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Large Stokes Shift Fluorescent Dyes Based on a Highly Substituted Terephthalic Acid Core

Andrew C. Benniston,*,† Thomas P. L. Winstanley,† Helge Lemmetyinen,‡ Nikolai V. Tkachenko,‡ Ross W. Harrington,§ and Corinne Wills‖

Molecular Photonics Laboratory, School of Chemistry, Newcastle University, Newcastle upon Tyne, NE1 7RU, U.K., Department of Chemistry and Bioengineering, Tampere University of Technology, P.O. Box 541, 33101 Finland, and Crystallography Laboratory, NMR Analytical Laboratory, School of Chemistry, Newcastle University, Newcastle upon Tyne, NE1 7RU, U.K.

a.c.benniston@ncl.ac.uk

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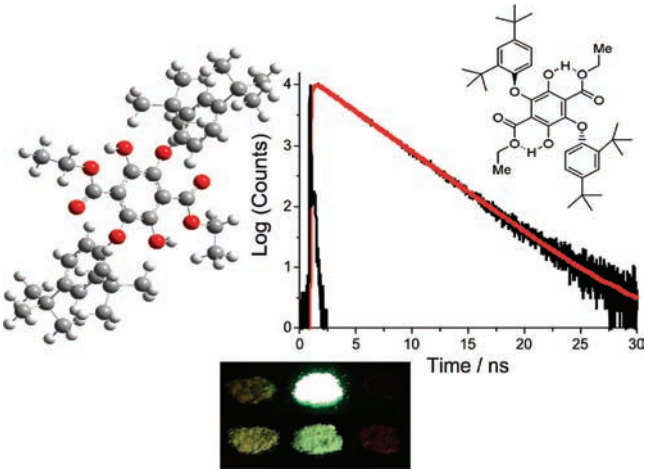
ABSTRACT



The synthesis of dyes based on a highly substituted terephthalic acid core is described, starting from readily available 2,5-dihydroxy-terephthalic acid diethyl ester. The dyes are highly colored, soluble in organic solvents and reasonably fluorescent in solution and in the solid state. The maxima for absorption and emission are around 402 and 502 nm, respectively. The fluorophores are readily cyclized to generate compounds which comprise the basic 6,13-dihydroxy-chromeno[2,3-*b*]xanthene-7,14-dione unit. These new derivatives are nonfluorescent.

Fluorescence is one of the most powerful tools used in diagnostics (e.g., ion sensing), because of its extreme sensitivity, low concentration of dye required, and ease in accumulating a good signal-to-noise.[1] A rather pertinent example is in the medical field where fluorophores are routinely used in cell imaging, analyte recognition[2] and the detection of radicals.[3] However, autofluorescence (i.e., background noise from other chromophores) can be a problem, especially if there is considerable overlap of fluorescence signals from multiple chromophores.[4] A number of solutions to the problem have been developed covering, for example, the use of time-gated spectroscopy[5] and lanthanide millisecond emitters,[6] delayed fluorescence,[7]

† Molecular Photonics Laboratory, Newcastle University.
‡ Tampere University of Technology.
§ Crystallography Laboratory, Newcastle University.
‖ NMR Analytical Laboratory, Newcastle University.

