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Switchable Dual Binding Mode Molecular Shuttle

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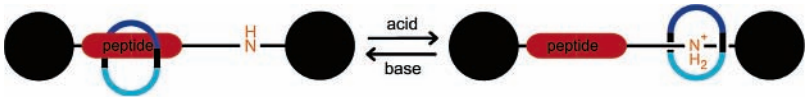
ABSTRACT



Protonation controls the location of a dual binding mode macrocycle in a [2]rotaxane. In the neutral form, amide–amide hydrogen bonds hold the macrocycle over a dipeptide residue; when the thread is protonated, polyether–ammonium cation interactions dominate and the macrocycle changes position.

Rotaxanes in which the position of the macrocyclic component can be changed by an external stimulus are among the simplest of molecular-scale mechanical devices.[1] Various stimuli have been employed to induce such switching, including metal binding,[2] configurational changes,[3] and alteration of the oxidation state[4] or protonation level[2f,4a,5] of the molecule. Here we report on the synthesis and operation of a pH-switchable molecular shuttle that uses different sets of intercomponent interactions to achieve distinct and differing coconformations in the neutral and protonated states.

Amide−amide hydrogen bonding of short peptide units with isophthalamide macrocycles is a well-established template route for the synthesis of rotaxanes.[6] Recently, the Loeb group, inspired by the ammonium cation−crown ether rotaxane system originally introduced by Busch[7] and Stoddart,[8] demonstrated[9] that a protonated *N*-benzylaniline group

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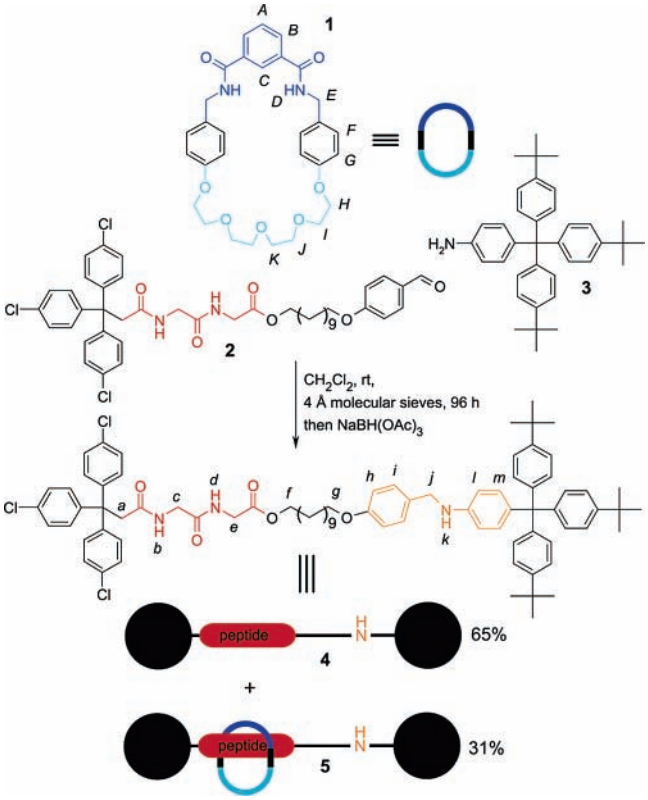
can be complexed as a pseudorotaxane by a crown ether. We wondered whether these two recognition motifs could be combined to generate a new type of dual binding mode, protonation-switched, molecular shuttle.

A target rotaxane incorporating glycylglycine and *N*-benzylaniline "stations" in the thread and an isophthalamide group and polyether chain in the macrocycle was synthesized using reductive amination to simultaneously generate the interlocked architecture and install the *N*-benzylaniline moiety (Scheme 1).[10] In CH_2Cl_2, macrocycle **1** hydrogen

Scheme 1. Synthesis of Thread **4** and [2]Rotaxane **5**



bonds to the monostoppered glycylglycine thread **2**, forming a pseudorotaxane.[6e] Covalent capture of the threaded intermediate by imine formation with bulky amine **3**, followed by in situ reduction with $NaBH(OAc)_3$, afforded the thread **4** and [2]rotaxane **5** in 65 and 31% yields, respectively (see Supporting Information).

