Flavin-Based [2]Rotaxanes

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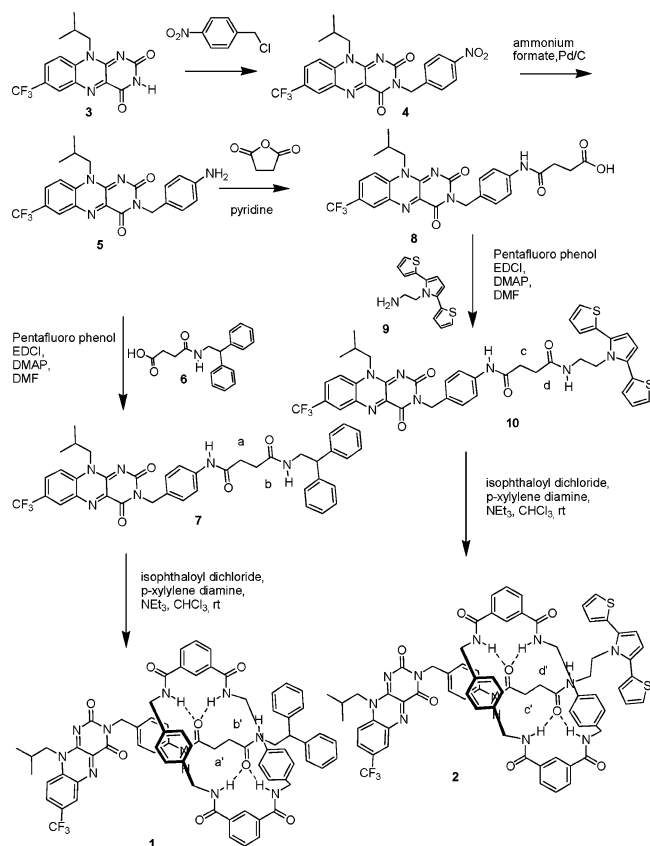
Received March 14, 2006

ABSTRACT
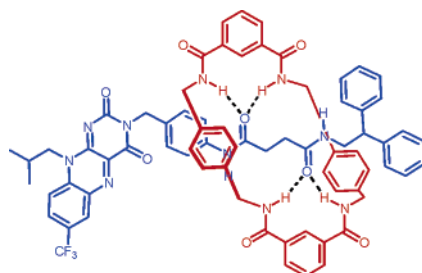
**We report the synthesis of flavin-stopped hydrogen bonded [2]rotaxanes 1 and 2. We also report the electrochemically controllable properties
of these systems in solution, and for derivative 2, as an electropolymerized thin film.**

Molecular machine-like processes are ubiquitous in biological systems, inspiring chemists to create synthetic mimics that have the ability to undergo controlled molecular motion.[1] For example, hydrogen bonded rotaxanes have become important systems for the development of chemically,[2] photochemically,[3] and electrochemically[4] controllable molecular machines. Although a wide range of moieties have been incorporated into the rotaxane architecture to induce and detect translational motion, there remains considerable
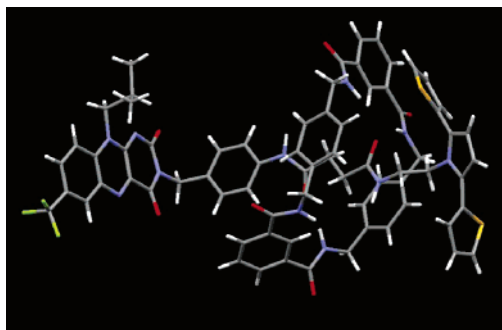
scope for incorporating new moieties to improve and extend their functions. A particularly attractive building block for incorporation into the axle unit is the biologically significant flavin unit, due to the electrochemically controllable hydrogen bonding properties,[5] tunable redox and recognition properties,[6] and interesting optical properties of this moiety. Here, we report the synthesis of flavin-based rotaxanes **1** and **2** and their electrochemical properties in solution, and in the case of **2**, as an electropolymerized thin film. Rotaxanes **1** and **2** were synthesized in reasonable yield using standard clipping methodologies as described in Scheme 1 and the Supporting Information. The rotaxanes had limited solubility in nonpolar solvents (e.g., chloroform, dichloromethane); however, good solubility was observed in more polar solvents, such as tetrahydrofuran and dimethyl sulfoxide. MALDI and low resolution fast-atom bombardment mass spectrometry, respectively, confirmed rotaxane structure for **1** ([M+] 1254) and **2** ([M+] 1332). Slow crystallization of rotaxane **2** from methanol provided crystals of sufficient