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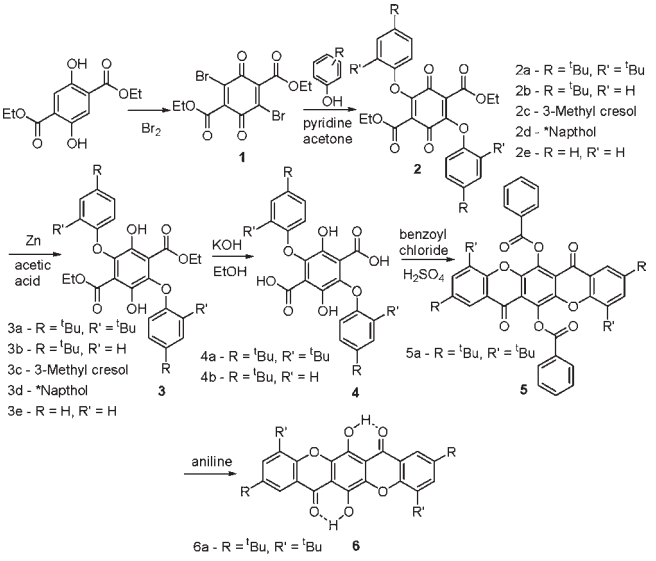
employment of long-wavelength absorbing/near I.R. emitters[8] and large Stokes' shift dyes.[9] Certainly this latter solution is promising if a suitable dye can be identified where the structures of the emissive and ground state are very different. Molecular systems based on coumarin are known to be large Stokes' shift emitters.[10] In a quest to develop new fluorescent materials we turned our attention to dyes prepared some time back as basic pigments. The intention was to identify a simple dye framework, which could be prepared in a few steps, in reasonable amounts, and from easily sourced starting materials. Ready functionalization to tune the electronic properties of the dye was an added proviso. The 6,13-dihydroxy-chromeno-[2,3-*b*]xanthene-7,14-dione unit was developed a while ago as a pigment, and it is interesting that the dye turns from red to dark blue in very concentrated acid.[11] No other properties of the compound were reported, especially any absorption and fluorescence spectra. The basic dye structure and appealing color change led us to believe that other derivatives would be worth pursuing. Here, the synthesis of several derivatives are described, focusing especially on the precursor compounds prior to final cyclization, based on a highly substituted terephthalic acid core. These compounds turn out to be highly fluorescent in solution and display large Stokes' shifts, plus they are strongly emissive in the crystalline state.

Scheme 1. Synthetic Procedures Used in the Preparation of a 6,13-Dihydroxy-chromeno[2,3-b]xanthene-7,14-dione Unit



Preparation of the dyes is shown in Scheme 1 starting from the commercially available 2,5-dihydroxy-terephthalic acid diethyl ester, and using procedures adapted from published work by Liebermann et al.[11] The reaction of liquid bromine with the ester in the solid state produced after work up and purification the quinone derivative **1** in a 95% yield. From this derivative the different aryloxy groups were introduced using the appropriate alcohol and reflux in pyridine and acetone. The percentage yields were all reasonable ranging from 66% for **2b** to 96% for **2a**. The reduction of the quinone derivatives **2** to form **3** proceeded well by reaction in acetic acid with zinc metal and sonication. At this stage it was noticed that the compounds were highly fluorescent in the crystalline state and as amorphous powders. Instead of taking all the compounds through the next three stages only two were selected to test conditions and to optimize yields. Base hydrolysis of compound **3a** and **3b** with KOH in ethanol afforded the carboxylic acids **4a** and **4b**, respectively. The reaction of **4a** with benzoyl chloride in the presence of conc. H_2SO_4 gave the cyclized product **5a** as a yellow solid in good yield. The removal of the benzoyl group by aniline reflux afforded the 6,13-dihydroxy-chromeno-[2,3-*b*]xanthene-7,14-dione derivatives **6a** as a red solid. The final compound was sparingly soluble in organic solvents such as dichloromethane and chloroform. It should be noted that the derivative without the tert-butyl groups is totally insoluble in common organic solvents. Dissolving the compounds in conc. H_2SO_4 produced a deep blue solution as reported previously, which disappeared as the acid was diluted very carefully with water. The red to blue color change does not occur in weaker acids such as HCl and HNO_3.

