

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

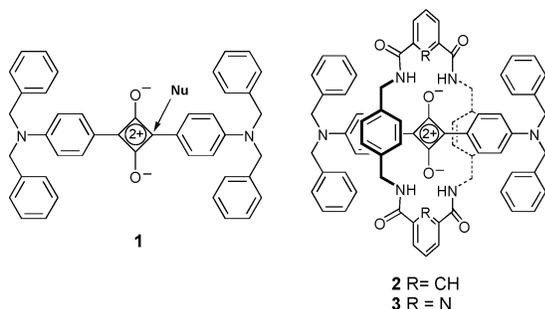
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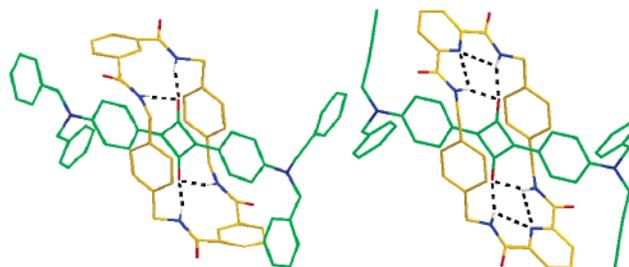
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Fluorescent dyes that absorb near-IR radiation have an increasing number of applications in materials science, biomedical science, and nanotechnology.<sup>1</sup> The squaraines are a particularly promising class of near-IR dyes that can be synthesized in a straightforward fashion.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup>

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.<sup>5</sup> 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.<sup>6</sup> 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.<sup>7</sup> 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,<sup>8</sup> 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



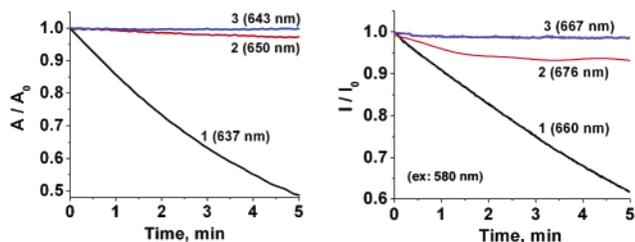
**Figure 1.** X-ray structures of rotaxane **2** (left) and **3** (right). Absent are solvent molecules in the lattice voids.

**Table 1.** Absorption and Emission of **1**, **2**, and **3** in THF–Water (4:1)

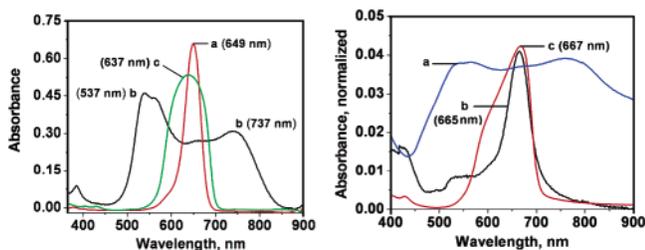
compound	$\lambda_{\text{abs}}$ (nm)	$\log \epsilon$	$\lambda_{\text{em}}$ (nm)	$\Phi_f$	$\tau$ (ns)
<b>1</b>	637	5.41	660	0.45	2.14
<b>2</b>	650	5.17	676	0.15	1.24
<b>3</b>	643	5.14	667	0.58	6.96

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.<sup>9</sup> As expected in the case of rotaxane **3**, with its 2,6-pyridine dicarboxamide-derived macrocycle, there is internal hydrogen bonding between the pyridyl nitrogen and the two adjacent amide NH residues.<sup>8a,10</sup> This internal hydrogen bonding locks the 2,6-pyridine dicarboxamide into a planar *syn* orientation and induces the macrocycle to contract compared to **2** (the centroid-to-centroid distance between the two parallel xylylene 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**.<sup>11</sup>

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



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



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

colorless within 48 h;<sup>3b</sup> a solution containing rotaxane **2** becomes colorless within a week, whereas rotaxane **3** retains its blue color for months. These reactivity results are attributed to the steric protection provided by the macrocycle.<sup>12</sup> The parallel xylylene units in the macrocycle sit almost perfectly over both faces of the electrophilic cyclobutene core of the squaraine thread and block nucleophilic attack. The more tightly packed pyridyl-containing macrocycle in rotaxane **3** offers the most steric protection. In comparison, the more flexible isophthalamide-containing macrocycle in **2** is more likely to adopt transient conformations that expose the squaraine thread to nucleophilic attack.

Squaraine dyes are known to form aggregates in mixed DMSO–water solutions, which broadens their absorption spectra.<sup>4</sup> As shown in Figure 3, a DMSO solution of squaraine **1** has a sharp absorption at 649 nm, whereas a 1:1 DMSO–water mixture has blue-shifted and red-shifted bands that are attributed to H- and J-aggregates, respectively. In contrast, addition of water to DMSO solutions containing rotaxanes **2** or **3** leads only to minor spectral broadening. Even a solution of rotaxane **3** in 1:9 DMSO–water exhibits a relatively sharp absorption band at 637 nm. Very similar results are obtained when the compounds are in the solid state. Broadening of squaraine absorption in the solid state has been attributed to intermolecular charge-transfer interactions between the dye molecules which have an interplanar distance of  $\sim 3.5$  Å.<sup>2</sup> In the case of rotaxanes **2** and **3**, the solid-state interplanar distances between squaraine threads are  $\sim 10.4$  and  $\sim 7.0$  Å, respectively,<sup>13</sup> and their absorption bands are narrower (Figure 3).

In summary, we report a simple, two-step synthesis of squaraine-derived rotaxanes. The encapsulating macrocycle greatly increases the chemical stability of the squaraine thread and inhibits aggrega-

tion-induced broadening of its absorption spectrum. Since it is straightforward to synthesize squaraines with unsymmetrical structures and as oligomers, it should be possible to prepare a wide range of squaraine-derived rotaxanes with useful photophysical, photochemical, and mechanical properties.<sup>2,14</sup>

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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>.

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- (9) Distances (Å) and angles ( $^{\circ}$ ) for the four unequal NH $\cdots$ O hydrogen bonds in **2**: 3.05, 165; 2.80, 163; 3.02, 163; 2.76, 164, and the four equal NH $\cdots$ O hydrogen bonds in **3**: 2.84, 157. Note that the benzylic carbons in the macrocycle of **2** are slightly disordered.
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- (13) The unit cell for **2** contains four chloroform molecules, whereas **3** contains two water molecules. See Supporting Information for pictures of crystal packing and additional structural views.
- (14) Squaraine dyes have been considered for applications such as bioimaging probes, photosensitizers for photodynamic therapy, chemosensors, xerographic photoreceptors, photovoltaic cells, conducting polymers, and materials for nonlinear optics; see ref 2c. For more recent references, see: (a) Oswald, B.; Patsenker, L.; Duschl, J.; Szmackinski, H.; Wolfbeis, O. S.; Terpetschnig, E. *Bioconjugate Chem.* **1999**, *10*, 925. (b) Ajayaghosh, A.; Eldo, J. *Org. Lett.* **2001**, *3*, 2595. (c) Arunkumar, E.; Chithra, P.; Ajayaghosh, A. *J. Am. Chem. Soc.* **2004**, *126*, 6590. (d) Ramaiah, D.; Eckert, I.; Arun, K. T.; Weidenfeller, L.; Epe, B. *Photochem. Photobiol.* **2004**, *79*, 99.

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