Fluorescence modulation in anion sensing by introducing intramolecular H-bonding interactions in host–guest adducts†

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Fluorescence signaling in anion binding is modulated from quenching to enhancement by intramolecular H-bonding stabilization of anion–ionophore adducts; the intramolecular H-bonding is suggested to suppress the quenching processes otherwise possible and increase the conformational rigidity of the anionic adducts, leading to fluorescence enhancement in a selective fashion towards cyanide ion, among the various anions examined.

The paramount importance of anions in the fields of medicine, biology and environmental pollution is ubiquitous; to mention two examples, the acute toxic effects of cyanide ions and the role of phosphate ions in DNA recognition.[1] Thus, the molecular recognition and sensing of anions have been a subject of intense research in multiple disciplines. As a result, a variety of anion recognition and sensing systems have been developed, such as hosts having positively-charged organic and organometallic ligands.[2] Recently, we introduced a novel anion recognition motif based on a neutral trifluoroacetophenone ionophore[3] that recognizes anions through reversible adduct formation. We have shown that by introducing a H-bonding donor, such as an *ortho*-carboxamido group, into the system, its binding affinity can be significantly enhanced to a useful level towards anions such as carboxylate and cyanide.[4] In our search for chemical sensors, we envisaged that the concept of intramolecular H-bonding stabilization[5] of anion–ionophore adducts may be extended to the development of fluorescence sensors, not simply for the enhancement of binding affinity but also for a dramatic modulation of fluorescence. We wish to report herein the modulation of fluorescence signaling in anion binding through intramolecular H-bonding interactions in anion–ionophore adducts, which, in particular, induces fluorescence enhancement rather than quenching, a highly desirable but rather challenging task in the development of anion sensors.[6]

The designed sensor, *ortho*-TFADA (**1**), consists of a trifluoroacetyl (TFA) moiety as the binding site and a dansyl (DA) moiety[7] as the signaling unit (Fig. 1). *ortho*-TFADA-signaled anion binding occurs with changes both in emission maximum (hypsochromic shift) and fluorescence intensity (enhancement), together with good guest selectivity. To the best of our knowledge, such a modulation of fluorescence in anion sensing by utilizing intramolecular H-bonding interactions in host–guest adducts is unprecedented.

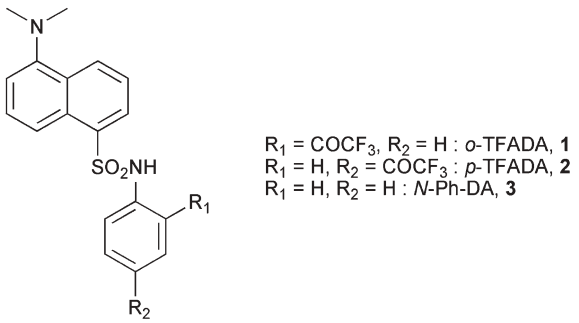

Fig. 1 Structures of *ortho*-TFADA (**1**), and reference compounds **2** and **3**.

We reasoned that the dansyl sulfonamide proton of *ortho*-TFADA can play a dual role: it can bestow H-bonding assistance to the TFA group for anion binding, as in the case of the carboxamide group in our previous report,[4] and more importantly, it may modulate the fluorescence signaling by stabilizing its anionic adduct. In the absence of such H-bonding stabilization, as in the case of dansyl derivative **3**, fluorescence quenching results because an anion guest interacts with the acidic sulfonamide proton. Similarly, fluorescence quenching would also result in the case of "non-stabilized" anionic adducts, such as from a *para* analogue of **1**, *para*-TFADA (**2**), as confirmed in this study. We also reasoned that the fluorescence intensity of an *ortho*-TFADA adduct may also increase upon adduct formation owing to the increased conformational rigidity[8] due to H-bonding stabilization. Furthermore, high guest selectivity may result in this type of sensing system because the signaling of the complexation process is likely to be dependent on the nature of the adducts from different guests.

