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Aldehyde-Appended Distyrylbenzenes: Amine Recognition in Water

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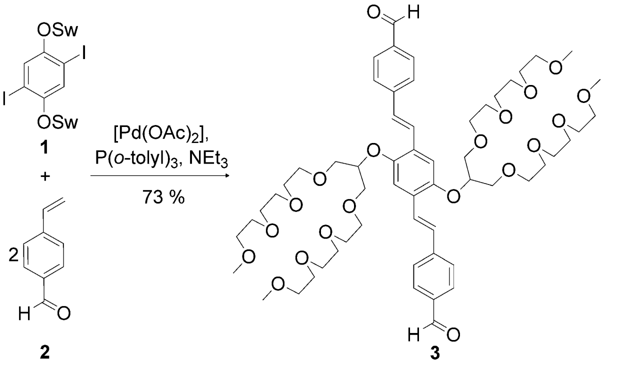
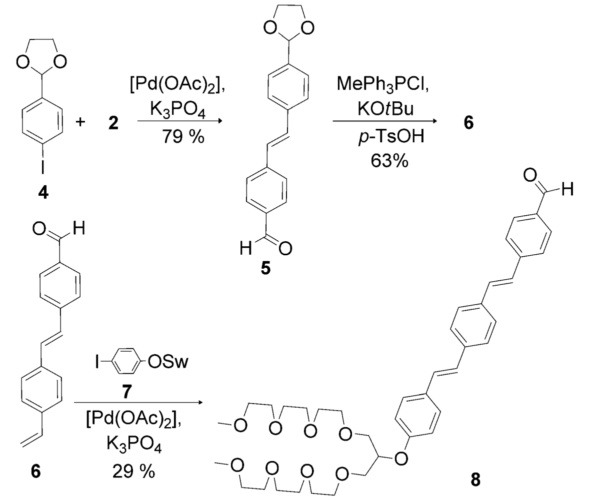
Detection of amines is important, because they are environmental, biological, and clinical analytes that can signal environmental hazard, food poisoning, or monitor disease states.[1] Recent examples of successful amine sensing include Suslick's colorimetric arrays, Lavigne's polythiophene carboxylic acids, Anslyn's receptors, and Kaneda's cyclodextrin dye.[2–6]

1,3-Dicarbonyl- and trifluoroacetyl-substituted dyes investigated by Mertz and Zimmerman, as well as by Glass and co-workers, display changes in fluorescence intensity and wavelength upon exposure to amines.[7] Also, phenol and aldehyde-functionalized cruciform fluorophores detect and discern amines.[8–10] However, most of the described sensor types work better in organic solvents than in water, with the notable exception of Lavigne's polymers and Glass's 1,3-dicarbonyl compounds. For bio- and environmental detection of amines, the dyes should work in an aqueous environment. A problem is the attachment of solubilizing substituents to the core, preventing the fluorescence quantum yield to drop when going from an organic solvent into water. This issue is circumvented by the attachment of branched oligo(ethylene)glycol side chains, which efficiently increase the quantum yield of fluorescent dyes in water.[11] Herein, we describe the synthesis and amine-responsive properties of the simple distyrylbenzenes (DSBs) **3** and **8** in water (Schemes 1 and 2).

Scheme 1 outlines the synthesis of DSB **3**. Starting from **1**, a double Heck reaction[12] with **2** led to **3** in 73% yield after silica-gel chromatography. To prepare a different topology of aldehyde-substituted DSBs, we selected **8** as a target with only one swallowtail substituent. Herein, we performed the Heck coupling of **4** with **2** and transformed the protected aldehyde **5** into the styrylstyrene derivative **6**. A final Heck coupling, now with the iodide **7**, gave the desired target **8**, but only in modest 29% yield (Scheme 2).



Scheme 1. Synthesis of **3** by Heck reaction.



Scheme 2. Synthesis of aldehyde **8** by a combination of Heck and Wittig reactions. *p*-TsOH = *para*-toluenesulfonic acid.

Figure 1 displays the optical spectra (absorption and emission) of **3** and **8** in water, in which both are soluble—**3** more so than **8**, which carries only one swallowtail substituent (Sw: branched oligoethyleneglycol). The emission of **3** is centered at $\lambda = 564$ nm, **8** emits at $\lambda = 538$ nm (Figure 1). In both cases, the fluorescence quantum yield is disappointingly low, <0.01 for **3** and 0.06 for **8**. The meager quantum yield of **3** is probably due to the relaxation of the excited π–π* state into an n–π* state, which is apparently lower in energy. Alternatively, other radiationless deactivation pathways may also operate. Whereas **3** is infinitely stable in aqueous solution, **8** gives a blue emissive species upon irradiation with a UV lamp ($\lambda_{max} = 365$ nm) after several hours.