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¹H NMR spectroscopy was used to gain insight into the structure of rotaxanes **1** and **2** in solution. It has been previously shown that this technique is a useful tool for studying translational motion in rotaxanes, as aromatic ring currents in the *p*-xylylene rings result in significant upfield shifts in the portion of the axle covered by the macrocycle.[7] Due to their limited solubility in nonpolar solvents, the NMR spectra of rotaxanes **1** and **2** and their corresponding macrocycle-free axles **7** and **10** were recorded in d_8-THF and d_6-DMSO. For both rotaxanes, the chemical shifts of the succinyl methylene protons were positioned significantly more upfield than the corresponding protons of their axles (**1** $\Delta\delta_H$: a−a′ and b−b′ = −1.4 ppm; **2** $\Delta\delta_H$: c−c′ and d−d′ = −1.4 ppm in d_8-THF). Furthermore, even in DMSO, which is a competitive solvent for hydrogen bonding interactions, significant upfield shifts for the succinyl methylene protons were observed (**1** $\Delta\delta_H$: a−a′ and b−b′ = −1.1 ppm; **2** $\Delta\delta_H$: c−c′ and d−d′ = −1.1 ppm in d_6-DMSO) (see Supporting Information). Thus the NMR data are consistent with good positional integrity of the wheel over the succinyl station in these diverse environments. For both rotaxanes in d_8-THF and d_6-DMSO, protons in close proximity to the succinamide NH protons of the station were also slightly shielded compared to the spectra of their corresponding axle units.

One of the attractive rationales for incorporating flavin derivatives into rotaxane architectures is the ability of this unit to undergo electrochemically tunable hydrogen bonding interactions with complementary guests.[8] Reduction of the flavin unit to its radical anion (**Fl•−**) state results in a significant increase in hydrogen bonding efficiency of their complexes, due to an increase in electronegativity of the oxygens of their carbonyl moieties. Therefore, for rotaxanes **1** or **2**, we anticipated that electrochemical generation of the **Fl•−** species should result in the redox-driven translocation of the macrocycle from the succinyl moiety to the reduced flavin species.

To test this hypothesis, we recorded the solution electrochemistry of rotaxanes **1** and **2** and their corresponding axle units **7** and **10**.[9] Comparing the cyclic voltammetry of both rotaxanes with their axle units revealed similar fairly complicated electrochemical behavior resulting from multiple redox waves. However, cycling up to −1.0 V (versus Ag/AgCl) resulted in clearly defined redox waves for the flavin moiety. In both cases, square wave voltammetry showed significant stabilization (+90 mV) of the **Fl•−** state for rotaxanes **1** and **2** (compared to the flavin units of the their corresponding axle), indicating that the flavin moiety be-

quality for X-ray structure determination. The X-ray structure of **2** is shown in Figure 1 and clearly proves rotaxane

Figure 1. X-ray crystal structure of **2**.

formation. The macrocycle forms bifurcated hydrogen bonds to the carbonyl oxygens of the succinamide group of the axle through three hydrogen bonds. The fourth NH moiety appears not to participate in hydrogen bonding to this axle unit; however, hydrogen bonding interactions are observed to a carbonyl group of an adjacent macrocycle. Interestingly, the macrocycle appears to adopt a boat-like confirmation, presumably due to the steric influence of the adjacent 2,5-dithienylpyrrole stopper.

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(8) Rotello, V. M.; Niemz, A. *Acc. Chem. Res.* **1999**, *32*, 44−52.

(9) All electrochemical experiments were performed using a CH Instruments 620A electrochemical workstation. The electrolyte solution (0.1 M) was prepared from recrystallized Bu$_4$N$^+$PF$_6^-$ using either dry THF for reductive scans or acetonitrile and toluene for electropolymerization processes. The solution was rigorously purged with nitrogen prior to use, and all electrochemical data were recorded under a nitrogen atmosphere. A three-electrode configuration was used with a platinum disk (2 mm diameter) working electrode, with either a silver wire pseudoreference electrode or a Ag/AgCl reference electrode. A platinum wire was used as the counter electrode.

