The Use of Molecular Dynamics to Predict the Stability of Squaraine Rotaxanes

Ruth Nelson¹, Jeffrey Baumes², Richard D. Connell², Ivan Murgu², Allen Oliver², Bradley Smith², Andrew Johnson¹,²
¹Concordia University, Portland, OR; ²University of Notre Dame, Notre Dame, IN

Abstract / Introduction
Squaraine rotaxanes are fluorescent molecules comprised of two parts—a dumbbell-shaped squaraine dye threaded through a ring-shaped macrocycle—that are held together by hydrogen bonding, hydrophobic effects, and the size of the opening in the macrocycle¹. Since the squaraine is an extremely electrophilic species², nucleophilic attack by water is possible when it slips out of the macrocycle. This results in a loss of fluorescence. These near-IR dyes have many applications, including effective labeling of bacterial cells³. Previous studies have shown that the unprotected squaraine dye is unstable, and the adamantlyl rotaxane degrades over time while the isophthalamidyl and pyridinyl rotaxanes remain stable⁴ (Fig. 2). In this study, we aim to determine if molecular dynamics (MD) is an effective method of ascertaining the relative stabilities of squaraine rotaxanes in solution.

Materials & Methods
Using the GAMESS software, the structures of the rotaxanes were optimized, and the charges were derived on HF optimized structures using the 6-31G* basis set. 100 ns MD trajectories were obtained using the NAMD program implementing the gaff force field at 300 K. The solvent was treated implicitly and a dielectric constant of 4.8 (chloroform) was chosen. The ptraj module of AmberTools 12 was used for all post-processing. Visualization was performed in Chimera.

Results

Figure 2- Rotaxane Stability vs. Time

Figure 1- The Pyridinyl Rotaxane

Figure 3- Squaraine-macrocycle hydrogen bond distance vs. time for adamantyl rotaxane

Figure 4- Flipped squaraine-macrocycle hydrogen bond distance vs. time for adamantyl rotaxane

Figure 5- Squaraine-macrocycle hydrogen bond distance vs. time for isophthalamidyl rotaxane

Figure 6- Squaraine-macrocycle hydrogen bond distance vs. time for pyridinyl rotaxane

Figure 7- Visualization of the rotation of the squaraine dye within the adamantyl macrocycle

Conclusions
Our results along with previous experimental findings demonstrate that the isophthalamidyl and pyridinyl macrocycles are able to protect the squaraine dye from nucleophilic attack in solution. MD simulations show that over the course of the trajectory the squaraine dye does not slip out of the macrocycle often, leading to the observed stabilities in solution. However, the squaraine dye is able to rotate and slip out of the adamantlyl macrocycle. These results are consistent with the NMR data and solution stability experiments performed by the Smith group⁵. This proof of concept study aimed to determine if MD could be used to determine solution stability of squaraine rotaxane dyes. Our results indicate that a straightforward and theoretical treatment of these supramolecular systems is possible, and that the methods used in this study may be implemented as an effective and efficient way to design new rotaxane systems in the future.

References
²Baumes, J. M.; Connell, R. D.; Johnson, A.; Murgu, I.; Oliver, A.; Smith, B. D. Unpublished work.

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