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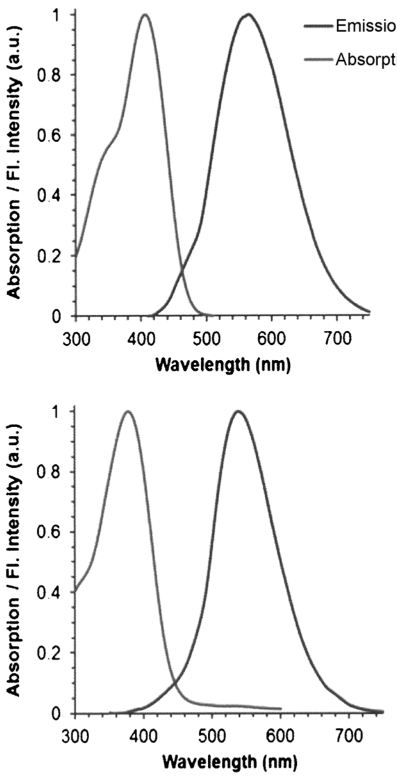

Figure 1. Absorption and emission spectra of **3** (3 μmolL^{-1}; top) and **8** (bottom) in water.

Both aqueous solutions of **3** and **8** were exposed to a series of different amines, and vibrant color changes occurred. Particularly, the dully yellowish fluorescent **3** (Figure 2) turned vibrantly green upon addition of primary amines and blue upon addition of primary diamines (Figure 2). The monoaldehyde **8** also showed color changes, however, much less distinct than those observed for **3**. Primary amines seem to induce quenching in **8**, and only 1,3-diaminopropane led to a significant blueshift in the emission. These observations are surprising and the performance of **8** is quite disappointing compared with that of **3**. From Figure 2, we can directly discern most amines just with the naked eye.

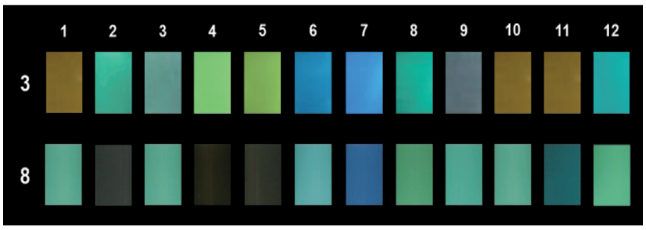

Figure 2. Amine-sensing panels of **3** (10 μmolL^{-1}; top) and **8** (10 μmolL^{-1}; bottom) in water: 1) reference; 2) butylamine; 3) *tert*-butylamine; 4) benzylamine; 5) cyclohexylamine; 6) ethylene diamine; 7) 1,3-diaminopropane; 8) cadaverine; 9) morpholine; 10) ephedrine; 11) 4-aminopyridine; 12) ethanolamine.

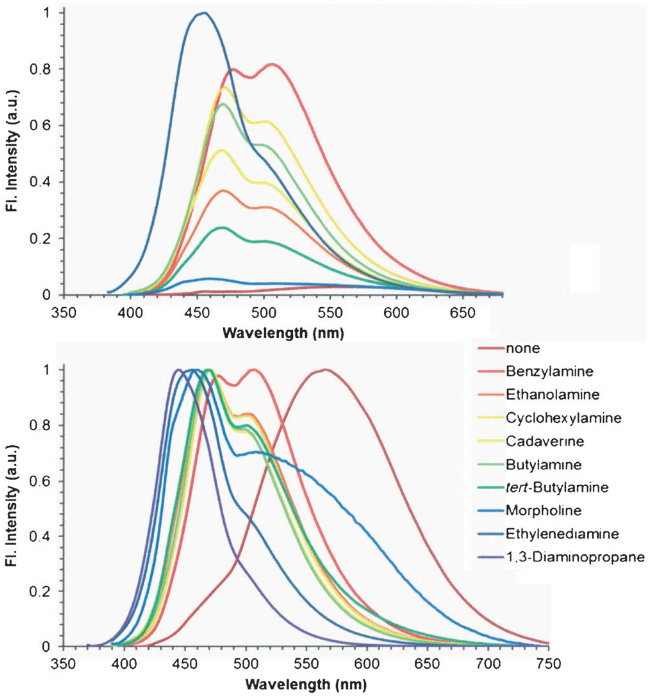

Figure 3. Non-normalized (top) and normalized (bottom) emission spectra of compound **3** (3 μmolL^{-1}) in water in the presence of different amines. The signal for 1,3-diaminopropane was omitted in the top spectrum, because its intensity is approximately ten times higher than that of the solution to which ethylenediamine was added.

