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Dmitry Aldakov

Manuel A. Palacios

Pavel Anzenbacher Jr.
Bowling Green State University, pavel@bgsu.edu

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Benzothiadiazoles and Dipyrrolyl Quinoxalines with Extended Conjugated Chromophores−Fluorophores and Anion Sensors

Dmitry Aldakov, Manuel A. Palacios, and
Pavel Anzenbacher, Jr.*

Department of Chemistry and Center for Photochemical Sciences, Bowling Green State University, Bowling Green, Ohio 43403

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Stable fluorescent chromophores find use in a growing number of practical applications, including their utility as laser dyes,[1] emitters in light-emitting diodes,[2] photoconductors,[3] optical data storage,[4] and optical switches.[5] Stable fluorophores with high quantum yields are widely used in fluorescent sensors[6] and labels.[7] These became very popular lately, owing to their potential for high sensitivity at low concentration coupled with decreased cost of the required equipment.[8]

Recently, we have described a new class of fluorescent anion sensors bearing extended conjugated chromophores[9] with incorporated 2,3-di(1*H*-2-pyrrolyl)quinoxaline, (DPQ), as the anion recognition element.[10] Literature shows that DPQ binds anions via hydrogen bonding between pyrrole NH and anions, the hydrogen bonding nature of the DPQ−anion complex was demonstrated by ^{1}H NMR.[10a] In this paper, we provide a full account of our efforts including synthesis and photophysical properties of DPQ-based fluorescent anion sensors with extended conjugated chromophores **S1**−**S6** (Figure 1), including their benzothiadiazole precursors **F1**−**F6**, which appears to be an interesting set of highly stable fluorescent chromophores.

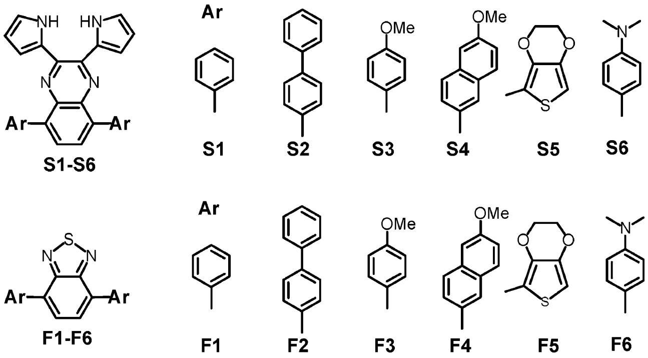
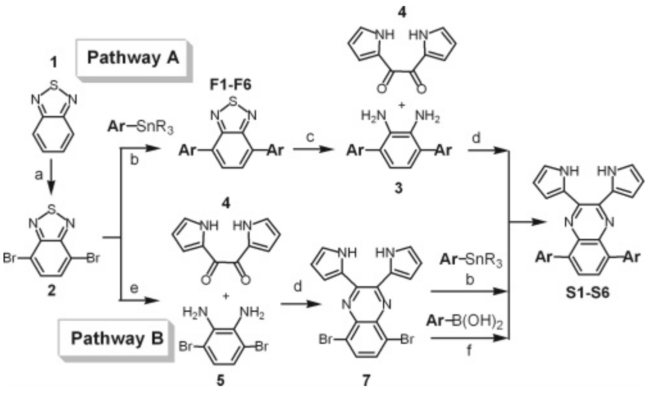


Figure 1. Structures of DPQ sensors with extended conjugated chromophores **S1**−**S6** and their benzothiadiazole precursors **F1**−**F6**.

Scheme 1. Synthesis of 5,8-Diaryl-2,3-dipyrrolylquinoxaline Sensors[a]



[a] Conditions: (a) HBr, H_2O_2, reflux; (b) PdCl$_2$(TPP)$_2$, THF, 100−120 °C; (c) LiAlH$_4$, THF, reflux; (d) AcOH, reflux; (e) NaBH$_4$-EtOH; (f) Pd(TPP)$_4$, toluene-aq. K$_2$CO$_3$.

