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Abstract


Introduction

Rotaxanes are assemblies of two or more molecules that are mechanically linked but chemically independent [1]. A typical system consists of two components, a ring molecule threaded by a dumbbell-shaped molecule. Rotaxanes are related to, but topologically distinct from catenanes, which consist of two or more interlocked rings. In a rotaxane, the bulky ends on the dumbbell-shaped component prevent spontaneous unthreading of the ring. If the ring can be induced to move from one initially favored “station” on the dumbbell to a second “station” as a consequence of some external stimulus, then a very basic molecular shuttle has been produced. (Effectively, the external stimulus is changing the preferential binding site.) This property, that relative movement of their ring and dumbbell-shaped components may be induced with an external stimulus, endows the rotaxane with device-like character. Switchable rotaxanes therefore represent some of the simplest systems with the essential features of a molecular device. These features suggest that such systems hold promise for use as components in real molecular devices [2,3].

It is our goal to develop computational modeling techniques for switchable rotaxane systems. Modeling currently plays an important role in the design and development of mechanical devices. It is desirable in order to circumvent the need for time-consuming and expensive fabrication of numerous prototype systems. Modeling and simulation are expected to provide a shortcut to functional molecular devices as well, by enabling the screening of proposed designs and modifications based on predicted performance. Herein we report semi-empirical electronic structure calculations for a switchable rotaxane that has been demonstrated experimentally by Martinez-Diaz et al. [4] and show that these calculations capture the essential “device-like” character of the system.

Theoretical Methods

The AM1 semi-empirical method [5] was chosen to carry out the computations on this rotaxane system. Since the system contains only H, C, N, and O, it lies within the scope of applicability of the AM1 method [5], which is widely accepted as one of the most reliable semi-empirical methods [6]. Unlike some other semi-empirical methods, AM1 has been found to be qualitatively acceptable for intermolecular hydrogen bonding [7], the dominant interaction...
between the macrocycle and the shaft in this rotaxane. The system considered here contains 179 atoms in the protonated state: 83 heavy atoms and 96 hydrogen atoms. A system of this size represents a challenge computationally, even for semi-empirical methods. Therefore, initial optimizations on the rotaxane sub-components (except for the shaft sub-component) were carried out using the MM+ molecular mechanics method [8] in order to generate starting structures for conformational searching. (The shaft sub-component was optimized at the AM1 level because it carries a +2 charge in the protonated state and is therefore more reliably treated with an electronic structure technique.) Conformational searching on each sub-component was performed by repeatedly setting all dihedral angles at random and subsequently optimizing the structure. Graphical model building, preliminary optimizations and conformational searching were carried out with the Hyperchem™ software package [9]. All optimizations on the full rotaxane system were semi-empirical AM1 electronic structure calculations carried out using the GAMESS suite of codes [10]. Solvent effects and counter-ions were neglected in this study, an approximation successfully applied in earlier studies of rotaxanes [11] and supported by the fact that the computational results accurately capture the device-like features of the system.

**Computational Methods**

A starting structure of the rotaxane molecule was constructed from its principle sub-components. There are three sub-component structures, the ring, shaft and stopper. The ring is a crown-ether, dibenzo [24] crown-8. The shaft contains a dialkylammonium center, a stopper (3,5-di-tert-butylbenzyl) and a bipyridinium unit. The stopper is 3,5-di-tert-butylbenzyl bromide. Low energy conformations were identified for each sub-component and optimized using the AM1 semi-empirical method. The rotaxane was then assembled from the optimized sub-components by computationally mimicking the SN2 mechanism by which it is synthesized.

The first step was to identify the low energy conformations of the sub-component structures that compose the [2] rotaxane (See Fig. 1(a, b, c)). The initial components were created with a graphical model building software package [9] and preliminary optimizations of those structures were carried out with the MM+ molecular mechanics method [8] to “clean” the structure of any unphysical features. Conformational searching [9] was performed on the initial component structures in order to generate physically reasonable conformers for subsequent optimization at the semi-empirical level. Conformational searches were performed on the shaft component in the protonated state since this is the initial state of the molecule experimentally [4].

**Figure 1a.** Low energy conformation of shaft sub-component.  
**Figure 1b.** Low energy conformation of stopper sub-component.
Searching was halted when it was found that duplicate structures were being generated. To identify duplicate structures, we define the average difference in the torsional degrees of freedom

$$\overline{\Delta \theta} = \frac{1}{n} \sqrt{\frac{1}{n} \sum_{i=1}^{n} (\theta_{i,a} - \theta_{i,b})^2}$$

where $\theta_{i,a}$ is the value of the $i^{th}$ torsional angle for the first system and $\theta_{i,b}$ is the corresponding torsional angle for the second system. The sum runs over all torsional angles. Structures of similar total energy with an average difference in the torsional less than 10 degrees were considered duplicates. Unique structures, which contributed a minimum of a tenth of a percent to the total population, were identified for each of the sub-components. The lowest energy structure of each sub-component was then optimized at the AM1 semi-empirical level. The optimized structures are shown in Fig. 1(a, b, c).