Figure 3 displays the normalized and the non-normalized emission spectra of **3** in water in presence of the different amines. Compared with the reference, all spectra are blueshifted. There are four distinct groups. Benzylamine only elicited a slight blueshift, whereas all of the other primary amines caused signals centered at $\lambda = 470$ nm with a significant vibronic shoulder that changes in height and therefore allows the discernment of the amines. Cadaverine, even though a diamine, is also in this group. Morpholine as a secondary amine showed yet a different spectral trace, and then ethylene diamine and 1,3-diaminopropane form the last group with the most blueshifted spectral features. The question is, how the differences in spectroscopic properties can be explained. The primary amines, ethanolamine and cadaverine, will form imines, which will maintain conjugation to the DSB unit, and therefore the emission features are only somewhat blueshifted. Ethylene diamine and 1,3-diaminopropane will form cyclic aminals with **3** or **8**, in which the conjugation to the carbonyl group is interrupted. Morpholine as a secondary amine will form a hemiaminal.

To test the structural hypotheses, ^{1}H NMR spectra of **3** with 1,3-diaminopropane and ethanolamine in D_2O/CD_3OD-mixtures were recorded (Figure 4). Ethanolamine gave the imine, whereas the addition of 1,3-diaminopropane to **3** gave mainly the aminal, as expected from the emission spectra and photographical results (Figure 5).

Imine formation of **3** is fast. Figure 5 shows the time dependence of the fluorescence-intensity signal. Addition of

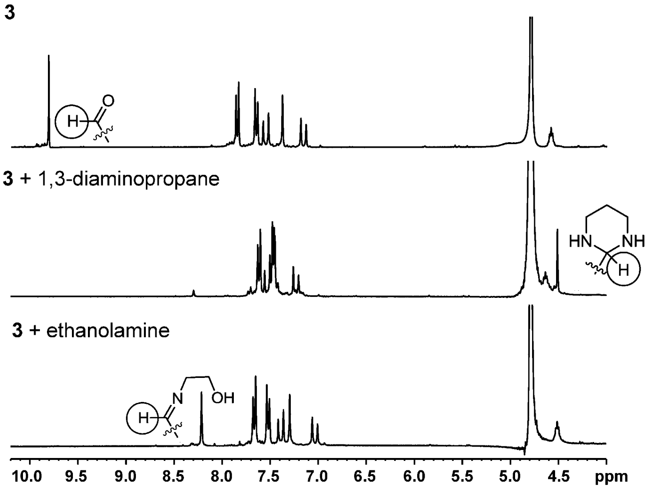

Figure 4. ^1H NMR spectra of **3** (5 mg in 0.5 mL D_2O/CD_3OD) in the presence of 1,3-diaminopropane (20 μL) and ethanolamine (20 μL). The upper trace displays the spectrum of dialdehyde **3**.

