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Selective fluorescence sensing of cyanide with an *o*-(carboxamido)trifluoroacetophenone fused with a cyano-1,2-diphenylethylene fluorophore

Hanna Lee, Yun Mi Chung, Kyo Han Ahn *

Department of Chemistry, Pohang University of Science and Technology (POSTECH), San 31 Hyoja-dong, Pohang 790-784, Republic of Korea

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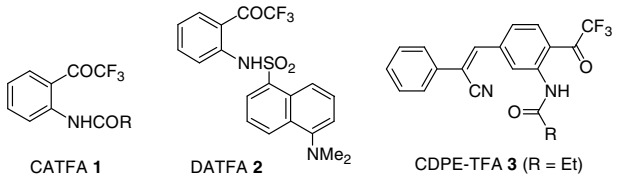
ABSTRACT

A novel fluorescence probe has been synthesized, which consists of *o*-(carboxamido)trifluoroacetophenone moiety as the recognition element and cyano-1,2-diphenylethylene moiety as the signaling unit. Fluorescence titrations of the probe with anions such as F^-, Cl^-, I^-, CN^-, SCN^-, AcO^-, $H_2PO_4^-$, HSO_4^-, and ClO_4^- as their Bu_4N^+ salts in acetonitrile show that CN^- is the most efficient quencher, AcO^- and F^- follow it, and other anions show little changes. In an aqueous medium, MeOH–water (9:1), the probe shows fluorescence quenching only toward cyanide and no changes toward the other anions.

The molecular recognition and sensing of anions have attracted much research interest with multiple disciplines,[1] because anions play significant roles in biological and chemical processes,[2] and have implications in medicine, catalysis and environment.[3] To mention a few are the acute toxic effects of cyanide ions and the role of phosphate ions in nucleotides.[4] In the development of recognition and sensing probes for such anions, a paramount challenge is how to achieve the necessary selectivity and high sensitivity toward target analytes. To achieve such goals, the insightful design of recognition motifs and corresponding fluorescence sensors has been pursued.

Recently, we have introduced a novel anion binding motif based on trifluoroacetophenone that recognizes anions such as carbonates by forming reversible covalent adducts.[5] The new trifluoroacetophenone system (CATFA **1**) has an *o*-carboxamido group, which stabilizes anionic adducts through H-bonding, and thus shows significantly enhanced binding affinity toward carboxylates.[6] This approach has been also used in the development of a novel fluorescence probe, the dansyl analogue DATFA **2**,[7] which selectively senses highly toxic cyanide ions. In the course of our studies on anion probes,[8] we have designed a new trifluoroacetophenone derivative (CDPE-TFA **3**) in which the binding element trifluoroacetyl group is fused with a signaling unit, the cyanodiphenylethylene (CDPE) moiety. In this fused form, the binding event occurring at the trifluoroacetyl group may be directly transduced to the signaling unit, which compares DATFA **2** in which case the trifluoroacetyl group is not conjugated to the dansyl fluorophore but linked through the sulfonamide bond. The cyanodiphenylethylene moiety has been used in various fluorescent materials.[9]



CATFA **1** DATFA **2** CDPE-TFA **3** (R = Et)

The desired CDPE-TFA **3** was synthesized starting from 2-nitroterephthalic acid (**5**) as depicted in Scheme 1. A key intermediate was the mono-protected aldehyde **8**, which was prepared by selective protection of the dialdehyde **7** in 47% isolated yield. Then, the Knoevenagel condensation of **8** with benzyl cyanide provided the CDPE derivative **9** in 72% isolated yield. Subsequent steps following the established reaction conditions[6–8] introduced the trifluoroacetyl and *N*-propionyl groups, leading to the desired product **3**. We have also synthesized a reference compound **4**, which has no

* Corresponding author. Tel.: +82 54 2792105; fax: +82 54 2793399.
E-mail address: ahn@postech.ac.kr (K. H. Ahn).