We undertook a very detailed analytical study for many of the compounds shown in Scheme 1, aware that very limited structural characterization was performed previously. In particular, many of the derivatives could be crystallized and their molecular structures determined by single-crystal X-ray analysis. Structures determined for **1, 2a-e, 3a-e,** are all collected in the Supporting Information (SI). An especially interesting case is for compound **3a** containing the two bulky tert-butyl groups. Analysis of the ^{1}H NMR spectrum for compound **3a** in a range of solvents (e.g., $CDCl_3$, d_4-MeOH) revealed the presence of two different conformations in solution at room temperature. This was most obvious for the two methylene groups of the ester, which are split into two sets of complex multiplets. Contamination of the sample with the quinone form is ruled out by comparison of the spectrum with that collected on **2a** in the same solvent. Several conformations are possible for **3a** depending on the relative orientation of the aryl groups and the H-bonding site at the ester (Scheme 2). There exists pathways to interconvert the conformations. Perhaps worth noting is the difference in point group symmetry between the syn and anti arrangements. For **A1** and **A3** the point group is C_i whereas for **S1** and **S3** the point group is C_2. The point group for the in-between conformations **A2** and **S2** is C_1.

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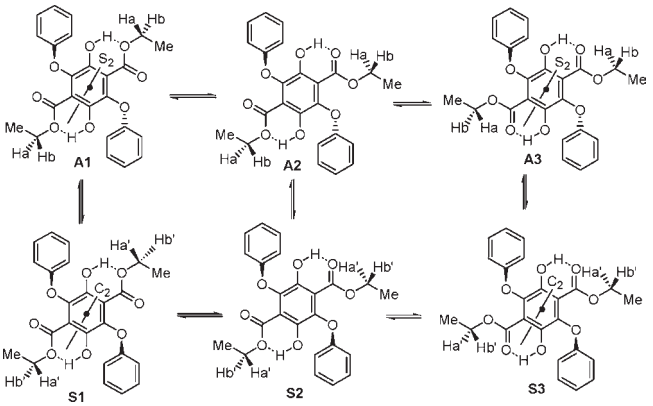
Scheme 2. Possible Conformations for **3a** Depending on the 'Up-Up' (Syn) and 'Up-Down' (Anti) Arrangement of the Two Aryl Groups and the Site for Intramolecular H-Bonding to the Ester[a]



[a] The *tert*-butyl groups are omitted for clarity, and the symmetry operations are shown (S_2 = inversion center).

Variable temperature (VT) NMR spectra for **3a** in d_{10}-*o*-xylene were recorded to see if coalescence of the two methylene multiplets occurred at high temperatures. Selected VT ^{1}H NMR spectra recorded over 180 K are shown in Figure 1. As the temperature is increased there is a clear downfield shift, and at around 333 K there is a loss in resolution for the two resonances. As the temperature is increased further coalescence for the methylene protons takes place at around 393 K. Least-squares fitting of the rates for exchange at each temperature to an Arrhenius model afforded an activation energy of 60 kJ mol^{-1} (see SI).

The inequivalence of the methylene protons and hence the complexity of the multiplets can be explained by the lack of a symmetry plane relating H_a to H_b and likewise $H_{a'}$ to $H_{b'}$. The bulky tert-butyl group restricts rotation of the phenyl ring and so this group is locked on one or the other sides of the putative plane, causing $H_{a/a'}$ and $H_{b/b'}$ to lie in different environments. Thus, for each conformer a sixteen line spectrum should be observed (i.e., two doublets of quartets). This is not quite seen because of overlapping peaks, but a simulation is remarkably similar to the observed spectrum.

The X-ray determined molecular structure for **3a** is shown in Figure 2. It is evident that the two aryl groups are disposed in the antiarrangement, and the intramolecular alcohol hydrogen bonds are associated with the carbonyl groups of the ester functionality (i.e., A3, Scheme 2). The ethyl groups for both esters are preorganized toward the aryl rings. The hydrogen of the ester methyl group appears to point toward the centroid of the aryl group (H-aryl distance = 3.02 Å). The bulky *tert*-butyl groups serve the purpose of keeping the molecular units of **3a** well separated in the crystal lattice. The crystal packing diagram (see SI) reveals that the terephthalate groups do not appear to stack, and the centroid to centroid distance is 7.6 Å. The fact that the asymmeric units are well separated is probably one reason for the observed fluorescence from crystalline samples of **3a**.