Sensors **S1**−**S6** with the extended aryl substituents of varying electronic nature were designed to provide a tool for systematic modulation of electronic density in the quinoxaline chromophore. This, in turn, was expected to lead to tuning the output emission wavelength as well as the anion binding affinity in the sensors **S1**−**S6**. Our previous studies suggest that even small changes in electronic density in the quinoxaline moiety affect the pyrrole hydrogen-bonding donors and the stability of the anion−sensor complex.[9a]

The synthesis of complexes **S1**−**S6** (Scheme 1) departs from 1,2,3-benzothiadiazole **1**, which was converted to the corresponding bromo derivative **2**.[11] In pathway A (Scheme 1), intermediate **2** was coupled via Stille reaction[12] with a suitable aryltributylstannyl derivative to yield benzothia-

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* Corresponding author. Phone: 419-372-2080. E-mail: pavel@bgnet.bgsu.edu.

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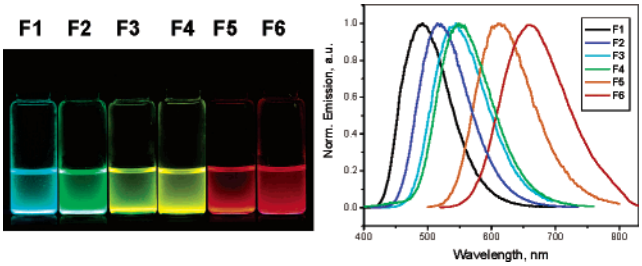

Figure 2. Photograph of 0.3 mM solutions of **F1**−**F6** in CH_2Cl_2 illuminated by black light (365 nm) and corresponding emission profiles.

Table 1. Photophysical Properties of F1−F6 (1.0 μM in CH_2Cl_2), Absorption Maximum (A_{max}), Emission Maximum (λ_F), Fluorescence Quantum Yield (Φ_F), and Lifetime (τ_F) at Room Temperature^a

compd	A_{max} (ϵ)^b	λ_F (nm)	$\Phi_F{}^c$	τ_F (ns)
F1	379 (9.1×10^3)	492	0.45	11.3
F2	411 (11.0×10^3)	542	0.55	12.3
F3	485 (6.60×10^3)	610	0.36	19.6
F4	470 (16.9×10^3)	662	0.08	5.0
F5	391 (15.5×10^3)	515	0.84	7.2
F6	416 (12.2×10^4)	551	0.37	8.5

^{a} All compounds were excited in their respective absorption maxima. ^{b} Units of L·mol^{-1}·cm^{-1}. ^{c} Determined using quinine sulfate (30 μM in 0.05 M H_2SO_4) as a standard.

diazole fluorophores **F1**−**F6**, which were then reduced by $LiAlH_4$ to the corresponding phenylene-diamines of general formula **3**. We note that the reduction of benzothiadiazole derivatives did not proceed smoothly and required $LiAlH_4$ in THF at reflux for 2 h, and the resulting diamines showed signs of photochemical degradation. Diamine intermediates **3** were then condensed with 1,2-di(1*H*-pyrrol-2-yl)ethane-1,2-dione **4** in refluxing acetic acid to give 5,8-diaryl-2,3-di(1*H*-pyrrol-2-yl)quinoxalines **S1**−**S6**.

The difficult reduction of diaryl benzothiadiazoles **F1**−**F6** and photochemical instability of intermediates **3** prompted us to develop an alternative route. Pathway B was designed to use the advantage of easily accessible 1,2-diamino-3,6-dibromobenzene **5**,[13] which was condensed with **4** to give 5,8-dibromo-2,3-di(1*H*-pyrrol-2-yl)quinoxaline **7**. Intermediate **7** was then coupled with suitable aryltributylstannyl derivatives (Stille reaction)[12] or aryl-boronic acids (Suzuki reaction)[14] to yield sensors **S1**−**S6**.

The synthesized benzothiadiazole precursors **F1**−**F6** display emission color tuning mediated by the aryl substituents, which is easily observed by a naked eye examination of their fluorescence in solution (Figure 2). While the strong emission (Table 1) was not entirely unexpected given the frequent use of benzothiadiazole in fluorescent materials and conjugated polymers,[15] we found that **F1**−**F6** are also very stable fluorophores that did not show appreciable photobleaching in oxygenated solutions even after several weeks. More importantly, **F1**−**F6** displayed absorption/emission tuning that to a large extent follows the electronic properties of the extended aryl substituents (Table 1).