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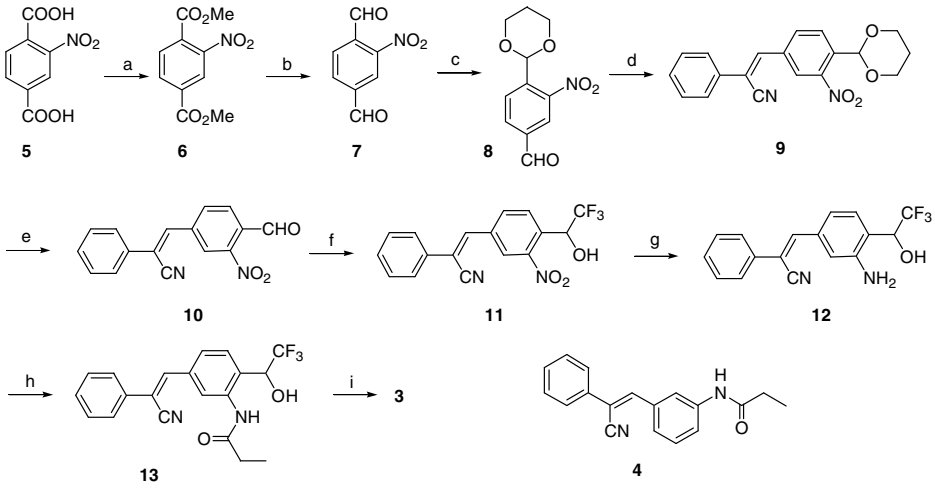


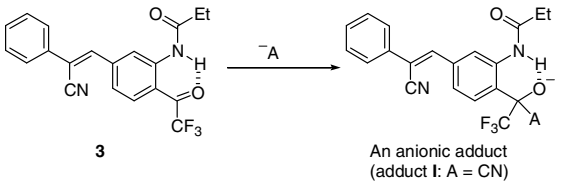
Scheme 1. Synthesis of CDPE-TFA **3**. Reagents and conditions: (a) $SOCl_2$, MeOH, 0 °C→reflux, 5 h, 76%; (b) 1.5 M DIBAL in toluene, toluene, −78 °C, 5 min, 84%; (c) 1,3-propanediol, *p*-TsOH, benzene, reflux, 2 h, 47%; (d) benzyl cyanide, 1.0 M *t*-BuOK in THF, *t*-BuOH/THF, 50 °C, 30 min, 72%; (e) 11-*N* HCl/THF (1:1), 25 °C, 30 min, 76%; (f) CsF, $TMSCF_3$, DME, 0 °C→25 °C, 3 h, 88%; (g) $SnCl_2{\cdot}H_2O$, EtOAc, 70 °C, 20 min, 76%; (h) EtCOCl, K_2CO_3, THF, 25 °C, 63%; (i) 1,10-phenanthroline, CuCl, 1,2-diethoxyhydrazine, K_2CO_3, THF, 70 °C, 50 min, 70%.

trifluoroacetyl unit. By changing the *N*-acyl group, we may further functionalize CDPE-TFA **3**.[†]

The photophysical properties of CDPE-TFA **3** were evaluated in CH_3CN: Its absorption spectrum displayed two absorption maxima at λ_{max} = 223 and 331 nm (ε = 14,680 $M^{-1}\,dm^{-1}$), characteristic peaks of the CDPE moiety.[9] When excited at λ_{ex} = 331 nm, probe **3** emitted fluorescence at λ_{max} = 476 nm.

We evaluated the sensing ability of **3** toward anions such as F^-, Cl^-, I^-, CN^-, SCN^-, AcO^-, $H_2PO_4^-$, HSO_4^-, and ClO_4^- as their Bu_4N^+ salts. The fluorescence spectra were recorded at λ_{ex} = 331 nm by adding increasing amounts of each anion to CDPE-TFA **3**, both dissolved in acetonitrile at 25 °C. In most cases, we observed little changes in the fluorescence intensity except for CN^-, F^-, and AcO^- anions (Fig. 1a).