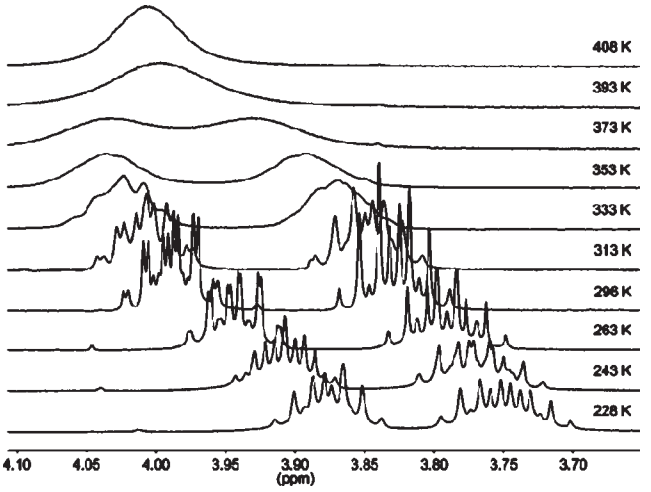


Figure 1. Selected variable temperature ^{1}H NMR spectra recorded for **3a** in d_{10}-*o*-xylene highlighting the methylene protons.

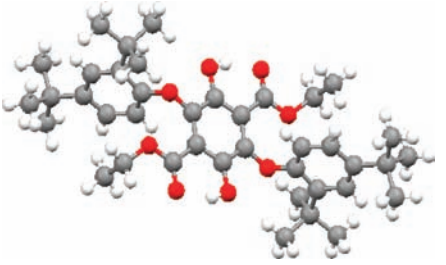


Figure 2. Single-crystal X-ray crystallographically determined molecular structure for **3a**.

Recognizing that the X-ray determined structure for **3a** may not necessarily be the true energy-minimized geometry, we undertook a preliminary computational molecular modeling study in the gas phase. In the first instance, the structure was minimized using a simple MM2 calculation, and the geometry was forced into either the anti or syn conformation. The two structures were then used to seed a DFT calculation using B3LYP and the 6-311G basis set using Gaussian 03.[12] We were able to identify at least three

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energy-minimized conformations reflecting a localized minimum and the ground-state structures (see SI). Surprisingly from the calculations it appears that the syn geometry is ~5 kJ mol^{-1} more stable than the anti conformation. For both structures the H-bonding motif is maintained at the terephthalate site (see SI). The one *tert*-butyl group and ethyl unit, plus the terephthlate hydroxyl and ring hydrogen, presumably impose steric constraints to free rotation of each terminal aryl group. Interestingly, one minimized structure to drop out of the calculation has the carbonyl group of the ester disposed out of conjugation with the aryl ring (see SI). This conformer is 21–25 kJ mol^{-1} less stable than the anti and syn forms and likely represents a structure somewhere along the potential energy surface between the two. We expect a more distinct picture to emerge for the interconversion process from currently underway comprehensive conformer searching calculations. It is feasible that to facilitate the anti–syn conversion the ester group rotates out of the plane to allow the O-aryl group to pass by unhindered. Such a suggestion is not unreasonable since preliminary molecular modeling calculations reveal that the energy barrier to rotation is extremely high if the O-aryl group is basically rotated around its axis (see SI).

The intermediate compounds (**3a**–**3e**) are noticeably fluorescent at room temperature in both the solid state and in fluid solution (Figure 3). The solid state fluorescence is