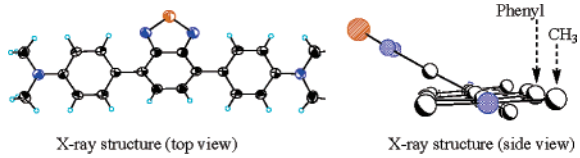

Figure 3. X-ray structure of **F6**. Thermal ellipsoids are scaled to 50% probability level.

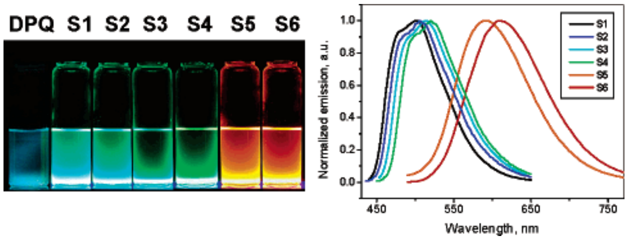

Figure 4. Photograph of 0.3 mM solutions of **S1**−**S6** in CH_2Cl_2 illuminated by black light (365 nm) and corresponding emission profiles.

Table 2. Photophysical Properties of S1−S6 (1.0 μM in CH_2Cl_2), Absorption Maximum (A_{max}), Emission Maximum (λ_F), Fluorescence Quantum Yield (Φ_F), and Lifetime (τ_F) at Room Temperature^a

compd	A_{max} (ϵ)^b	λ_F (nm)	$\Phi_F{}^c$	τ_F (ns)
DPQ	410 (1.10×10^4)	490	0.15	1.8
S1	422 (1.27×10^4)	500	0.25	2.1
S2	346 (5.0×10^3)	506	0.38	2.6
S3	419 (1.81×10^4)	514	0.24	2.5
S4	416 (1.66×10^4)	520	0.13	2.7
S5	450 (1.79×10^4)	595	0.22	10.1
S6	425 (2.19×10^4)	610	0.26	3.1

^{a} All compounds were excited in their respective absorption maxima. ^{b} Units of L·mol^{-1}·cm^{-1}. ^{c} Determined using quinine sulfate (30 μM in 0.05 M H_2SO_4) as a standard.

Strong fluorescence as well as high chemical and photochemical stability of **F1**−**F6**, together with the ease of tuning the photophysical properties based on utilization of EWG/EDG attached to the 5,8-aryls, make these derivatives potentially useful as laser dyes. Interestingly, the fluorescence quantum yield and lifetimes within the **F1**−**F6** series do not show a clear trend. Such effects are observed in aromatic chromophores[16] and may be ascribed to varying oscillator strength of the chromophore.[17] The effective electronic communication between the 5,8-substituted aryls and 1,2,3-benzothiadiazole is shown in the X-ray structure of **F6**. This structure shows how despite the steric hindrance of the phenyl *ortho*-hydrogens and the unshared electron pair on the benzothiadiazole nitrogen are almost coplanar with each other to maximize the conjugation (Figure 3).

Compared to the starting benzothiadiazole precursors **F1**−**F6**, sensors **S1**−**S6** do not display the well-spaced emission signatures. As expected, the presence of 5,8-aryl substituents in sensors **S1**−**S6** results in both a dramatic increase of emission intensity and shifted emission maximum as compared to the parent DPQ ($\lambda_f = 490$ nm, $\Phi_f = 0.15$) (Figure 4, Table 2). This feature suggests that these sensors may be

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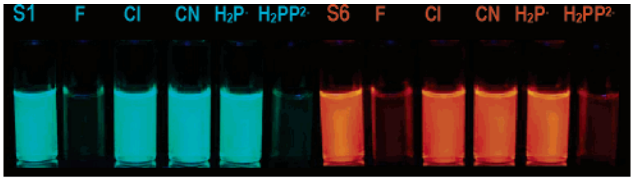

Figure 5. Changes in emission of sensors **S1** and **S6** (50 μM in CH_2Cl_2) upon the addition of fluoride (F^-), chloride (Cl^-), cyanide (CN^-), dihydrogenphosphate (H_2P^-), and dihydrogenpyrophosphate (H_2PP^{2-}) anions. Vials were illuminated by black light (365 nm).

