Squaraine-Derived Rotaxanes: Sterically Protected Fluorescent Near-IR Dyes

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Fluorescent dyes that absorb near-IR radiation have an increasing number of applications in materials science, biomedical science, and nanotechnology. The squaraines are a particularly promising class of near-IR dyes that can be synthesized in a straightforward fashion. They have an intense but narrow absorption band at around 650 nm, and they generally emit with high quantum yield and have excellent photostability. Like most near-IR dyes, they have two attributes that can limit their eventual utility. By definition, they have a low HOMO–LUMO band gap, and thus they are susceptible to chemical attack. Indeed, their selective reactivity with strong nucleophiles has been used as a detection method for cyanide anion and thiol-containing biomolecules. These nucleophiles attack the electron-deficient cyclobutene ring (see arrow in structure 1), which leads to loss of the dye’s blue color. The second potential drawback with squaraine dyes is their propensity to form aggregates, which leads to substantial broadening of their absorption bands.

A possible solution to both of these problems is to encapsulate the dyes inside a protective molecular container. The literature describes supramolecular encapsulation strategies using macrocyclic host molecules such as cyclodextrins, but this approach suffers from its inherent reversibility. An innovative alternative is to irreversibly encapsulate the dye as a rotaxane. The pioneering group of Anderson and co-workers has reported on rotaxanes with photoactive threads such as azo and cyanine dyes. Their general approach is to use hydrophobic forces to thread the dye through the cavity of a cyclodextrin or cyclophane macrocycle and then cap the ends of the dye with bulky stopper groups. While this capping strategy may also work with squaraines, we were attracted to an alternative approach, namely, a hydrogen bond directed clipping reaction around the core of a dumbbell-shaped squaraine dye. The structure of the central region of a squaraine dye, such as 1, is dominated by a resonance contributor that has two oxyanions attached to a cyclobutene dication. It occurred to us that this structure can act as a pre-organized template for a Leigh-type amide rotaxane reaction, and we report here a two-step synthesis of compounds 2 and 3, the first examples of squaraine-derived rotaxanes. We also describe the photophysical properties of this new class of near-IR dyes, which have greatly enhanced chemical stability and diminished chromophore interactions.

Squaraine 1 was prepared in a 35% yield by heating dibenzyl aniline and squaric acid. It was then treated with the appropriate diacid dichloride and para-xylylenediamine to give rotaxanes 2 and 3 in yields of 28 and 30%, respectively. The X-ray crystal structures of rotaxanes 2 and 3 are depicted in Figure 1. The structures have the following notable features. The macrocycles adopt chair conformations, with the 1,3-dicarboxamide motifs engaged in bifurcated hydrogen bonds with the squaraine oxygen atoms. As expected in the case of rotaxane 3, with its 2,6-pyridyl dicarboxamide-derived macrocycle, there is internal hydrogen bonding between the pyridyl nitrogen and the two adjacent amide NH residues. This internal hydrogen bonding locks the 2,6-pyridine dicarboxamide in a planar syn orientation and induces the macrocycle to contract compared to 2 (the centroid-to-centroid distance between the two parallel xyylene units in 3 and 2 is 6.61 and 7.05 Å, respectively). In other words, the pyridyl-containing macrocycle in 3 is more rigid and wraps more tightly around the cyclobutene core of the squaraine thread than the isophthalamide-containing macrocycle in 2.

The photophysical properties of compounds 1–3 are listed in Table 1. The rotaxanes have similar absorption and emission wavelengths as the precursor squaraine, 1, but they have different quantum yields. The quantum yield for rotaxane 2 is significantly decreased, whereas rotaxane 3 with its pyridyl-containing macrocycle has a slightly higher quantum yield than 1. Chemical stabilities were determined in the following way. Separate samples of 1, 2, and 3 in THF–water (4:1) were treated with excess cysteine at pH 6. The subsequent time-dependent changes in absorption and emission are shown in Figure 2. The reaction of cysteine with squaraine dye 1 has a half-life of approximately 5 min; whereas the isophthalamide-containing rotaxane 2 undergoes a substantially slower reaction, and the pyridyl-containing rotaxane 3 is essentially inert. The same reactivity order is observed when the three dyes are left standing in a solution of THF–water (4:1). A solution containing squaraine 1 undergoes hydrolytic decomposition and is inert.
colorless within 48 h,\textsuperscript{3b} a solution containing rotaxane \textbf{2} becomes colorless within a week, whereas rotaxane \textbf{3} retains its blue color for months. These reactivity results are attributed to the steric protection provided by the macrocycle.\textsuperscript{12} The parallel xylylene units for months. These reactivity results are attributed to the steric protection provided by the macrocycle.\textsuperscript{12} The parallel xylylene units sit almost perfectly over both faces of the squaraine thread to nucleophilic attack. The more tightly packed pyridyl-containing molecules which have an interplanar distance of \textasciitilde3.5 \AA. In summary, we report a simple, two-step synthesis of squaraine-derived rotaxanes with useful photophysical, photochemical, and mechanical properties.\textsuperscript{2,14}

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Supporting Information Available: Synthetic procedures and X-ray crystal data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

![Figure 2](image1)

**Figure 2.** Change in absorption (left) and emission (right) upon addition of cysteine (5 mM) to 5 \textmu M solutions of \textbf{1}, \textbf{2}, or \textbf{3} in THF–water (4:1) at pH 6.0 and 22 °C.

![Figure 3](image2)

**Figure 3.** Partial absorption spectra. Left: 6.5 \textmu M solutions of (a) \textbf{1} in DMSO, (b) \textbf{2} in THF–water (1:1), and (c) \textbf{3} in DMSO–water (1:9). Right: solid-state films of (a) \textbf{1}, (b) \textbf{2}, and (c) \textbf{3}.

References


(9) Distances (A) and angles (°) for the four unequal NH–O hydrogen bonds in \textbf{2}: 3.05, 165; 2.80, 163; 3.02, 163; 2.76, 164, and the four equal NH–O hydrogen bonds in \textbf{3}: 2.84, 157. Note that the benzylic carbons in the macrocycle of \textbf{2} are slightly disordered.


(11) Unlike the usual Leigh-type rotaxanes, the NMR spectra of rotaxanes \textbf{2} and \textbf{3} in THF-d$_4$ do not exhibit dynamic NMR behavior over the temperature range of 298–203 K. It is likely that the macrocycle pirouettes around the squaraine thread, but the molecular symmetry does not allow this motion to be detected by NMR.


(13) The unit cell for \textbf{2} contains four chloroform molecules, whereas \textbf{3} contains two water molecules. See Supporting Information for pictures of crystal packing and additional structural views.


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