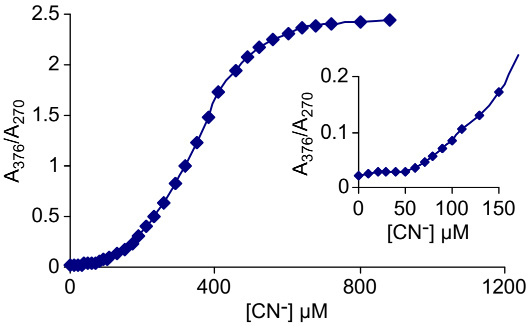


Figure 3. Plot of A_{376nm}/A_{270nm} versus $[CN^-]$ on titration of **2b** (20 μM, MeOH) with TBA CN.

ues. Thus, any interaction between two benzimidazolium units placed at 1,3 or 1,4 positions in **3b**/**4b** is ruled out.

The gradual addition of TBA CN to a solution of **3b** (10 μM, MeOH) caused the gradual decrease in absorbance intensity at 270 nm with concomitant increase in absorbance intensity at 376 nm (Fig. 4). The evaluation of these spectral data obtained by titration of **3b** with TBA CN in MeOH shows the formation of 1:1 and 1:2 (**3b**:CN) complexes. The presence of two slopes in the titration curve shows that cyanide ion and **3b** interact in a stepwise manner. The larger slope for the addition of the first cyanide ion than that for the addition of the second cyanide ion points that the presence of two benzimidazolium units though not conjugated to each other, facilitates the interaction with cyanide ion which is reflected in the increased sensitivity of **3b** toward the first cyanide ion (lower limit 1 μM) in comparison to that observed in case of **2b** (lower limit 60 μM). Probe **4b** on titration with TBA CN showed similar enhanced sensitivity toward cyanide ion.

In case of **3b** and **4b**, the plot of ratio of absorbances at 270 nm and 376 nm shows an increase in the ratio from 0.01 to 3.49 implying nearly 350 times increase in ratio while varying the cyanide amounts from 1 μM to 270 μM (Fig. 5). Therefore, probes **3b** and **4b** are significantly more sensitive to cyanide ions than probe **2b**.

In order to evaluate the probe sensitivity toward inorganic cyanide ions, the titration of **3b** against NaCN in MeOH–H_2O (1:1) was performed. Under these conditions, **3b** is most sensitive to cyanide ions between 50 μM and 240 μM concentration. However, even 10 μM cyanide ions could be determined easily using ratiometric approach (Fig. 6). However, due to poor solubility of **3b**, its sensitivity toward the cyanide ion in water could not be determined.

The mode of interaction of **3b** with cyanide anion could be determined by using ^1H NMR titrations. ^1H NMR spectrum of **3b** (2 mM, CD_3OD–$CDCl_3$) on addition of TBA CN showed the appearance of new signals upfield in comparison to that of **3b**. The intensity of these signals increased with gradual addition of TBA CN and was completed at 6.0 equiv of TBA CN. ^1H NMR spectrum of **3a–CN** complex, isolated by addition of 10 equiv of NaCN to solution of **3a**, shows a similar upfield shift of N–CH_2 signal from δ 5.89 to δ 4.58 and C-2H and nitro aryl signals from δ 10.54, 8.61, 8.16 to δ 8.89/8.44, 8.03, 6.80, respectively. These observations confirm that the addition of cyanide ions at C-2 of benzimidazolium moieties in **3a** leads to the formation of a neutral complex (Fig. 7). Therefore, the conversion of benzimidazolium to 1,2-dihydrobenzimidazole moiety releases internal charge transfer from the nitrogen lone pair to nitro unit and is responsible for color change from colorless to yellow.