The desired *ortho*-TFADA and reference compounds **2** and **3** were synthesized by simple and straight-forward means.‡ The photophysical properties of *ortho*-TFADA were evaluated in CH_3CN. The absorption spectrum of *ortho*-TFADA displayed strong absorption maxima at 260 and 350 nm, characteristic of the dansyl moiety. When excited at 350 nm, *ortho*-TFADA showed strong fluorescence emission at 530 nm, as expected.[7]

The anion sensing ability of **1** was evaluated by fluorescence titration against increasing concentrations of each anion (as tetrabutylammonium salts) in CH_3CN. In line with our expectations, in the case of ^-CN, we observed a 5-fold fluorescence enhancement against sensor **1**, accompanied by a hypsochromic

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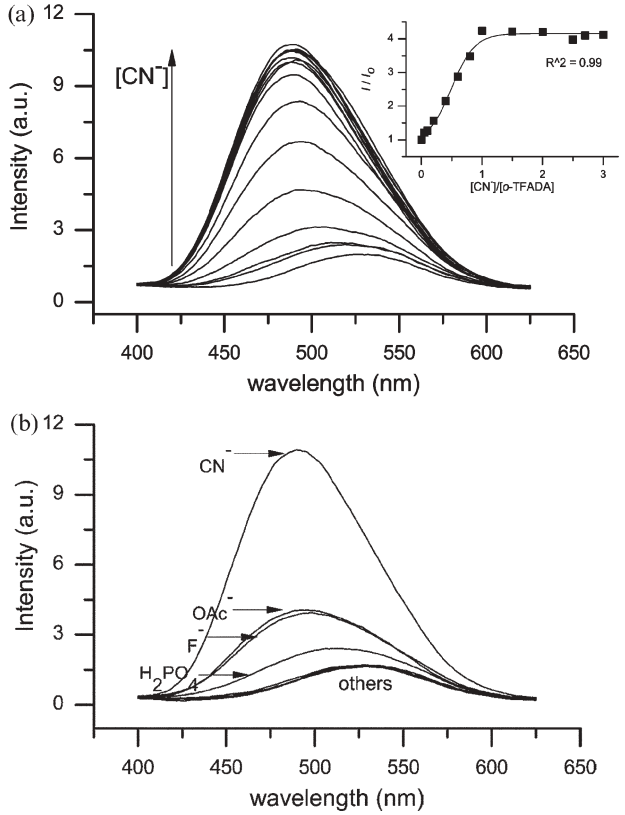
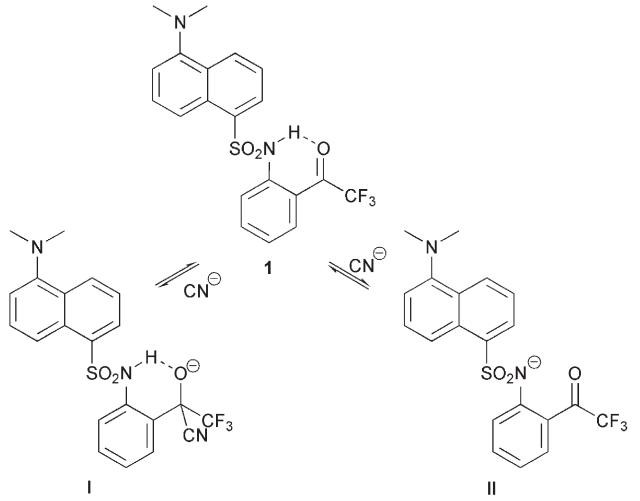


Fig. 2 (a) Fluorescence titration of **1** (20 μM) with increasing amounts of cyanide ion. Inset: dependence of fluorescence intensity (I/I_o) with respect to [CN^-]/[*ortho*-TFADA]; (b) Collected emission plots obtained for an equimolar mixture of **1** (20 μM) and each of the anion guests.

shift (up to 36 nm) (Fig. 2a). The selectivity and sensitivity of **1** towards various anions are collectively presented in Fig. 2b. As can be seen, AcO^- and F^- displayed rather weak fluorescence enhancement (~2 times) with the same hypsochromic shift (~32 nm), while $H_2PO_4^-$ showed even weaker enhancement. For the other anions examined (HSO_4^-, ClO_4^-, F^-, Cl^-, Br^- and ^-SCN), the fluorescence emission spectrum of **1** remained almost undisturbed. It is worth mentioning that none of the anions resulted in the fluorescence quenching of **1**.