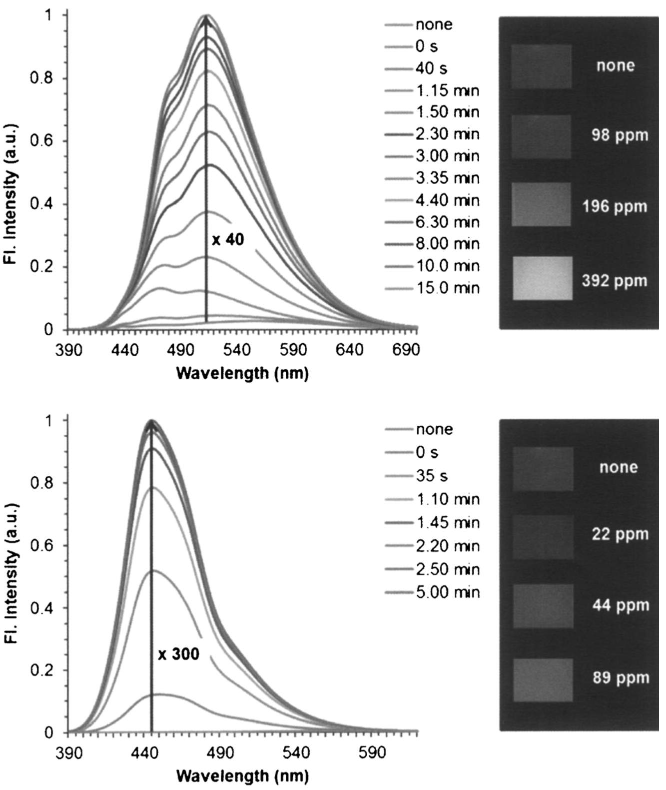

Figure 5. Time-dependent evolution of the emission wavelength and emission intensity for the reaction of **3** (3 μmol L^{-1}) with benzylamine (0.3 vol %, 30 mM; top) and with 1,3-diaminopropane (0.03 vol %, 4 mM; bottom). The photographic panels show solutions of **3** with an increasing amount of benzylamine (top) and 1,3-diaminopropane (bottom) after 3 h of reaction.

benzylamine (0.3 %) resulted in 40-fold increased emission after 10 min. When **3** reacts with 1,3-diaminopropane (0.03 %), even a 300-fold increased fluorescence intensity accompanied by a wavelength shift is complete in 2.5 min. Therefore, both the imine and the aminal formation must be favored under these conditions. For benzylamine, solutions of **3** containing 196 ppm (1.83 mM) of amine already displayed a significant emission color change, whereas for 1,3-diaminopropane, a concentration about 22 ppm (0.30 mM) was sufficient for signal generation (Figure 5).

Aldehydes reacted with amines in water. One might expect the resulting imines or aminals to hydrolyze. Scouting the older literature, both Sprung and Layer noted that the formation of aldimines from aromatic aldehydes with aliphatic primary amines proceeded in water.[13]

Aqueous solutions of **3** and **8** were exposed to biogenic amines (dopamine, histamine, tryptamine, tyramine, 4-aminobutyrate (GABA), acetaminophene, epinephrine, and diclofenac). Tryptamine and diclofenac showed color changes for both aldehydes. In a second set of experiments, aqueous solutions of **3** or **8** were exposed to the 20 natural amino acids. Herein, only a few amino acids reacted, and **3** gave consistently more vibrant responses than **8** (Figure 6).

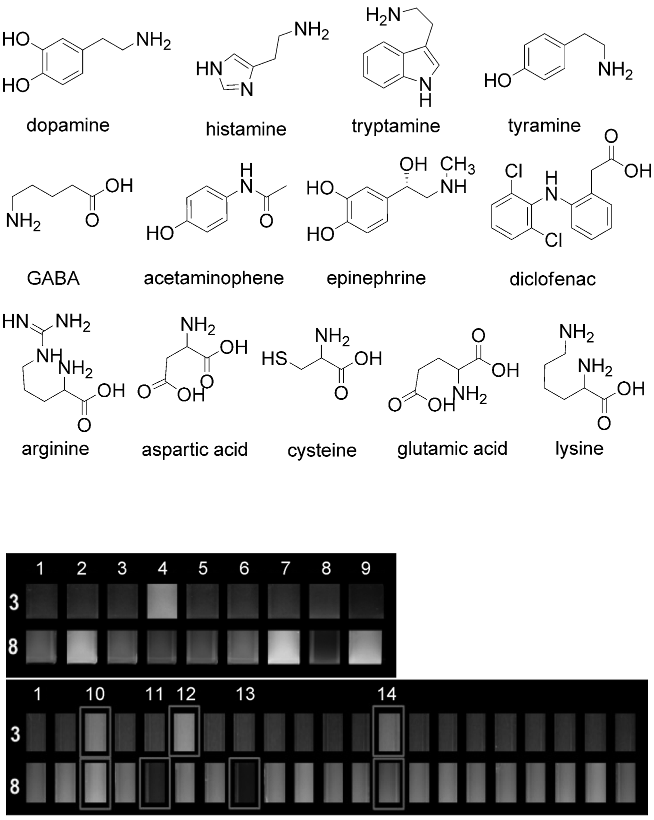

Figure 6. Exposure of aqueous solutions of **3** (10 μmol L^{-1}) and **8** to different biogenic amines (0.5 vol %): 1) reference; 2) dopamine; 3) histamine; 4) tryptamine; 5) tyramine; 6) γ-aminobutanoic acid; 7) acetaminophene; 8) epinephrine; 9) diclofenac (top). Exposure (bottom) to different amino acids: 10) arginine; 11) aspartic acid; 12) cysteine; 13) glutamic acid; 14) lysine.