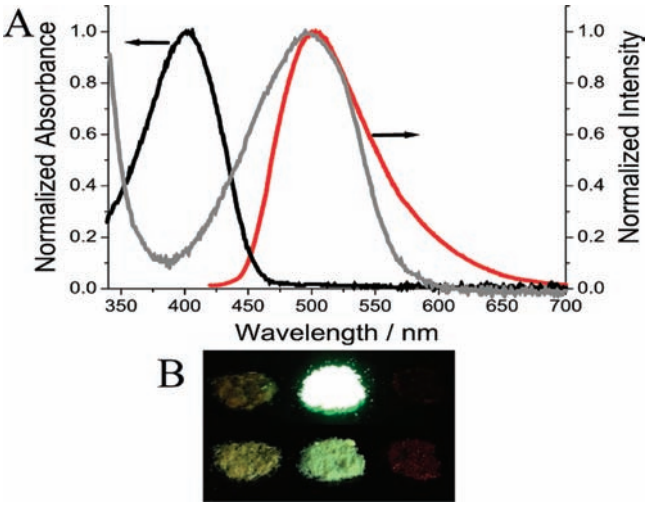

Figure 3. (A) Ambient temperature absorption (black, **3a**; gray, **6a**) and fluorescence (red, **3a**) spectra in dilute toluene. (B) Pictures of solid samples of (left to right) **1**, **3a**, and **6a** under UV illumination (top) and normal light (bottom).

certainly absent for precursor samples such as **1** and **2a**–**e**.

As a typical example the ambient temperature absorption and fluorescence spectra for **3a** in toluene are shown in Figure 3. A relatively strong broad electronic absorption band is located with a maximum at $\lambda_{ABS} = 402$ nm and a molar absorption coefficient $\varepsilon_{max} = 13\,000\ M^{-1}\,cm^{-1}$. The fluorescence profile located at $\lambda_{FLU} = 502$ nm mirrors the absorption spectrum in overall appearance, and the quantum yield of fluorescence (ϕ_{FLU}) is 0.19. What is very noticeable is the large Stokes shift of 100 nm for **3a**, which implies that the structures of the emitting state and ground state are rather different. Fluorescence decay, as measured by single-photon counting, for **3a** was strictly monoexponential with a lifetime (τ_S) of 3.3 ns. The rate for radiative decay ($k_{RAD} = \phi_{FLU}/\tau_S$) of $5.8 \times 10^7\ s^{-1}$ is in remarkably good agreement ($k_{RAD} = 7.4 \times 10^7\ s^{-1}$) with that calculated using the modified Strickler–Berg expression.[13] As expected, the rate of nonradiative decay for the first-excited singlet state ($k_{NR} = 1/\tau_S - k_{RAD}$) of $2.5 \times 10^8\ s^{-1}$ dominates. Alteration in the aryl substituents had no obvious effect on the photophysical properties of the other compounds. In comparison, the absorption maximum for the final fully ring-closed compound **6a** is red-shifted by some 95 nm (Figure 3), in part because of the increased π-conjugation. However, no discernible fluorescence is observed from the molecule in fluid solution or the solid state. What is especially noticeable is the fluorescent nature of the benzoyl protected precursor **5a** and the accompanied shift in λ_{ABS} to 402 nm. Once again in the solid state the compound is fluorescent. It would appear that the color for **6a** is dependent on the dihydroxybenzene motif. Intramolecular hydrogen bonding to form two six-membered rings is very credible, as well as an accompanied proton shift (single tautomerization). The efficient first-excited state deactivation is likely linked to the OH stretching vibration that serves to enhance nonradiative decay as predicted by the energy-gap law.[14]

We have demonstrated that highly substituted terephthalate-based compounds are highly blue emitters in the solid state and in solution. Following three further basic reactions the compounds are converted to the 6,13-dihydroxy-chromeno[2,3-*b*]xanthene-7,14-dione derivatives. Although these compounds are highly red colored, they are nonfluorescent. Reaction at the dihydroxy groups, however, converts the color back to yellow and restores fluorescence. We expect to utilize these two effects for the sensing of strong alkylating agents associated with nerve agents.[15]

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Supporting Information Available. Experimental details, copies of NMR spectra for compounds, Arrhenius plot, crystal packing diagram, computer calculated energy minimized structures, energy barrier calculation. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) The modified expression is $k_{RAD} \approx 3 \times 10^{-9}\ \nu^2 \varepsilon_{max} \Delta\nu_{1/2}$, where ν is the peak maximum (cm^{-1}) and $\Delta\nu_{1/2}$ is the peak width at half-height (cm^{-1}) for the fitted spectrum (see SI).

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