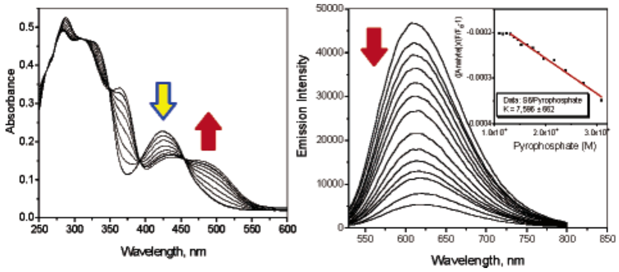

Figure 6. Changes in absorption and photoluminescence intensity of **S6** (10 and 2 μM in CH_2Cl_2, respectively) upon addition of pyrophosphate (0−357 μM). Excitation was perfomed at 454 nm (isosbestic point in UV−Vis). The inset shows single-reciprocal transformation of the isotherm and fit.

used in lower concentration thus allowing for achieving higher sensitivity.

Visual inspection of solutions of the sensors **S1**−**S6** (10 μM in CH_2Cl_2) before and after addition of anions in the form of their hydrated tetra-*n*-butylammonium salts[18] showed a dramatic change in fluorescence as well as in color after addition of both fluoride and pyrophosphate, which suggests strong binding. Conversely, addition of cyanide, dihydrogenphosphate, or chloride resulted in weak or no change in color, respectively (Figure 5). As expected,[9,10] other anions such as bromide, sulfate, cyanate, thiocyanate, and nitrate did not show appreciable change in absorption/emission spectra and were not investigated further. Previous studies suggest that the affinity order $F^- \approx H_2PP^{2-} \gg H_2P^- \geq Cl^-$ is a result of high surface charge concentration in a small fluoride anion and pyrophosphate dianion (H_2PP^{2-}). This also explains why structurally similar but monoanionic dihydrogenphosphate (H_2P^-) is not bound by our sensors.[9a]

Quantitative measurements of anion affinity were performed by monitoring the changes in the absorbance spectra of sensors **S1**−**S6** upon addition of an anion. The titration experiments were performed using fluorescence for signal transduction. This is because the fluorescence is significantly more sensitive and allows for unambiguous sensing at low concentrations (0.5−100 μM). Examples of UV−Vis and fluorescence titration experiments are shown in Figure 6; see also Table 3.

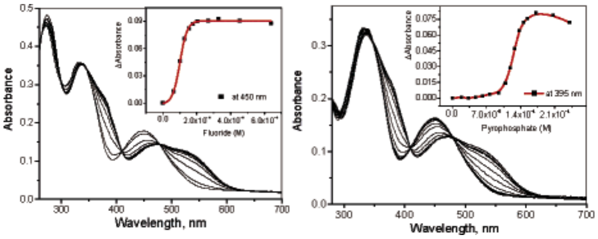

Figure 7. Changes in absorption spectra of **S5** (10 μM) in polar solvents titrated by aqueous anion solutions. Left: in DMSO upon the addition of aqueous fluoride (0−0.61 mM in the cell). Right: in MeCN upon the addition of aqueous pyrophosphate (0−2.50 mM in the cell).

Table 3. Affinity Constants Recorded for Sensors S1−S6 (2.0 μM in CH_2Cl_2), Titrated by Anions[18] at Room Temperature[a]

anion	fluoride	chloride	pyrophosphate	phosphate
DPQ	18 200	<50	14 300	<100
S1	51 300	<100	93 700	<200
S2	∼12 200[b]	<100	∼30 000[b]	<100
S3	24 700	<100	58 900	<100
S4	10 200	<100	24 300	<100
S5	25 600	<100	57 300	<100
S6	27 500	<50	39 000	<50

[a] All compounds were excited in their respective lowest lying isosbestic points. [b] Binding isotherms show biphasic behavior due to $\pi-\pi$ interactions of sensors. The affinity constants were estimated with significant error; ±25%.