Being cognizant of the selective behavior of our sensor *ortho*-TFADA, we set about ascertaining the role of its sulfonamide proton in the observed fluorescence enhancement towards ^-CN: its fluorescence behavior towards ^-CN can be compared with that of *para* analogue **2**, in which case fluorescence quenching was observed. The result indicates that the anionic species resulting from the interaction of *para*-TFADA with the cyanide ion shows fluorescence quenching behavior.[9] Therefore, the contrasting fluorescence behavior of *ortho*-TFADA and *para*-TFADA in the presence of ^-CN indicates that the *ortho* sulfonamide proton plays a vital role. Based on the results of *para*-TFADA, the carbonyl addition intermediate, such as **I**, only stabilized by intramolecular H-bonding in case of *ortho*-TFADA, should be responsible for the observed fluorescence enhancement (Scheme 1), whereas another possible intermediate, **II**, would show fluorescence quenching. The formation of adduct **I** should thus be favored over the possible deprotonation process that leads to **II**, as confirmed by NMR analyses. It should be noted that the sulfonamide proton in



Scheme 1 A plausible equilibrium between *ortho*-TFADA (**1**) and a cyanide ion.

ortho-TFADA is stabilized *via* intramolecular H-bonding and thus is less acidic than that of its *para* analogue. The intramolecular H-bonding seems to perturb the molecular orbital of the alkoxide adduct in such a way that possible quenching processes, otherwise effective in the absence of such H-bonding, are diminished.§ In addition, the conformational rigidity of a six-membered cyclic intermediate of type **I**, *via* the intramolecular H-bonding, could partially account for the enhanced fluorescence.[8,10]

The formation of cyanide adduct **I** is evident from NMR analyses. Upon 1 : 1 adduct formation, the sulfonamide NH proton shifted downfield ($\Delta\delta$ = 3.6) and the TFA carbonyl carbon in **1** at δ 182.8 disappeared. Also, the CF_3 group showed an upfield shift ($\Delta\delta$ = 10.6) in its ^{19}F NMR spectrum. Additionally, the hypsochromic shifts in the fluorescence emission maximum of *ortho*-TFADA in the presence of anions augment the evidence for adduct formation (Fig. 2b). The anionic adduct formation seems to perturb the energy gap between S_1 and S_0 states, thus resulting in the hypsochromic shift, although such an explanation would warrant further study. It can be understood that anions which did not show any hypsochromic shift (^-SCN, HSO_4^-, Cl^-, Br^-) did not form adducts of type **I**. Furthermore, we have already demonstrated that a carboxamide proton *ortho* to the trifluoroacetyl group enhances its binding ability towards various anions, in which we have realized the highest stabilizing effect for a cyanide ion.[4] Therefore, the fluorescence behavior of *ortho*-TFADA towards anions can be explained, based on the relative affinity of the anions for the trifluoroacetyl group, *i.e.*, the "carbonyl affinity" and the nature of the adduct formed.¶

The association constant for the complexation process of *ortho*-TFADA with cyanide ion (K_{ass} = 3 × 10^5 M^{-1}) was obtained from the observed fluorescence enhancement data.‖

The ability of *ortho*-TFADA to signal selectively the binding of ^-CN was checked in the presence of an excess of competing anions. Fluorescence enhancement was observed under such conditions, albeit slightly lower (80% enhancement compared to that observed in the absence of the competing anions). This property of our sensor makes it attractive. Although the present sensor has poor water solubility, thus hampering its study in aqueous media, we are very much aware that this type of signaling

mechanism, involving intramolecular H-bonding, should work well in aqueous media** which would lead to the development of a selective cyanide sensor of practical utility.