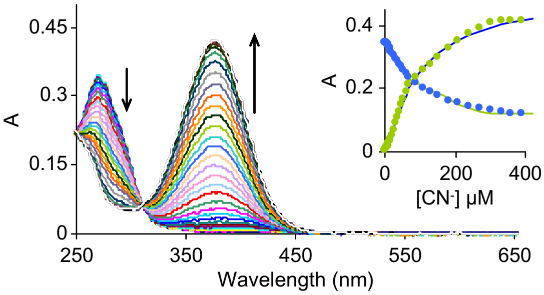


Figure 4. Changes in UV–vis spectrum of **3b** (10 μM, MeOH) on gradual addition of TBA CN.

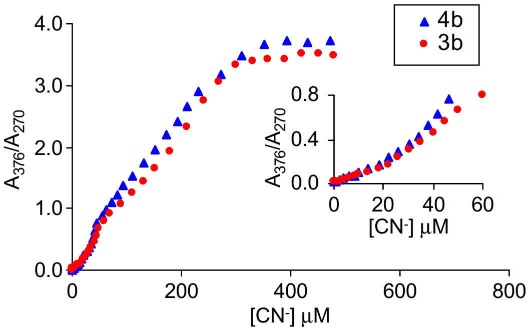


Figure 5. Plots of A_{376nm}/A_{270nm} versus [CN^-] on titration of **3b** and **4b** (10 μM, MeOH) with TBA CN.

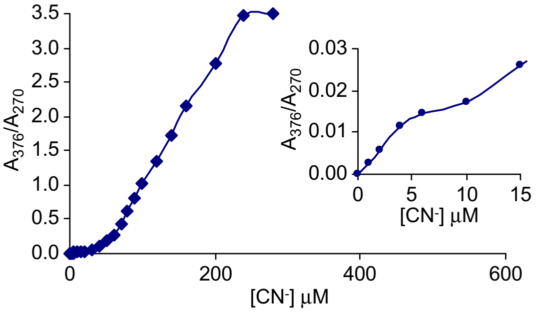


Figure 6. Plot of A_{376nm}/A_{270nm} versus [CN^-] on titration of **3b** (10 μM, MeOH–H_2O: 1:1) with NaCN.

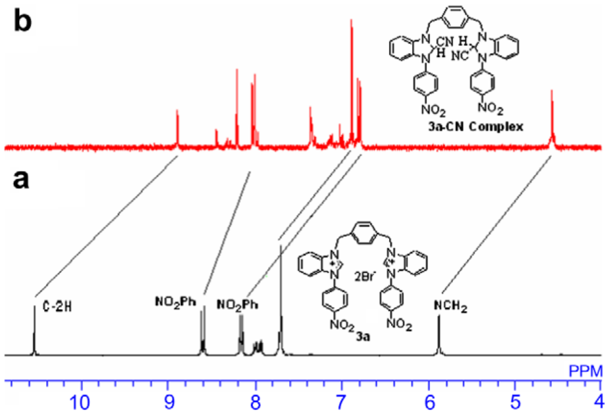


Figure 7. ^1H NMR spectra of (a) **3a** (free ligand) and (b) **3a–CN** adduct in DMSO-d_6.

The interference of other anions in the estimation of CN^- ions evaluated by measuring the UV–vis absorption changes in a series of solutions containing **3b** with different amounts of CN^- ions and other anions (AcO^-, HSO_4^-, $H_2PO_4^-$, F^-, Cl^-, Br^-, NO_3^-, ClO_4^-, and SCN^-) in concentrations that were 100 times greater than that of CN^- ion in MeOH was found to be minimal.

Thus, 1,4- and 1,3-bis-[1-(4-nitrophenyl)-benzimidazolium-3-methylene]benzene derivatives **3b** and **4b** based on nucleophilic addition of cyanide ion at C-2 elaborate ratiometric chromogenic probes for the cyanide ion in the concentration range 1–270 μM—the desirable concentration range for practical applications.

Acknowledgments

We thank CSIR and DST, New Delhi for financial assistance and UGC for Center of Advanced Studies.