The ^{1}H NMR spectra (Figure 1) of thread **4**, rotaxane **5**, and macrocycle **1** confirm the interlocked nature of **5** and

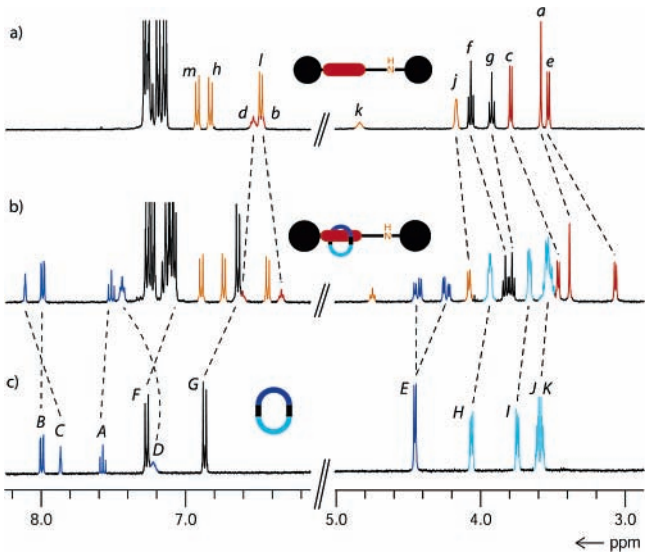


Figure 1. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of (a) thread **4**, (b) rotaxane **5**, and (c) macrocycle **1**. The lettering corresponds to the proton assignments shown in Scheme 1.

show that in the neutral form of the rotaxane the macrocycle is largely localized on the peptide region of the thread (Scheme 2). The upfield shifts of the methylene resonances of the peptide station (H_a 0.20, H_c 0.32, and H_e 0.46 ppm, cf. Figure 1b and Figure 1a) in **5** are characteristic[6] of aromatic shielding by the encapsulating macrocycle. The greater shielding of H_e suggests the macrocycle hydrogen bonds primarily to the central glycylglycine carbonyl unit and only to a lesser extent to the comparatively hindered amide carbonyl adjacent to the stopper (Scheme 2).[6e] The ester carbonyl is a weaker hydrogen bond acceptor than the amides[11] and does not appear to contribute significantly to the intercomponent binding.

The thread amide resonances, H_b and H_d, are shifted upfield (0.13 ppm) and downfield (0.10 ppm), respectively, in the rotaxane as a result of the collective influences of (i) aromatic shielding (upfield shift), (ii) hydrogen bonding to the macrocycle polyether oxygens (downfield shift), and (iii) inductive effects of the hydrogen bonding to the thread carbonyl groups (downfield shift). There is no evidence of

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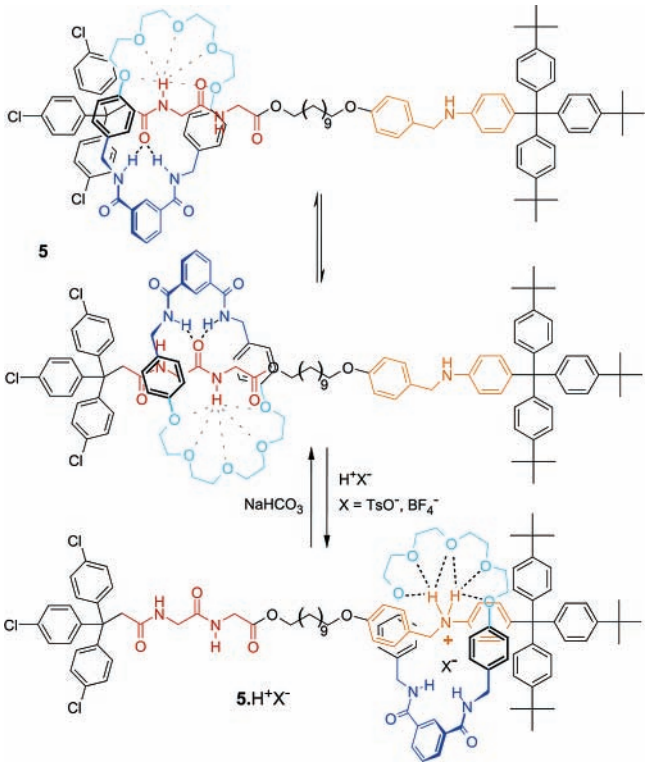
Scheme 2. Principal Intercomponent Binding Modes of **5** in Its Neutral and Protonated Forms[a]