The fluorescence data collected in Figure 1a compare the relative intensity at the given guest concentration, showing that CN^- is the most efficient quencher among the anions examined, then AcO^- and F^- follow, and other anions show little changes. The emission response depending on the anions is similar with the tendency observed previously in the case of DATFA **2**.[7] Formation of the anionic adduct between **3** and an anion ($\mathbf{A}^-$) will be dependent on the anion's carbonyl carbon affinity, which is in the order: $CN^- \gg AcO^- > F^- > H_2PO_4^-$, Cl^-, I^-, CN^-, SCN^-, HSO_4^-, and ClO_4^-.



3 An anionic adduct (adduct **I**: A = CN)

As it was pointed out in the previous works,[7,8b] the trifluoroacetyl group in probe **3** is also intramolecularly hydrogen bonded as its alkoxide adduct; however, the latter adduct is more stabilized by its stronger 'charged' hydrogen bonding than the case in which such intramolecular hydrogen bonding is absent. Thus, the fluorescence titration results suggest that the anionic adduct is responsible for the fluorescence quenching. The adduct formation can be readily characterized by spectroscopic titrations, as already confirmed for the CATFA analogues in the previous works. ^{19}F NMR titrations provided a clear evidence for the adduct formation: As expected, the CF_3 group in the probe **3** appeared as singlet at 4.3 ppm, shifted to −6.4 ppm (singlet) upon addition of 1.0 equiv of CN^- (as Bu_4N^+ salt) in CD_3CN. Also, only both the probe **3** and the adduct peaks appeared with little chemical shifts when 0.5 equiv of the anion was added.

The fluorescence titration of probe **3** with CN^- (0–30 equiv) gave an interesting quenching result, as inferred from a plot of F/F_0 versus equivalent of the cyanide ion. The plot can be divided into two regions in which fluorescence response is different (Fig. 2): A nonlinear change up to 3 equiv of cyanide and a linear change after that point. In the former region, two different species, **3** and its cyanide adduct **I**, seem to be contributing to the fluorescence intensity observed, resulting in the nonlinear change. In the latter

[†] Characterization data of selected compounds. Compound **8**: mp 96.1–96.3 °C (CH_2Cl_2/hexanes = 1/5); R_f = 0.36 (hexanes/EtOAc = 4/1); ^1H NMR (300 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.23 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 6.04 (s, 1H), 4.20 (dd, *J* = 5.8, 5.2 Hz, 2H), 3.97 (td, *J* = 9.8, 2.3 Hz, 2H), 2.08–2.21 (m, 1H), 1.44 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 189.7, 189.6, 148.8, 137.7, 137.0, 132.8, 128.8, 124.7, 96.5, 67.7, 25.5; HRMS (FAB) calcd for $C_{11}H_{11}NO_5$ ($M+H^+$): 238.0715; found, 238.0721. Compound **9**: mp = 136.8–137.5 °C (hexanes/CH_2Cl_2 = 5/1); R_f = 0.23 (hexanes/EtOAc = 9/1); ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 5.8 Hz, 2H), 7.51 (s, 1H), 7.44–7.49 (m, 3H), 6.09 (s, 1H), 4.24 (dd, *J* = 5.8, 5.2 Hz, 2H), 4.00 (td, *J* = 9.8, 2.3 Hz, 2H), 2.15–2.23 (m, 1H), 1.46 (d, *J* = 13.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.6, 138.6, 135.2, 134.0, 133.5, 132.3, 130.1, 129.3, 128.7, 126.3, 124.9, 117.1, 115.2, 96.8, 67.8, 25.7; MS (EI) *m*/*z* calcd for $C_{19}H_{16}N_2O_4$ (M^+): 336.1110; found, 336.1112. Compound **11**: mp = 160.7–161.5 °C (hexanes/CH_2Cl_2 = 5:1); R_f = 0.18 (hexanes/EtOAc = 4/1); ^1H NMR (300 MHz, $CDCl_3$ + DMSO) δ 8.39 (s, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.59 (s, 1H), 7.42–7.51 (m, 3H), 6.69 (d, *J* = 5.8 Hz, 1H), 6.12 (m, *J* = 5.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$ + DMSO) δ 148.1, 137.8, 134.8, 132.7, 132.3, 131.3, 130.1, 129.6, 128.7, 125.6, 124.6, 121.8, 116.5, 114.8, 66.1, 65.6, 65.2, 64.8 (q, *J* = 32.3 Hz, *C*F_3); ^{19}F NMR (282 MHz, $CDCl_3$ + DMSO) δ −0.97; MS (EI) *m*/*z* calcd for $C_{17}H_{11}F_3N_2O_3$ (M^+): 348.07; found, 348.07. Compound **3**: mp = 116.0–116.7 °C (hexanes/CH_2Cl_2 = 4:1); R_f = 0.36 (hexanes/EtOAc = 7/3); ^1H NMR (300 MHz, $CDCl_3$) δ 11.0 (s, 1H), 9.18 (s, 1H), 8.07 (dd, *J* = 6.5, 2.2 Hz, 1H), 7.93 (dd, *J* = 6.9, 1.8 Hz, 1H), 7.71 (m, 2H), 7.57 (s, 1H), 7.45–7.48 (m, 3H), 2.55 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 183.4, 182.9, 182.5, 182.0 (q, *J* = 34.7 Hz, –*C*OCF_3), 173.6, 144.1, 142.3, 139.7, 133.6, 132.63, 132.58, 132.52, 132.47 (q, *J* = 4.7 Hz (coupled with F), aromatic-C), 130.4, 129.4, 126.5, 122.8, 122.4, 121.5, 118.5, 116.8, 115.5, 114.7 (q, *J* = 99.3 Hz, –*C*F_3), 117.1, 110.8, 31.9, 9.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ 6.82; MS (EI) *m*/*z* calcd for $C_{20}H_{15}F_3N_2O_2$ (M^+): 372.1086; found, 372.1082. Compound **4**: mp = 127.9–128.2 °C (hexanes/CH_2Cl_2 = 4/1); R_f = 0.36 (hexanes/EtOAc = 3/2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.68–7.58 (m, 4H), 7.53–7.36 (m, 6H), 2.42 (q, 2H), 1.25 (t, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.6, 142.1, 138.8, 134.6, 134.4, 129.8, 129.5, 129.3, 126.2, 125.1, 122.0, 120.2, 118.1, 112.2, 30.9, 9.8; MS (EI) *m*/*z* calcd for $C_{18}H_{16}N_2O$ (M^+): 276.1263; found, 276.1265.