comes hydrogen bonded to the macrocycle unit upon reduction of the flavin (Figure 2). Due to the fairly rigid
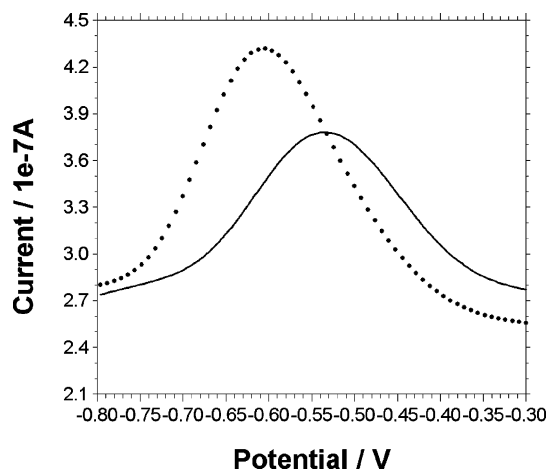
Figure 2. Square wave voltammograms of **2** (—) and **10** (· · ·) (~1 × 10^{-4} M) recorded in THF (0.1 M Bu$_4$NPF$_6$) (versus Ag/AgCl).

nature of the axle moieties, it is likely that the electrochemical data arise from the redox-induced translocation of the macrocycle from the succinyl moiety to the **Fl$^{•-}$** moiety,[4] rather than a bending of the axle unit to accommodate **Fl$^{•-}$**—macrocycle hydrogen bond formation.[10]

With electrochemically tunable interactions confirmed for rotaxanes **1** and **2** in solution, we next turned our attention onto whether we could exploit the ability of the 2,5-dithienylpyrrole unit of **2** and **10** to produce flavin-functionalized electrodes,[11] as the transferal of solution-based molecular machines to the solid state is a vital next step for the development of pragmatic functional systems.[12] Flavin-functionalized electrodes were formed by the dynamic electropolymerization of **2** or **10** onto a platinum disk electrode (see Figure 3 and Supporting Information). The electropolymerizations from a solution in CH$_3$CN/toluene (1:1) resulted in the appearance of a new redox wave centered around +0.15 V. Interestingly, the presence of the macrocyclic wheel did not significantly influence the electropolymerization process, as the half-wave potential of the developing polymer backbones were essentially the same. In accordance with previously reported data for the electropolymerization of 2,5-dithienylpyrroles, polymer growth appeared to stop after a few redox cycles.[13] Therefore, we

(10) Experiments are underway in our laboratory on related compounds to investigate whether redox-induced shuttling occurs in rotaxanes of this type. The results from these investigations will be reported in due course.

(11) For examples of flavins electropolymerized onto electrode surfaces, see: (a) Cosnier, S.; Décout, J.-L.; Fontecave, M.; Frier, C.; Innocent, C. *Electroanal.* **1998**, *10*, 521−525. (b) Ivanova, Y. N.; Karyakin, A. A.; *Electrochem. Commun.* **2004**, *6*, 120−125. (c) Cooke, G.; Garety, J. F.; Mabruk, S.; Rotello, V. M.; Surpateanu, G.; Woisel, P. *Chem. Commun.* **2004**, 2722−2723.

(12) (a) Chia, S.; Cao, J.; Stoddart, J. F.; Zink, J. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 2447−2451. (b) Cooke, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4860−4870.
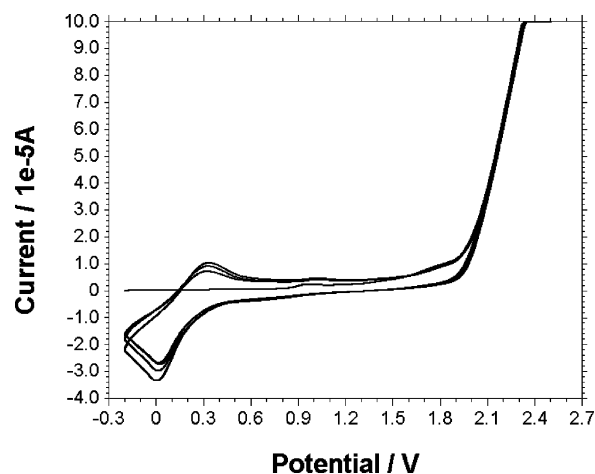
Figure 3. Cyclic voltammogram showing electropolymerization of **2** (from a ~1 × 10^{-4} M solution in toluene/acetonitrile, 1:1) onto a platinum working electrode (versus Ag/AgCl). Scan rate = 500 mV s^{-1}; 4 cycles.

decided to limit the number of potentiodynamic scans to 4 cycles to both encourage clearly defined electropolymerization processes and help prevent multilayer architectures occurring in the resulting polymer films.

