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Fluorescence "Turn-On" Sensing of Carboxylate Anions with Oligothiophene-Based *o*-(Carboxamido)trifluoroacetophenones

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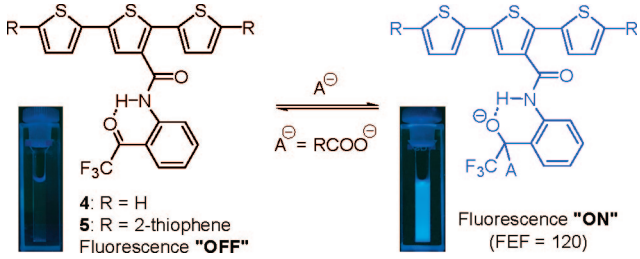

o-(Carboxamido)trifluoroacetophenones containing ter- or pentathiophene moiety as a fluorophore exhibit fluorescence enhancement upon binding carboxylate anions. Particularly, the terthiophene derivative shows a large fluorescence enhancement factor (FEF = 120). The enhancement is explained by intramolecular H-bonding stabilization of an anion−ionophore adduct, through which a possible quenching process, the n−π^* transition from the trifluoroacetophenone moiety, is eliminated.

Molecular sensing of anions has attracted growing attention given that anions play important roles in chemical and biological processes. Chemosensors based on anion-induced fluorescence changes are particularly attractive because of the simplicity and high detection limit of fluorescence detection methods.[1] The development of fluorescence "turn-on"-type sensors for anions of biological importance remains a challenging object, because anions may act as fluorescence quenchers and thus fluorescence quenching rather than enhancement is observed in many cases.[2] In some cases the fluorescence enhancement results from anion sensing;[3] however, only marginal enhancement in the fluorescence emission results with rare exceptions.[4] Therefore, there is need to develop fluorescence turn-on sensors for anions based on new disciplines.

Trifluoroacetophenone derivatives **1** (Figure 1) have been utilized as unique ionophores for anions that reversibly add to the trifluoroacetyl carbonyl carbon to form the corresponding anion−ionophore adducts.[5] Recently, we introduced the second generation of trifluoroacetophenone ionophores, *o*-(carboxamido)trifluoroacetophenones **2**,[6a] in which the carboxamide group stabilizes the alkoxide adducts through enhanced intramolecular H-bonding. The new ionophores **2** show significantly enhanced binding affinity toward anions such as cyanide and carboxylates.[6b] This approach of intramolecular H-bond stabilization of anion−ionophore adducts also enabled us to introduce a novel fluorescence sensor such as the dansyl derivative **3**, in which the sulfonamide NH acts as the H-bond donor.[6c] The dansyl derivative **3** shows fluorescence enhancement rather than quenching, upon addition of anions such as cyanide. We were particularly interested in the fluorescence sensing of carboxy-

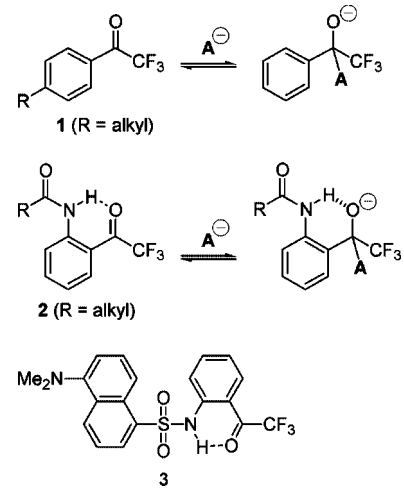

FIGURE 1. Structures of trifluoroacetophenone derivatives **1** and **2**, their anionic adducts, and dansyl analogue **3**.