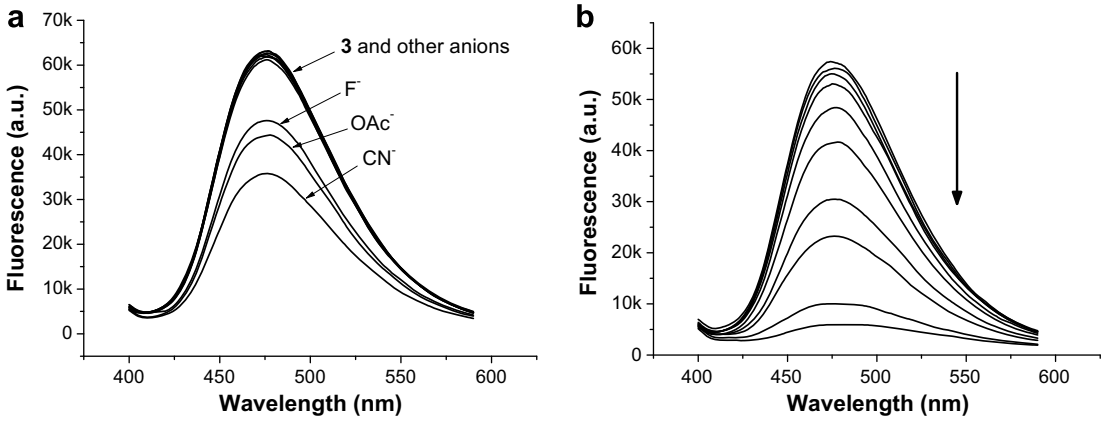


Figure 1. (a) Comparison of the emission spectra obtained when probe **3** (3.0 μM) was treated with each of the anions (1.0 equiv of Cl^-, I^-, CN^-, SCN^-, $H_2PO_4^-$, HSO_4^-, ClO_4^-, CN^-, F^-, and AcO^- as Bu_4N^+ salts) in CH_3CN at 25 °C. (b) Fluorescence titration of **3** (3.0 μM) with increasing amount of cyanide (from the top: 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0, 5.0, and 10 equiv) in CH_3CN at 25 °C.

