Using the Rotaxane Mechanical Bond to Enhance Chemical Reactivity

Jeffrey M. Baumes, Ivan Murgu, Allen Oliver, and Bradley D. Smith*

Department of Chemistry and Biochemistry, 236 Nieuwland Science Hall, University of Notre Dame, Notre Dame, Indiana 46556, United States
smith.115@nd.edu

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ABSTRACT

Rates of cycloreversion for squaraine rotaxane mono(endoperoxides) were enhanced by structural modifications that increased cross-component steric destabilization of the inward directed 9,10-anthracene endoperoxide group. The largest rate enhancements were obtained when the surrounding macrocycle contained two 2,6-pyridine dicarboxamide bridging units, which induced a cavity contraction effect. The precursor fluorescent, near-IR, squaraine rotaxanes are effectively photostable because the mono(endoperoxide) products, formed by reaction with photogenerated singlet oxygen, rapidly cyclorevert back to the original squaraine rotaxane.

[2]Rotaxanes are interlocked molecules comprised of a dumbbell-shaped thread encapsulated by a macrocycle.1 The two components are permanently connected because the stopper groups at each end of the thread are too large to pass through the macrocycle. By definition, this mechanical bond forces the interlocked components into close proximity, and there are many examples in the literature showing how one component can sterically protect the other from chemical attack.2 Here we describe a concept that works in the reverse manner—the close proximity of the two interlocked components induces steric strain in one of them and enhances chemical reactivity.3


the rotaxane to form mono(endoperoxide) 3EP in quantitative yield (Scheme 1). Upon sitting, 3EP undergoes spontaneous cycloreversion back to the starting squaraine rotaxane with a half-life of 3.2 h at 38 °C.5 The cycloreversion reaction releases singlet oxygen and emits near-infrared light that can pass through skin and tissue. To develop this discovery into practical applications we have started a systematic investigation of the structural parameters that control the rate of squaraine rotaxane mono(endoperoxide) cycloreversion. In this report, we compare the reactivity of endoperoxides 3EP—8EP and find that the rate of cycloreversion can be controlled in a systematic manner by making subtle changes in the rotaxane structure.

Rates of aromatic endoperoxide cycloreversion are known to be sensitive to steric effects, and we attributed the facile cycloreversion of 3EP to steric destabilization of its internally directed 9,10-anthracene endoperoxide group by the encapsulated squaraine dye.6 The series 3EP—8EP tests this hypothesis by introducing different degrees of cross-component steric strain. The structures evaluate the effectiveness of two strategies to modulate the strain: macrocycle cavity contraction and stopper group crowding of the macrocycle (Figure 1).

The macrocycle contraction effect was achieved by switching the two bridging units in the surrounding rotaxane macrocycle from isophthalamide (1) to 2,6-pyridine dicarboxamide (2). Published X-ray structures of related squaraine rotaxanes (plus the three structures described below) demonstrate consistently that internal hydrogen bonding of the amide NH residues with the adjacent pyridyl nitrogen atoms contracts the surrounding macrocycle and wraps it more tightly around the encapsulated squaraine.7 The degree of macrocycle contraction is reflected by the centroid-to-centroid distance $d$ between the two cofacial aryl walls of the macrocycle, and $d$ decreases from 6.91—7.18 Å when there are two bridging isophthalamides to 6.61—6.78 Å when there are two bridging 2,6-pyridine dicarboxamides (Figure 2).

With this macrocycle contraction effect in mind, we reasoned that the strain energy in mono(endoperoxide) 4EP

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[Scheme 1]

[Figure 1. Two structural strategies to modulate cross-component steric strain in a squaraine rotaxane mono(endoperoxide). In both cases the structure on the right induces more strain on the endoperoxide group, which accelerates the rate of cycloreversion and oxygen release.]

[Macrocyclic Cavity Contraction vs. Stopper Group Crowding]
would be greater than that in 3EP, and we were pleased when preliminary kinetic studies at room temperature indicated that the cycloreversion of 4EP was so fast that accurate measurements could not be made. To enable a direct comparison, we employed an NMR method to determine the rates of mono(endoperoxide) cycloreversion at the same low temperature of 10 °C. Briefly, an NMR tube containing a sample of the parent squaraine rotaxane in aerated CDCl$_3$ was maintained at 0 °C and irradiated with red light for enough time to photogenerate the corresponding mono(endoperoxide) in sufficient amounts to allow accurate kinetic measurements. The tube was transferred to a spectrometer whose probe was precooled to 10 °C and the rate of cycloreversion was determined by monitoring the changes in NMR signal intensities. As illustrated in Figure 3, the kinetic plots exhibited first-order behavior. The derived rate constants show that mono(endoperoxide) 4EP, with a surrounding macrocycle containing two bridging 2,6-pyridine dicarboxamide units, undergoes cycloreversion 250 times faster than 3EP.

In principle, another way to increase strain energy in the surrounding endoperoxide macrocycle is to induce cross-component, steric crowding of the macrocycle by the bulky stopper groups at each end of the encapsulated squaraine thread. We reasoned that this effect would be maximized by shortening the length of the encapsulated squaraine and making it harder for the macrocycle to avoid steric interaction with the stopper groups (Figure 1). Support for the idea was gained by comparing the conformationally different X-ray crystal structures of two separate samples of 7 (Figure 4).