[a] For $X^- = TsO^-$, the macrocycle amides H-bond to the anion; for $X^- = BF_4^-$, they do not.

any interaction between the macrocycle and the secondary amine group. For the rotaxane macrocycle, the 0.22 ppm (cf. Figure 1b and Figure 1c) downfield shift of the amide protons (H_D) indicates significant amide−amide hydrogen bonding with the thread. The polyether protons (H_H−H_K) are shifted upfield by roughly 0.1 ppm, confirming that the polyether oxygens accept hydrogen bonds from the thread amides. As the thread is unsymmetrical, the faces of the macrocycle are diastereotopic in the rotaxane. This effect is seen most clearly in the ABX system of H_E (Figure 1b).

Protonation of **5** with 1 equiv of *p*-toluenesulfonic acid results in significant changes to the ^{1}H NMR spectrum in CD_3CN (Figure 2b). Aromatic shielding is observed for the thread protons adjacent to the ammonium unit (H_j) and the macrocycle benzyl groups (H_F and H_G), indicating that the preferred position of the ring is now over the anilide ammonium station (Scheme 2). Interestingly, the signals for the thread amide protons in the protonated rotaxane appear at 6.6 ppm, almost the same as in the neutral thread (**4**). In the protonated thread, however, these signals occur at 6.9 and 6.95 ppm, suggesting inter- or intramolecular interactions exist between the amide carbonyls and the ammonium group

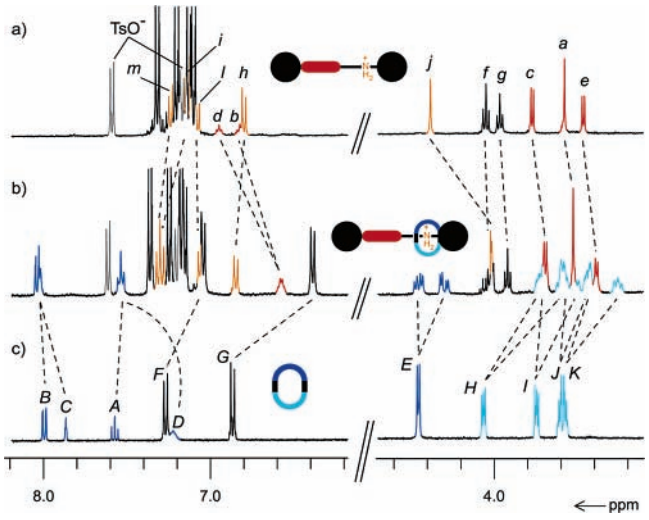


Figure 2. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of (a) protonated thread **4**·TsOH, (b) protonated rotaxane **5**·TsOH, and (c) macrocycle **1**. The lettering corresponds to the proton assignments shown in Scheme 1.

in the protonated unrotaxanated thread. Thus, the presence of the macrocycle effectively "insulates" the amides of the thread from the ammonium center.

The ring amide protons appear 0.2 ppm downfield in **5**·H^+ (Figure 2b) with respect to **5** (Figure 1b), which is likely due to hydrogen bonding to the tosylate counterion.[12] When an alternative, noncoordinating, acid such as HBF_4 is used, the H_D resonance appears at the same position as in the free macrocycle, but the ring still resides over the ammonium group indicating that the macrocycle−anion interaction is not crucial for the shuttling process.

In conclusion, rotaxane **5**/**5**·H^+ is a novel type of molecular shuttle that switches the macrocycle between two distinct translational forms with high positional integrity by exploiting both amide−amide hydrogen bonding and crown ether−ammonium cation interactions. The incorporation of multiple recognition motifs into molecular structures is likely to prove important for controlling component and substrate motion in future generations of molecular-level machines.[13]

Supporting Information Available: General synthetic experimental procedure, characterization, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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