Although CH_2Cl_2 is not a solvent of choice for inorganic anions,[19] we have been limited by the fact that our sensors are poorly soluble in polar solvents and may undergo aggregation. Naturally, we were also interested in exploring the anion sensing in polar/water compatible solvents such as MeCN or DMSO. Particularly water, albeit a natural medium for most anions, poses a challenge for anion binding and sensing as it is an effective competitor for hydrogen bonding. Nevertheless, we have carried out a series of titration experiments in MeCN as well as in DMSO using aqueous solutions of anions. While these experiments revealed similar behavior of sensors, the actual binding isotherms showed sigmoidal progression. We ascribe this to multiple equilibria, presumably involving solvation/hydration of ionic species. Although such isotherms did not allow for calculation of the actual affinity constants, these experiments (Figure 7) suggest that sensors **S1**−**S6** may actually be used to sense anions administered in water.

Encouraged by the fact that even simple sensors utilizing hydrogen bonding may successfully be used to sense anions administered in the form of their aqueous solutions, we explored this idea further. Because sensors **S1**−**S6** are not soluble in polar solvents, we decided to embed them in a compatible polymer matrixes and membranes. Particularly poly(vinyl chloride) (PVC)[20] and polyurethane (PU)[21] embedded sensors were reported in the literature. We reasoned that the hydrophilic PU matrix may provide low polarity environment that would accommodate the sensors while allowing the interaction with the anions administered as aqueous samples. We have devised a simple assay, in which

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(18) The degree of hydration of each of the respective anion salts was determined from the elemental analysis. Thus fluoride was used as hexahydrate, while chloride, hydrogenpyrophosphate, and dihydrogenphosphate were found to be dihydrates, respectively.

(19) We have used the sensing experiments performed in CH_2Cl_2 to calculate the affinity constants because the large amount of the relevant data was previously described in this solvent[9,10] and also because of the poor solvation of anions in this solvent. Solvation of salts often complicates the binding equilibria and may render the fitting unreliable.

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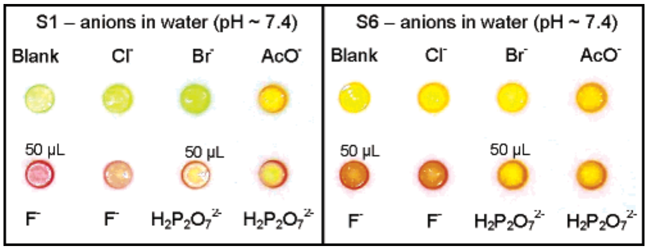

Figure 8. Color response of **S1** and **S6** in polyurethane (0.6% weight) in the presence of aqueous anion solutions (10 mM, 25 μL, unless indicated otherwise).

the individual wells in a multi-well dish were coated with a thin film of PU-embedded sensors (0.6% sensor in PU, w/w). Aqueous solutions of anions (25 or 50 μL, 10 mM, pH = 7.4) were then applied into the individual wells, and the dish was incubated at 40 °C for 1 h. Interestingly, the same effect is also obtained when the assay is developed in a microwave oven for 1−2 min. The wells containing solutions of fluoride and pyrophosphate showed a characteristic change in color corresponding to binding. The wells containing only water or nonbinding anions such as chloride, bromide, cyanide, or dihydrogenphosphate did not show appreciable change in color (Figure 8).

In conclusion, a new class of fluorescent heterocycles potentially useful as chromophores and sensors were prepared by a simple methodology utilizing Suzuki and Stille cross-coupling. The resulting materials show bright fluorescence and remarkable emission tuning. Compounds **S1**−**S6** were shown to display anion-induced fluorescence quenching thus acting as potential sensors for inorganic anions. The anion titration experiments using sensors **S1**−**S6** revealed affinity for small or multiply charged anions such as fluoride and dihydrogenpyrophosphate. Preliminary experiments in water-miscible solvents showed that the anion binding/sensing process is not disrupted when anions are added in the form of aqueous solutions. Finally, multi-well assays utilizing polyurethane-embedded sensors allow for colorimetric screening of aqueous anion solutions indicating that the described compounds and approach may yield inexpensive yet effective fluorescence-based anion−sensor assays in the future. Further efforts toward this end are underway.

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Supporting Information Available: Synthetic procedures, UV−Vis and fluorescence titration experiments, binding isotherms, and crystallographic data for F4 in CIF format. This information is available free of charge at http://pubs.acs.org.

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