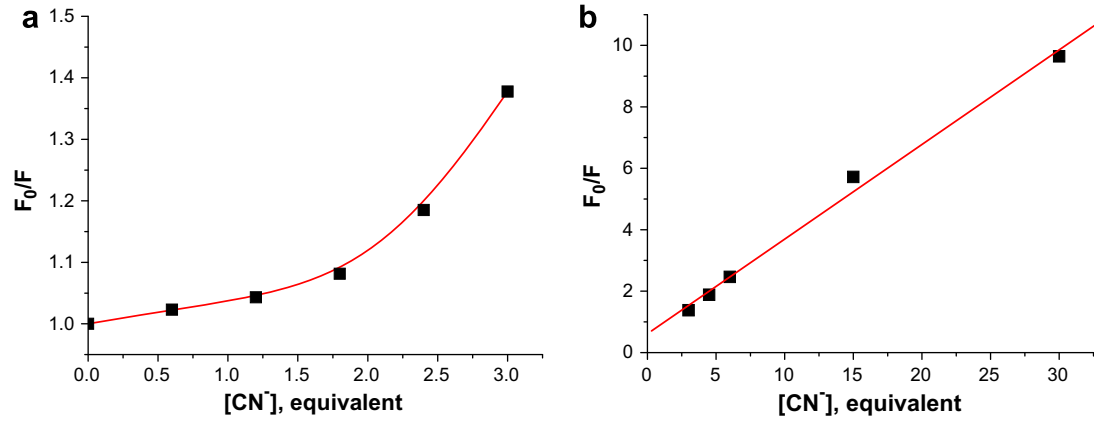


Figure 2. The plot of F_0/F versus equivalent of [CN^-] for the titration of **3** (3.0 μM) with CN^- (0–30 equiv) in CH_3CN at 25 °C, which is divided into two regions: (a) $0 \leqslant [CN^-] \leqslant 3.0$ equiv; (b) 3.0 equiv $\leqslant [CN^-]$.

region, little of free **3** would exist because the association constant between CN^- and **3** is large ($K_{ass} \sim 10^5\ M^{-1}$),[6] and thus quenching would occur mainly from the interactions between adduct **I** and CN^-. The absorption spectra measured for the titration solutions with increasing amounts of cyanide (λ_{max} = 332, 325, 318, 315 nm for the solutions containing 1.0, 2.0, 5.0, and 10.0 equiv of CN^-, respectively) showed little spectral changes from that of **3**, and only gradual hypsochromic shifts and very small changes in the intensity were observed. Although further experiments such as luminescence lifetime measurements depending on the concentration of quenchers can provide valuable information on the quenching mechanism, we tentatively suggest that dynamic quenching is a dominant process for the latter region because molecular interactions other than collision are hard to imagine between the adduct **I** and cyanide. The Stern–Volmer plot shown in Figure 2b intercepts not exactly 1.0 but slightly deviated value from it, which suggests that the dynamic quenching process may be dominant but not exclusive.[10] This fluorescence intensity behavior depending on the cyanide equivalent also supports the formation of a 1:1 adduct species I, and, furthermore, the fluorescence quenching is mainly due to the adduct formation.

The quantum yields were determined for the cyanide–**3** mixtures in which the amounts of cyanide were changed from 0 to 1.0 equiv. A plot of Φ/Φ_0 versus [CN^-]/[**3**] showed a linear decrease, from Φ_0 = 0.030 (**3** only) to $\Phi_{1:1}$ = 0.018 (a 1:1 mixture, mostly the adduct **I**). The smaller value of $\Phi_{1:1}$ compared to Φ_0 supports the observed quenching behavior as shown in Figure 2a. The quenching probably results from a photo-induced electron transfer, from the anionic adduct to the CDPE moiety: The π–π^* transition from the CDPE fluorophore is likely to be quenched by the electron transfer from the alkoxide nonbonding orbital.