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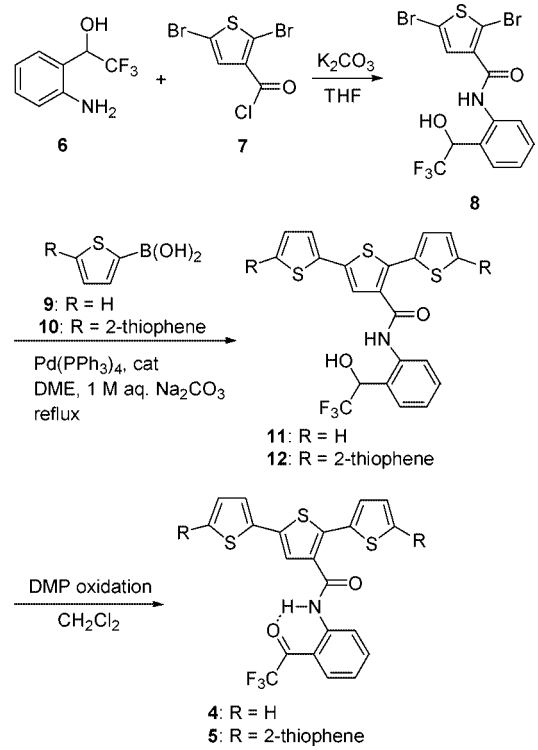
lates,[5] an important class of organic compounds together with amines. Although chemosensor **3**detected an acetate ion in the fluorescence enhancement mode, the fluorescence enhancement factor was small (FEF = 2.5), and also the binding mode did not follow a 1:1 stoichiometry. We have suspected that, in addition to the carbonyl carbon adduct, a deprotonated species forms owing to the presence of acidic sulfonamide proton, and this deprotonated species seems to influence the binding mode as well as the fluorescence enhancement. To alleviate the deprotonated species, we have designed new fluorescence sensors in which the recognition motif is connected to the fluorophore through a carboxamide functionality, of which the proton is less acidic than that of the sulfonamide group. As the fluorophore, we have selected oligothiophenes for future elaboration of the chemosensors into polymeric materials. Such polymeric materials may be also used for sequestering anions by using the reversibility of binding.

Oligothiophenes have attracted considerable research interest owing to their use as organic semiconductors for the realization of devices such as field effect transistors, light-emitting diodes, or photovoltaic cells.[7] Also, oligothiophenes together with monothiophenes readily undergo oxidative or electro-polymerization to the corresponding polythiophenes.[8] Despite their intrinsic fluorescence and facile polymerization properties, little effort has been made in the development of fluorescent sensors based on oligothiophenes.[9] Herein, we report new fluorescence sensors based on terthiophene (**4**) and pentathiophene (**5**) moieties (Scheme 1), which sense carboxylates with large fluorescence enhancement (FEF = up to 120) and in a 1:1 binding mode.

Compounds **4** and **5** were synthesized following the routes described in Scheme 1. Coupling of aniline **6**, prepared from 2-nitrobenzaldehyde, with acid chloride **7**, prepared from 3-thienoic acid, afforded amide **8** in 62% yield, which was then subjected to the Suzuki−Miyaura coupling with thiopheneboronic acids **9** and **10** to give oligothiophenes **11** and **12** in 80−85% isolated yields, respectively. Finally, the Dess−Martin oxidation of **11** and **12** afforded desired **4** and **5** in 55−59% isolated yields, respectively (Supporting Information).

Photophysical properties of compounds **4** and **5** were evaluated in CH_3CN. Compound **4** displayed strong absorption maxima at 241, 256, and 347 nm (ϵ = 17,550 M^{-1} cm^{-1}), and **5** displayed strong absorption maxima at 242 and 403 nm (ϵ = 36,080 M^{-1} cm^{-1}). Compound **4** showed very weak fluorescence emission at 410 nm when excited at 347 nm, whereas **5** showed moderate fluorescence emission at 508 nm when excited at 403 nm. The sensing ability of compounds **4** and **5** was evaluated by fluorescence titrations against increasing concentrations of anions such as AcO^-, F^-, Cl^-, Br^-, NCS^-, $H_2PO_4^-$, and HSO_4^- (as Bu_4N^+ salts) in acetonitrile. Although we focused on carboxylate sensing, CN^- was also examined as a reference anion because our previous data show that *o*-(carboxamido)trifluoroacetophenone ionophores recognize it most strongly. The results of fluorescence

SCHEME 1. Synthesis of Chemosensors 4 and 5



titration of **4** at 8.0 μM concentration toward AcO^- and collective emission data for all the anions are shown in Figure 2.