![Figure 2](image1.png)

**Figure 2.** The centroid-to-centroid distance $d$ between the two cofacial aryl walls in the surrounding macrocycle of squaraine rotaxane crystal structures depends on the two macrocycle bridging units. When the bridging units are 2,6-pyridine dicarboxamides there is internal hydrogen bonding of the amide NH residues with the adjacent pyridyl nitrogen atoms (see insert), which contracts the macrocycle cavity.\(^7\)

![Figure 3](image2.png)

**Figure 3.** First-order kinetic data for cycloreversion of squaraine rotaxane mono(endoperoxides) at 10 °C in CDCl$_3$.

In one structure (Figure 4b), the macrocycle adopts a flattened chair conformation with $d = 6.91$ Å, whereas the other structure (Figure 4c) shows the macrocycle as a bent chair conformation with $d = 7.16$ Å. Moreover, a third independent crystal structure of squaraine rotaxane 5 (Figure 4a), with the same surrounding macrocycle but slightly different thread component, also exhibited a flattened chair with $d = 6.95$ Å. These structures suggested to us that squaraine rotaxane endoperoxides with shortened thread components and bulky stopper groups might force the surrounding macrocycle to adopt a flattened chair with decreased distance $d$. This in turn might increase putative cross-component strain on the internally directed endoperoxide group and accelerate the rate of cycloreversion. Therefore, we prepared squaraine rotaxanes 5, 6, and 7 with the shortened encapsulated squaraine threads 10, 11, and 12, respectively, and converted them to the corresponding mono(endoperoxides). This allowed direct comparison of the cycloreversion rates for 3EP, 5EP, 6EP, and 7EP, with each rotaxane having exactly the same reactive macrocyclic mono(endoperoxide) component (i.e., mono(endoperoxide) of 1) but different encapsulated squaraine threads. Compared to 3EP (with relatively long squaraine thread) we found that cycloreversion for 5EP, 6EP, and 7EP (each with a different shortened squaraine thread) was faster by factors of 1.7, 1.1, and 2.2, respectively. These modest enhancements indicate that stopper group crowding has only a minor effect on the stability and reactivity of the surrounding macrocycle mono(endoperoxide).\(^8\)
As a final kinetic test of our [2]rotaxane cross-component, steric strain hypothesis we measured the rate of cycloreversion for mono(endoperoxide) 8EP whose structure combines the large macrocycle cavity contraction effect in 4EP (which produced a cycloreversion rate enhancement of 250) with the small stopper group crowding effect in 5EP (which produced a cycloreversion rate enhancement of 1.7). The parent squaraine rotaxane 8 was readily synthesized, and as expected, extended irradiation of an aerated NMR sample at room temperature produced negligible accumulation (<5%) of the corresponding mono(endoperoxide) 8EP. However, at low temperature the cycloreversion was slowed sufficiently to restore the original squaraine rotaxane. Most notably, a rapid cycloreversion to release the trapped oxygen and singlet oxygen undergoes photostable. The mono(endoperoxide) product that is formed can create modified squaraine rotaxanes that are effectively photostable.

For example, extended irradiation of squaraine rotaxane 3 in air leads to quantitative formation of the mono(endoperoxide) 3EP, which subsequently undergoes clean but relatively slow spontaneous cycloreversion with a half-life of 3.2 h at 38 °C (Scheme 1). The propensity to react with singlet oxygen means that squaraine rotaxanes incorporating macrocycle 1 will not act as inert fluorescence imaging probes; however, the unusual ability of the mono(endoperoxide) products to slowly release singlet oxygen produces a potentially valuable chemiluminescent effect.\(^{5}\) The new information in this report is that subtle structural changes can create modified squaraine rotaxanes that are effectively photostable. The mono(endoperoxide) product that is formed by reaction with photogenerated singlet oxygen undergoes a rapid cycloreversion to release the trapped oxygen and restore the original squaraine rotaxane. Most notably, squaraine rotaxane mono(endoperoxides) with 2 as the precursor surrounding macrocycle (containing two bridging 2,6-pyridine dicarboxamides) exhibit a 250-fold enhancement in cycloreversion compared to analogues that have 1 as the precursor surrounding macrocycle. The enhanced reactivity is attributed to the increased cross-component steric strain that is induced by contraction of the rotaxane macrocyclic cavity. Because of this effect, the steady state fraction of mono(endoperoxide) 4EP that is formed by extended irradiation of squaraine rotaxane 4 at room temperature in air is never more than a few percent.\(^{9}\) In other words, squaraine rotaxanes, with macrocycles composed of anthracene wall units and bridging 2,6-pyridine dicarboxamides are remarkably resistant to photobleaching. These extremely bright, near-infrared fluorophores also exhibit an unusually large Stokes shift of >40 nm, a highly desired technical feature that facilitates many types of fluorescence applications.\(^{10}\) Indeed, we have already produced a useful fluorescence bioimaging probe based on 4 as a highly photostable substitute fluorophore for the commonly used near-infrared cyanine dye Cy-5.5.\(^{11}\) From a broader perspective, it will be interesting to see if other strain-sensitive reactions can be accelerated by strategies that harness the energy of the mechanical bond.\(^{12}\)

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**Supporting Information Available:** Synthesis, spectral data, X-ray structure details, and kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

\(^{8}\) It is not clear if the minor rate effect induced by the bulky stopper groups in 5EP, 6EP, and 7EP is because they do not force the surrounding macrocycle to adopt a flattened chair or, alternatively, the flattened chair is not strained enough to exhibit a high rate of cycloreversion.

\(^{9}\) The very low photochemical conversion of 4 into 4EP at room temperature is not due to an inability of 4 to photogenerate singlet oxygen. Chemical trapping experiments, using 1,3-diphenylisobenzofuran to react with photogenerated singlet oxygen, showed that irradiation of separate samples of squaraine rotaxanes 3 or 4 produced about the same amounts of singlet oxygen (see the Supporting Information).