A critical role of the *o*-trifluoroacetyl group in the fluorescence behavior of probe **3** was examined with the reference compound **4**. The fluorescence titration of **4** (3.0 μM) with increasing amounts of CN^- (up to 100 equiv) at λ_{ex} = 310 nm in acetonitrile showed little changes in the fluorescence spectra, which again demonstrates that the molecular interaction between anions and the trifluoroacetyl group is a determining factor for the fluorescence behavior observed. As already demonstrated in the previous studies, CN^- has the strongest carbonyl carbon affinity among the anions examined, whereas anions such as AcO^- and F^- have lower affinity and other anions have very weak affinity.[6,7] The formation of adduct **I** should be dependent on the anion's carbonyl carbon affinity, which led to the observed fluorescence behavior dependent on the anions.

The fact that probe **3** recognizes anions through reversible covalent adducts (RCA), not through H-bonding interactions, the most widely used paradigm in molecular recognition and sensing, suggests that we may achieve a selectivity pattern completely different from the fluorescence probes based on H-bonding interactions in aqueous media. In other words, the anion selectivity

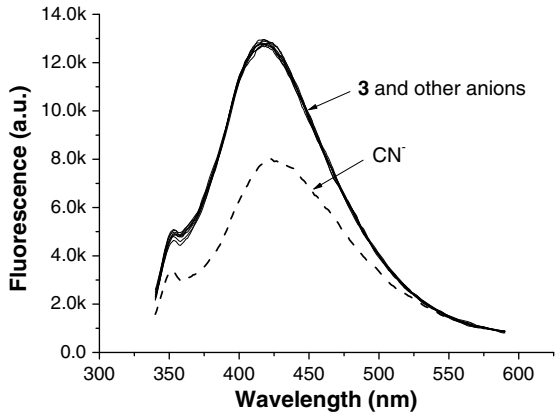


Figure 3. Comparison of the relative fluorescence intensity obtained for the equimolar mixture between the probe **3** (10 μM) and each of the anions (10 equiv of F^-, Cl^-, I^-, CN^-, SCN^-, AcO^-, $H_2PO_4^-$, HSO_4^-, and ClO_4^- as Bu_4N^+ salts) at λ_{ex} = 314 nm in MeOH–water (9:1).

may be modulated in protic solvents that provide competing H-bonding interactions toward anions. Anions such as F^- and AcO^-, particularly F^-, have strong H-bonding ability, and thus are favorably sensed over other anions in organic media by H-bond assisted fluorescence probes. However, such a preference is generally lost in aqueous media due to the competing H-bond interactions between the anions and solvents (strong solvation). This fact is also a major limitation for sensing such anions in aqueous media. The recognition of anions through the RCA mechanism is in stark contrast to the H-bond-based recognition mode. We have shown that cyanide is preferably recognized by the TFA-based ionophores. In addition, cyanide has poor H-bonding ability compared to F^- and AcO^-. Both properties suggest that CN^- may be completely discriminated from the competing F^- and AcO^- if we use aqueous solvents. Indeed this is the case. When probe **3** was titrated with the anions in an aqueous medium, MeOH–H_2O (9:1),[‡] only CN^- showed significant fluorescence quenching, and the competing anions F^- and AcO^- showed little changes (Fig. 3).

Thus, a complete selectivity toward CN^- is achieved with the fluorescence probe **3** in an aqueous medium.[11] The result demonstrates that the recognition through the RCA mechanism is a promising approach to develop new ionophores or sensors with a selectivity pattern completely different from the widely used, H-bonding-based approaches. Recently, the concept of stabilization of anionic adducts by intramolecular H-bonding has been utilized by others for cyanide sensing.[12]

In summary, we have synthesized a novel fluorescence probe, in which a recognition element, *o*-(carboxamido)trifluoroacetophenone, is fused with a signaling unit, cyano-1,2-diphenylethylene moiety. The probe recognizes cyanide through the formation of reversible covalent adduct, and gives selective fluorescence quenching in acetonitrile. In an aqueous medium, the probe shows fluorescence quenching only toward cyanide among various anions examined.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.065.

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[‡] For solubility reason, methanol is used as co-solvent.