When the experiments were repeated in different buffered solutions, no reaction was observed in acidic buffers, and basic buffers (>pH 7) gave identical results to the experiments performed with **3** in distilled water. Amino acids did not react well with aldehydes to give the corresponding aldimines.[14] Only amino acids (Figure 6), which have an additional SH or NH$_2$ group, such as cysteine, arginine, or lysine, reacted with **3**, whereas **8** also displayed a weak interaction with some other amino acids. The presence of the electronegative carboxylate might reduce the reactivity of the amino group towards the aldehyde, and the formation of the aldimine is therefore not competitive anymore.

In conclusion, we have synthesized two aldehyde-substituted DSBs, **3** and **8**, and investigated their reaction with amines in water. Both **3** and **8** formed imines or cyclic aminals depending on the structure of the employed amine. Turn on and blueshift of the fluorescence resulted. The dialdehyde **3** discerned and identified different amines as could be demonstrated by photography. Both **3** and **8** gave fairly unique color responses towards biogenic amines and amino acids that can undergo aminal or thioacetal formation. One does not need highly electronegative, trifluoromethyl-substituted keto groups, or reactive 1,3-dicarbonyl compounds to obtain working sensor-type dyes. Aromatic aldehyde groups alone are powerful sensory appendages that react with amines accompanied by a change of the emission color and intensity in concentration ranges useful for biological applications.

Experimental Section

Synthesis of 4,4′-((1*E*,1′*E*)-(2,5-bis(2,5,8,11,15,18,21,24-octaoxapentacosan-13-yloxy)-1,4-phenylene)bis(ethene-2,1-diyl))dibenzaldehyde (3): Under a nitrogen atmosphere, the di-iodide **1** (500 mg, 457 μmol, 1.00 equiv) and 4-ethenylbenzaldehyde (**2**; 139 mg, 1.05 mmol, 2.30 equiv) were dissolved in dry DMF (10 mL). Then [Pd(OAc)$_2$] (4.10 mg, 18.3 μmol, 0.04 equiv), tris(*o*-tolyl)phosphine (28.0 mg, 91.3 μmol, 0.20 equiv), and triethylamine (0.5 mL) were added. The mixture was stirred at 95 °C for 52 h. After the reaction mixture was cooled to RT, it was poured into water (100 mL) to give a yellow suspension, which was extracted with dichloromethane (5 × 100 mL). The combined organic layers were dried over MgSO$_4$, and the solvents were removed under reduced pressure. The brown residue was purified by silica-gel chromatography (ethyl acetate/methanol 19:1), to afford the desired compound as a viscous yellow oil (369 mg, 334 μmol, 73 %). ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 9.99$ (s, 2H), 7.87 (d, ^3J(H,H) = 8.3 Hz, 4H), 7.69–7.64 (m, 6H), 7.38 (s, 2H), 7.15 (d, ^3J(H,H) = 16.5 Hz, 2H), 4.54 (quint, ^3J(H,H) = 4.9 Hz, 2H), 3.79–3.78 (m, 8H), 3.71–3.56 (m, 40H), 3.51–3.47 (m, 8H), 3.33 ppm (s, 12H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 191.71$ (2C), 151.47 (2C) 144.06 (2C), 135.39 (2C), 130.37 (4C), 128.98 (2C), 128.14 (2C), 127.15 (4C), 126.87 (2C), 114.64 (2C), 79.90 (2C), 72.02 (4C), 71.19 (4C), 70.8770.62 (m, 20C), 59.12 ppm (4C); HRMS (ESI): *m/z* calcd for $C_{58}H_{86}O_{20}+H^+$: 1103.5791 [$M+H^+$], found: 1103.5780; *m/z* calcd for $C_{58}H_{86}O_{20}+Na^+$: 1125.5610 [$M+Na^+$]; found: 1025.5593; *m/z* calcd for $C_{58}H_{86}O_{20}+K^+$: 1141.5350 [$M+K^+$]; found: 1141.5337; elemental analysis calcd (%) for $C_{58}H_{86}O_{20}$: C 63.14, H 7.86; found: C 62.77, H 8.01.

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Keywords: aldehydes · aldimines · amines · fluorescence · sensors

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Sensors

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Aldehyde-Appended Distyrylbenzenes: Amine Recognition in Water

Change in water: Aqueous solutions of aldehyde-substituted, water-soluble distyrylbenzenes reacted with amines to give imines or aminals with dramatically changed fluorescence. This approach allowed the detection and recognition of amines in water (see figure).