In line with our expectation, both **4** and **5** gave notable enhancement in the fluorescent intensity for anions such as CN^-, AcO^-, F^-, and $H_2PO_4^-$, whereas little or very small enhancement for other anions. Of particular note is that the relative fluorescence intensity among the three anions is much different, showing the largest value in the cases of CN^- and AcO^-, followed by F^- and then $H_2PO_4^-$. The enhancement was dramatic and sensor **4** gave a 120-fold enhancement toward AcO^- at the saturation point (Figure 2a). Interestingly, sensor **4** shows a little difference between CN^- and AcO^-, while **5** shows a large difference. The fluorescence enhancement was accompanied with a slight bathochromic shift (2.0 nm) in the case of **4**, whereas there was no shift in the case of **5** (Figure 2b,c). If we compare the fluorescence titration results, particularly those obtained by **4**, with those reported by the dansyl derivative **3**, two notable differences are observable: (i) **4** discriminates AcO^- over F^- and $H_2PO_4^-$, whereas **3** does not; (ii) **4** shows a dramatic increase in the fluorescence intensity particularly toward carboxylate ions such as AcO^-, but **3** does not. These differences are promising properties for further elaboration of **4** and its derivatives into polymeric sensing materials for carboxylate functions in biomolecules such as oligopeptides and proteins.

Since the binding interactions between the sensors and carboxylate ions should be the same, other carboxylate anions such as propanoate and pentanoate showed fluorescence enhancement similar to that of acetate (Supporting Information).

It is worth mentioning that none of the anions examined showed fluorescence quenching, except for $H_2SO_4^-$ in which

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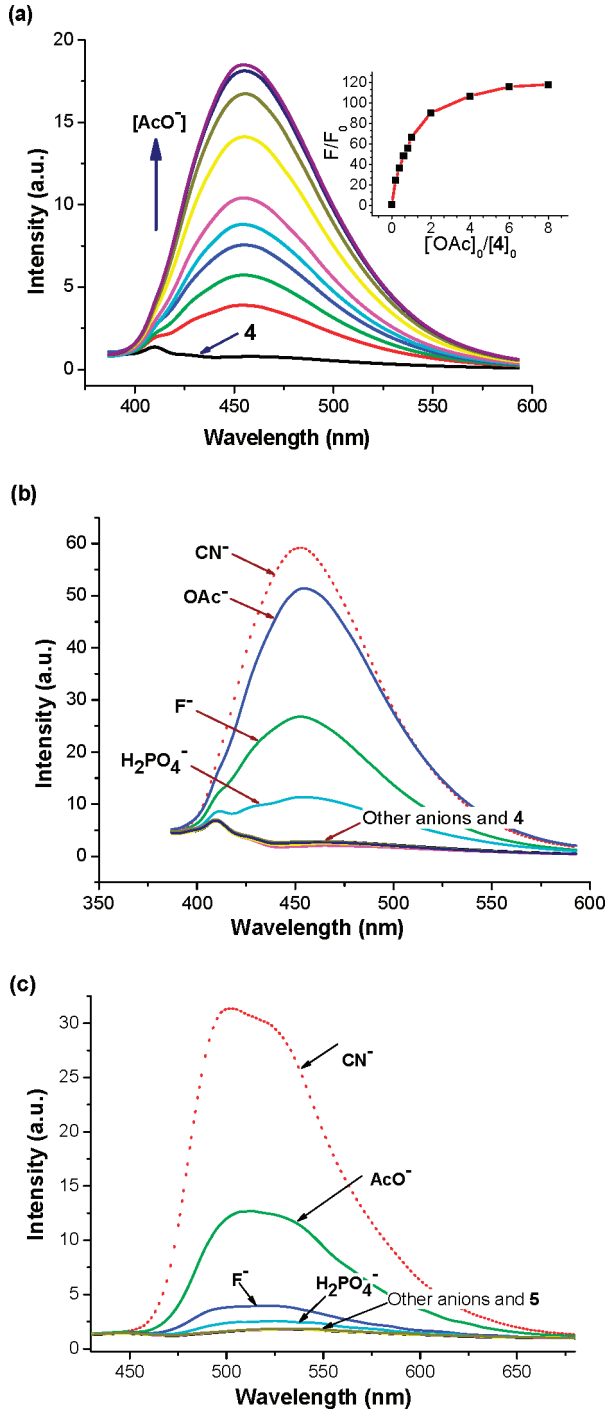

FIGURE 2. (a) Fluorescence spectra of **4** (8.0 μM) with increasing amounts of acetate ion (λ_{ex} = 347 nm). Inset: dependence of fluorescence intensity (I/I_0) with respect to $[AcO^-]_0/[\mathbf{4}]_0$. (b) Collected fluorescence spectra obtained for an equimolar mixture of **4** (8.0 μM) and each of the anion guests. (c) Collected fluorescence spectra obtained for an equimolar mixture of **5** (4.0 μM) and each of the anion guests (from the top: CN^-, AcO^-, F^-, $H_2PO_4^-$, SCN^-, Cl^-, Br^-, and HSO_4^-; λ_{ex} = 403 nm).