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12. *General procedure*: 1-(4-nitrophenyl)-benzimidazole (1 mmol, 239 mg) and dodecylbromide (2 mmol, 500 mg) were heated overnight at 80–90 °C, the reaction mixture was cooled to room temperature and diethyl ether was added to remove excess of dodecylbromide and then the separated white-colored solid was filtered to get pure compound **2a** (60% yield, 290 mg). The solution of NH_4PF_6 (244 mg, 1.5 mmol) in water was added dropwise to the solution **2a** (119 mg, 0.5 mmol) in methanol and the separated white solid was filtered off to get pure **2b**.
    Probe **2b**: (100 mg, 66% yield). Mp 75 °C; FAB mass M^+ *m/z* 409 $[M+H]^+$; ^1H NMR (CD_3CN): δ 0.88 (t, 3H, $J = 6.8$ Hz, CH_3), 1.27 (br s, 14H, 7 × CH_2), 1.37–1.48 (m, 4H, 2 × CH_2), 2.05 (q, 2H, $J = 7.5$ Hz, CH_2), 4.53 (t, 2H, $J = 7.5$ Hz, CH_2), 7.75–7.83 (m, 3H, 3 × ArH), 7.95 (d, 2H, $J = 6.9$ Hz, 2 × ArH), 8.00–8.03 (m, 1H, ArH), 8.54 (d, 2H, $J = 6.9$ Hz, 2 × ArH), 9.29 (s, 1H, ArH); ^{13}C NMR (CD_3CN): δ 14.3, 23.7, 26.9, 29.5, 29.6, 29.9, 30.0, 30.1, 30.2, 32.5, 48.8, 114.5, 114.9, 126.7, 127.5, 128.7, 129.1, 132.4, 132.6, 138.9, 141.7, 149.9. ($C_{25}H_{34}N_3O_2\ PF_6$ requires C, 54.25; H, 6.15; N, 7.59. Found C, 54.47; H, 6.02; N, 7.82).
    Probe **3b**: 75% yield. Mp 252 °C; FAB mass M^+ *m/z* 727 $[M^{2+} + PF_6^-]$; ^1H NMR (CD_3CN): δ 5.78 (s, 4H, 2 × CH_2), 7.60 (d, 4H, $J = 7.5$ Hz, ArH), 7.75–7.84 (m, 8H, 8 × ArH), 7.95 (d, 4H, $J = 9.3$ Hz, 4 × ArH), 8.54 (d, 4H, $J = 9.3$ Hz, 4 × ArH), 9.39 (s, 2H, 2 × ArH); ^{13}C NMR (CD_3CN): δ 50.6, 113.5, 113.8, 125.5, 126.4, 127.6, 128.1 129.2, 131.0, 131.5, 133.3, 137.5, 141.1, 148.7. ($C_{34}H_{26}N_6O_4\ P_2F_{12}$ requires C, 46.79; H, 2.98; N, 9.63. Found C, 46.57; H, 2.88; N, 9.54).
    Probe **4b**: 74% yield. Mp 265 °C; FAB mass M^+ *m/z* 769 $[M^{2+} + PF_6^-]$; ^1H NMR (CD_3CN): δ 2.30 (s, 3H, CH_3), 2.44 (s, 6H, 2 × CH_3), 5.74 (s, 4H, 2 × CH_2), 7.35 (s, 1H, ArH), 7.79–7.87 (m, 10H, 10 × ArH), 8.15 (d, 2H, $J = 6.6$ Hz, 2 × ArH), 8.42 (d, H, $J = 6.9$ Hz, 4 × ArH), 8.60 (s, 2H, 2 × ArH); ^{13}C NMR (CD_3CN): δ 16.4, 20.1, 47.3, 114.5, 114.9, 126.3, 127.4, 127.7, 128.8, 129.5, 132.7, 132.9, 133.1, 138.6, 140.4, 141.2, 142.7, 149.7. ($C_{37}H_{32}N_6O_4\ P_2F_{12}$ requires C, 48.58; H, 3.50; N, 9.19. Found C, 48.52; H, 3.42; N, 9.32).