The next step was to construct the [2] rotaxane from the sub-components identified in the previous step. The self-assembly approach to the [2] rotaxane indicates that threading of the ring occurs followed by stoppering, which takes place by an SN2 reaction [4]. The rotaxane was constructed stepwise by computationally mimicking the synthetic mechanism using the sub-components as reactants. Decreasing the N-C bond distance and simultaneously increasing the C-Br distance achieved this (See Figure 2a). At each step the structure was optimized while restraining the N-C and C-Br distances. The steps were continued until a typical N-C bond distance [12] was reached and the C-Br distance was sufficiently long that any interaction between the two atoms could be neglected. Fig. 2b shows the variations in bond distance and energy at each step of the construction of the [2] rotaxane. Once the distance between the carbon and bromine atoms was sufficiently long the Br⁻ was removed.
The initial structure of the protonated [2] rotaxane was achieved by removing all restraints and fully optimizing the system. The initial structure for the deprotonated [2] rotaxane was produced by removing a hydrogen atom from the NH$_2^+$ center of the optimized protonated system and reoptimizing with no restraints.

The final step was to track the shuttling action of the [2] rotaxane. This was accomplished by correlating the energy of the system to the position of the ring in both the protonated and deprotonated states. To generate trial structures, the initial rotaxane structure (from the SN2-mimicking construction) was modified by translating and rotating the ring about the shaft. The translations/rotations were performed in two phases on both the protonated and deprotonated systems. Two phases were necessary as a result of a bend in the shaft (See Fig. 4), which required a new axis of translation/rotation to be defined after approximately 10 angstroms of translation. In total, for both the protonated and deprotonated species, 190 structures were optimized. The structural optimizations produced 89 structures, 48 protonated and 41 deprotonated. The energies from each of the two sets of structures, protonated and deprotonated, were sorted and Boltzmann statistics were applied.

**Results and Discussion**

It has been established experimentally that the mobile component of this rotaxane system, DB24C8, resides initially on the dialkylammonium station and that it is possible to deprotonate the NH$_2^+$ center with base and “drive” the ring to the bipyridinium station [4]. Through our AM1 semi-empirical calculations we have been able to replicate this feature.

As can be seen by Fig. 2b the internal energy of the system decreases during construction. Given that association of the shaft and macrocycle is most probably entropically unfavorable, an accompanying decrease in internal energy is presumably necessary for a practical synthetic mechanism. For the fully assembled rotaxane in the protonated state, the heavily dominant structure places the ring around the dialkylammonium station (See Figure 3). Upon deprotonation the ring is driven to the opposite side of the shaft where the bipyridinium station is located. In the deprotonated system there are two heavily dominant structures. In these structures the ring is oriented asymmetrically around the bipyridinium station (See Figures 4a and 4b).
**Figure 3.** Low energy structure of the protonated rotaxane.

**Figure 4a**

**Figure 4b**

**Figure 4.** Low energy structure of the deprotonated rotaxane.
This asymmetric positioning around the bipyridinium station in the deprotonated state is in agreement with the results determined using proton NMR [4]. In agreement with experimental findings [4] the calculations predict that the DB24C8 ring resides initially on the NH2 and upon deprotonation with a base the preference of the ring location changes at which point it shuttles to the bipyridinium station.

Conclusions

A computational procedure has been applied to identify the energetically preferred co-conformations of a pH-switchable rotaxane in both its protonated and deprotonated states. By finding the lowest energy structures it is possible to identify the preferred location of ring binding on both the protonated and deprotonated shafts. The preferred locations determined computationally are in agreement with what was found experimentally [4]. The computational scheme therefore captures the key device-like characteristic of the rotaxane. These results suggest that semi-empirical methods may be of value in the analysis of molecular machines where ab initio techniques are computationally prohibitive due to the large size of the molecular systems. We propose that such calculations may be useful for a priori predictions of the effect of proposed structural modifications on the shuttling action and therefore serve as a screening tool for selection of future synthetic targets.

Acknowledgements

This work was funded in part by the NSF-NER program, startup funds from Drexel University, and Dupont Corp. in the form of a Dupont Young Professor award to KS.

References