case a little quenching was observed with **5**. Both compounds **4** and **5** themselves gave low fluorescence quantum yields, plausibly owing to the presence of trifluoroacetophenone moiety of which n$-\pi^*$ transition seems to cause fluorescence quenching.[10]

The fluorescence quantum yield increases as the amount of acetate adduct increases (Supporting Information). Therefore,

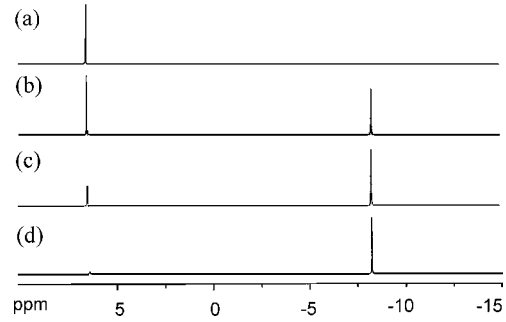

FIGURE 3. ^{19}F NMR spectra of (a) **4** and its acetate mixtures: (b) 1.0, (c) 2.0, and (d) 4.0 equiv of AcO^- (as Bu_4N^+ salt); taken in $CDCl_3$ at 25 °C.

the carbonyl adducts should be responsible for the fluorescence enhancement observed. Although the fluorescence quantum yield increases as the carbonyl adduct forms, still the quantum yield at the saturation point (Φ_F = 0.0081 in the case of **4**; Φ_F = 0.0796 in the case of **5**) is smaller compared to that of the ter- or pentathiophene itself (terthiophene, Φ_F = 0.07; pentathiophene, Φ_F = 0.28, in dioxane).[11] This comparison suggests that the carboxamide substitution to the oligothiophenes may lead to less efficient fluorophores.[12]

The molecular sensing of anions such as acetate reported so far shows fluorescence quenching rather than enhancement in most cases,[2d−j] as mentioned above. However, our oligothiophene-based sensor **4** shows a large fluorescence enhancement upon anion binding. It is clear that the intramolecular H-bonding plays a key role for the fluorescence enhancement, because a similar system that lacks an *ortho*-H-bonding acceptor shows fluorescence quenching, as demonstrated previously with a *para*-analogue of **3**.[6c] The stabilization of anionic adducts through intramolecular H-bonding seems to suppress possible quenching processes by anionic guest, its adduct species, or both, otherwise effective in the absence of such H-bonding. In addition, the intramolecular H-bonding increases the conformational rigidity of the adduct, partially contributing to the fluorescence enhancement. The large fluorescence enhancement observed with **4** and **5** are likely owing to the elimination of the n$-\pi^*$ transition from the trifluoroacetyl carbonyl conjugated to the benzene ring upon binding carboxylate ions, which seems to intervene the $\pi-\pi^*$ transition levels and thus quench the emission from the oligothiophene fluorophores through a donor-excited photoinduced electron transfer mechanism.[12a]

The formation of anionic adducts is evident from ^1H and ^{19}F NMR analyses. Peaks for both **4** and its acetate adduct appeared separately, indicating that the equilibration for the adduct formation is slow compared to the NMR time scale. The amide NH proton of **4**, appearing at δ 11.0 ppm, shifted upfield ($\Delta\delta$ = 0.2) upon addition of acetate. Also, the CF_3 group of **4**, appearing at δ 6.5 ppm, shifted upfield (−8.4 ppm; $\Delta\delta$ = 14.9) upon addition of the acetate anion (Figure 3). Similar upfield shifts were observed in the case of **5** upon acetate binding (Supporting Information).