After washing the flavin-functionalized working electrodes with copious amounts of acetone and allowing the polymer films to dry in air, the electrodes were placed into a 0.1 M solution of Bu$_4$N$^+$PF$_6^-$ in THF and their cyclic and square wave voltammetries were recorded between 0.2 and −0.9 V (see Figure 4 and Supporting Information). The poly-
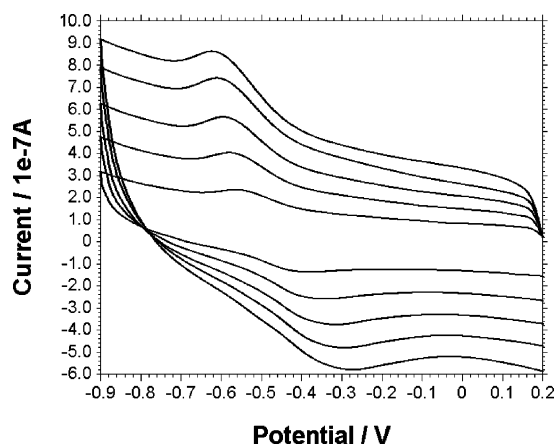

Figure 4. CVs of electropolymerized **10** (following four electropolymerization cycles from acetonitrile/toluene) recorded in THF (0.1 M Bu$_4$NPF$_6$). Scan rate = 1 (largest current), 0.8, 0.6, 0.4, 0.2 (smallest current) Vs^{-1}. ΔE_{fwhm} = 0.15 V, 9.5 × 10^{-7} C, Γ = 9.8 × 10^{-12} mol cm^{-2} (using 1 Vs^{-1} scan rate) (versus Ag/AgCl).

merization process gave rise to a single redox wave in their cyclic voltammograms (between these voltages), presumably

due to the formation of the flavin radical anion species, $2_{rad}-$ or $10_{rad}-$, respectively, within the polymer films. The CVs of electropolymerized thin films of **2** or **10** recorded at different scan rates displayed a linear increase in current with scan rate for the flavin reduction process, which is indicative of surface-confined behavior. The monolayers proved to be reasonably stable, displaying a similar current/voltage response for more than 10 scan cycles. The estimated surface coverages of the electropolymerized films of **2** ($\Gamma = 2.5 \times 10^{-12}$ mol cm^{-2}) or **10** ($\Gamma = 9.8 \times 10^{-12}$ mol cm^{-2}) (polymerized from a 1×10^{-4} M solution in CH$_3$CN/toluene), calculated from the average charge recorded under the reduction wave of the flavin, are consistent with a submonolayer coverage.

We have investigated the redox properties of the films using square wave voltammetry (SWV). The data for the surface-confined **2** and **10** are consistent with their square wave data recorded in solution (Figure 5); however, only a +20−30 mV shift of the redox wave corresponding to the $2_{rad}-$ state was observed (compared to data obtained for the formation of $10_{rad}-$), indicating that the electropolymerization process diminishes hydrogen bond-mediated stabilization of $2_{rad}-$, presumably due to steric effects within the film. Furthermore, the polymerization process seems to promote the formation of a second redox wave at −0.25 V, which is presumably due to inter- or intramolecular proton transfer.[5]

In summary, we have described a new class of electrochemically tunable rotaxanes incorporating a flavin moiety. We have shown that electrochemical reduction of the flavin unit results in significant stabilization of the flavin radical anion state of the axle moiety in the solution state, and to a lesser extent at the solid−liquid interface of an electropolymerized thin film. We are currently exploiting the
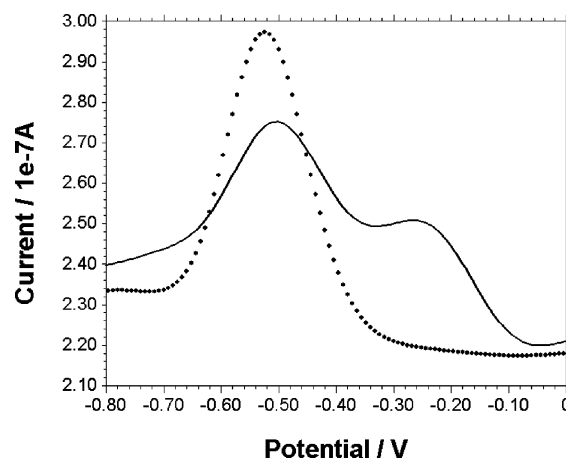
Figure 5. Square wave voltammograms of electropolymerized thin films of **2** (—) and **10** (· · ·) (versus Ag/AgCl).

tunable electrochemical properties and interesting fluorescence properties of the flavin unit to synthesize the next generation of flavin rotaxanes. Our endeavors in these areas will be reported in due course.

Supporting Information Available: Synthetic procedures and characterization of all new compounds. Electrochemical data and X-ray crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060620Q

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