In summary, we have demonstrated for the first time that the fluorescence signaling of anion binding can be modulated by intramolecular H-bonding stabilization of anion–ionophore adducts. Through this approach, fluorescence enhancement rather than quenching is realized in anion sensing using a neutral organic sensor. The fluorescence enhancement observed is attributed to the stabilization of the anion–ionophore adducts from possible quenching processes, in addition to the conformational restrictions imposed by the intramolecular H-bonding. The present system also shows noticeable cyanide selectivity in acetonitrile and is expected on rational grounds to be integrated into a new sensor system effective in water that is under active investigation.**

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Notes and references

‡ Selected data for **1**: Yellow solid; mp 169.3–169.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (s, 6 H), 7.04 (t, J = 7.8 Hz, 1 H), 7.11 (d, J = 7.8 Hz, 1 H), 7.51 (t, J = 8.1 Hz, 2 H), 7.59 (t, J = 8.1 Hz, 1 H), 7.71 (d, J = 8.7 Hz, 1 H), 7.77 (d, J = 6.3 Hz, 1 H), 8.27 (d, J = 8.7 Hz, 1 H), 8.37 (d, J = 7.5 Hz, 1 H), 8.54 (d, J = 8.7 Hz, 1 H) and 10.94 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.5, 183.0, 182.6, 182.1 (q, J = 34.9 Hz), 152.3, 142.8, 137.4, 133.8, 132.3, 132.2, 132.1, 132.0 (q, J = 4.1 Hz), 130.8, 130.1, 129.5, 129.2, 123.1, 122.6, 118.7, 118.5, 118.4, 115.8, 115.7, 114.5 and 45.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ 6.66; HRMS (EI) calc. for $C_{20}H_{17}F_3N_2O_3S$ (M^+) 422.0912, found (m/z) 422.0891. Selected data for **2**: Pale green solid: mp 66.8–67.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (s, 6 H), 7.19–7.13 (m, 3 H), 7.57–7.53 (m, 2 H), 7.86 (d, J = 8.1 Hz, 2 H), 8.32 (d, J = 8.7 Hz, 1 H), 8.37 (d, J = 8.2 Hz, 1 H) and 8.56 (d, J = 8.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 179.4, 178.9, 178.5 (q, J = 34.7 Hz), 152.6, 143.7, 133.7, 132.2, 132.1, 132.0, 130.8, 130.2, 129.6, 129.3, 125.4, 122.6, 118.8, 114.9, 110.0 (q, J = 289.5), 123.3, 118.2, 118.1, 115.7 and 45.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ 5.01; HRMS (EI) calc. for $C_{20}H_{17}F_3N_2O_3S$ (M^+) 422.0912, found (m/z) 422.0917.

§ Acetate and phosphate ions also gave similar fluorescence quenching with *para*-TFADA and *N*-Ph-DA. A PET-type process may be suggested as a fluorescence quenching mechanism for these species.

¶ The cyanide adduct of **1** showed a higher quantum yield (Φ = 0.15) than that of the acetate adduct (Φ = 0.04). It should be also noted that the quantum yield of **1** itself (and also **2**) was much lower (Φ = 0.006) than that of its cyanide adduct, and *N*-Ph-DA that has no trifluoroacetyl group (Φ = 0.27).

‖ In the case of the acetate ion, the binding constant could not be determined under an assumption of 1 : 1 binding, from which we infer that at any given time, there exist more than two fluorescing species, probably due to intermolecular H-bonding interactions. A complete mechanistic study will be detailed separately in a full account.

** Usually, polar solvents are known to compete more with intermolecular H-bonding interactions than intramolecular H-bonding. We have found that a chromogenic sensor based on TFACA shows a dramatic anion selectivity in an aqueous media. This will be published elsewhere.

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