To obtain thermodynamic data for the binding process between **4** and acetate, we carried out isothermal titration

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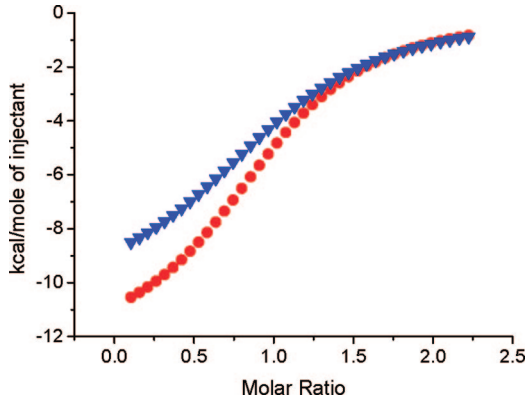

FIGURE 4. ITC titrations of **4** (●) and **5** (▼) with acetate ion (as Bu_4N^+ salt) at 303 K in acetonitrile.

calorimetry (ITC). The thermodynamic data ($\Delta H° = -12.5$ kcal/mol and $-\Delta TS° = 6.3$ kcal/mol, $K_{ass} = 3.1 \times 10^4$ M^{-1}, $T = 303$ *K*) obtained for the molecular interaction between **4** and acetate ion indicate that the complex formation is driven by a major favorable enthalpy change and a minor unfavorable entropy change, which also supports the covalent adduct formation. Also, the ITC binding isotherms were best fit by a one-site binding model with a 1:1 binding stoichiometry (Figure 4).[13] The association constant obtained for the complexation process between **4** and the acetate ion was similar to that obtained in the case of **2** but smaller than that obtained in the case of **3**. A similar level of thermodynamic parameters was obtained for the binding process between **5** and the acetate ion ($\Delta H° = -10.7$ kcal/mol, $-T\Delta S° = 4.7$ kcal/mol, $K_{ass} = 2.2 \times 10^4$ M^{-1}).

Furthermore, we have already demonstrated that a carboxamide proton *ortho* to the trifluoroacetyl group enhances its binding ability toward anions such as carboxylates.[6a] Therefore, the fluorescence behavior of **4** and **5** depending on the anions can be explained by comparing the relative affinity of the anions toward the trifluoroacetyl group, which is in the order: $CN^- > OAc^- > F^- > H_2PO_4^- >$ other anions.

In summary, we have synthesized ter- and pentathiophene derivatives of *o*-(carboxamido)trifluoroacetophenones as fluorescence turn-on sensors for carboxylate anions. Both oligothiophene derivatives detect carboxylate anions with fluorescence enhancement. Particularly, the terthiophene-based sensor **4** shows a large fluorescence enhancement factor of 120 as well as improved selectivity toward carboxylate anions over competing anions, compared to the previous dansyl derivative **3**. Thus, highly efficient fluorescence turn-on sensing of carboxylate anions has been achieved, which will find further applications in the development of chemosensors for biological molecules containing carboxylate groups.

(13) F^- shows a complex binding mode toward **4**, whereas $H_2PO_4^-$ shows a major 1:1 binding mode with other minor modes; The former anion can bind to the carboxamide protons of the sensor itself and its adduct, whereas the latter seems to bind similarly but to a lesser degree.

Experimental Section

For experimental details for the synthesis all the compounds and titrations (NMR, fluorescence, and ITC), see Supporting Information.

***N*-[2-(2,2,2-Trifluoroacetyl)phenyl]-2,5-di(thiophen-2-yl)thiophene-3-carboxamide (4).** $R_f = 0.5$ (hexane/EtOAc = 4/1); mp 111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.19 (s, 1H), 8.95 (d, J = 6.0 Hz, 1H), 7.94−7.91 (m, 1H), 7.71 (td, J = 15.9, 1.2 Hz, 1H), 7.48 (s, 1H), 7.36−7.35 (m, 2H), 7.29−7.17 (m, 3H), 7.06−7.00 (m, 2H); HRMS (FAB) calcd for $C_{21}H_{12}F_3NO_2S_3$ (M + H) 464.0061, found 464.0063.

***N*-[2-(2,2,2-Trifluoroacetyl)phenyl]-2,5-di(thiophen-2-yl)thiophene-3-carboxamide (5).** $R_f = 0.4$−0.6 (hexane/EtOAc = 4/1); mp 171 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.34 (s, 1H), 8.96 (d, J = 9.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.75 (t, J = 6 Hz, 1H), 7.48 (s, 1H), 6.91−7.40 (m, 11H); HRMS (FAB) calcd for $C_{29}H_{16}F_3NO_2S_5$ (M + H) 627.9815, found 627.9812.

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Supporting Information Available: Details for the synthesis of compounds **4** and **5** and anion titration data (^{1}H/^{19}F NMR, fluorescence, and ITC). This material is available free of charge via the Internet at http://pubs.acs.org.

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