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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b03394 • Publication Date (Web): 02 May 2018

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Spontaneous Assembly of Rotaxanes From a Primary Amine, Crown Ether and Electrophile

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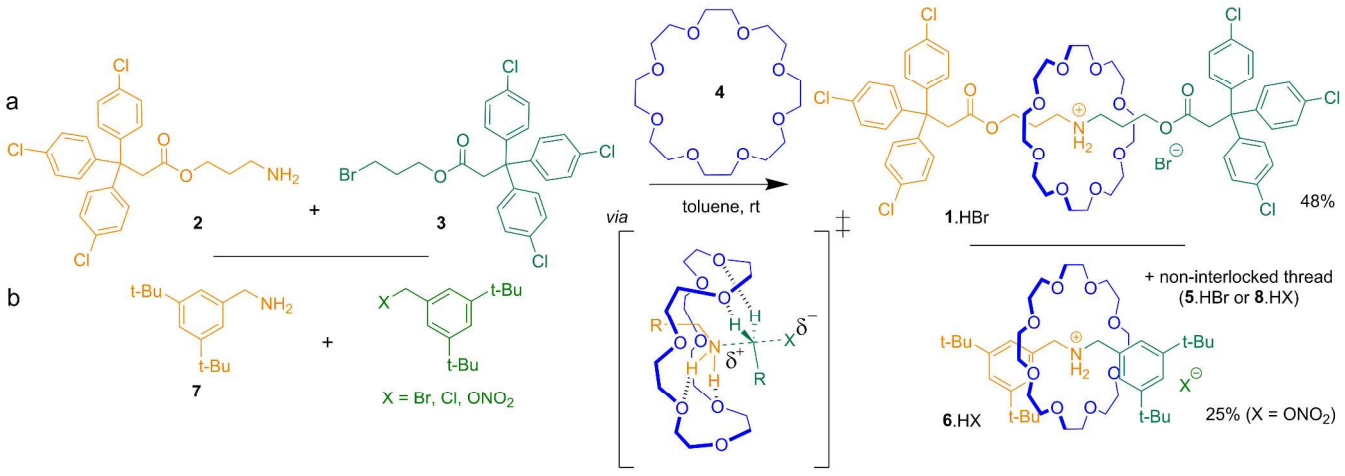
Supporting Information Placeholder

ABSTRACT: We report the synthesis of crown ether-ammonium, amide and amine [2]rotaxanes *via* transition state stabilization of axle-forming reactions. In contrast to the two-step 'clipping' and 'capping' strategies generally used for rotaxane synthesis, here the components assemble into the interlocked molecule in a single, reagent-less, step under kinetic control. The crown ether accelerates the reaction of the axle-forming components through the cavity to give the threaded product in a form of metal-free active template synthesis. Rotaxane formation can proceed through the stabilization of different transition states featuring 5-coordinate (e.g. S_N2) or 4-coordinate (e.g. acylation, Michael addition) carbon. Examples prepared using the approach include crown-ether-peptide rotaxanes and switchable molecular shuttles.

The most common strategy for making rotaxanes is the covalent capture of a pre-formed threaded or entwined supramolecular complex (typically by 'clipping' or 'capping').[1] Molecular designs and reaction conditions are generally chosen to maximize intercomponent binding so that as much as possible of the pseudo-rotaxane intermediate is initially present. Yet the rotaxane yield is often significantly lower than would be expected based solely on binding thermodynamics; unbound species tend to react faster than a pseudo-rotaxane (for steric, solvation and other reasons), and used in conjunction with irreversible covalent capture reactions this leads to significant amounts of non-interlocked products through Le Chatelier's principle. Here we report on the one-step synthesis of rotaxanes from crown ethers and primary amines in which, despite the macrocycle having a modest association constant for the thread building blocks (<35 M^{-1}), a covalent-bond-forming reaction to form the axle is significantly accelerated by the macrocycle through its cavity so that it proceeds more quickly than that to form the non-interlocked thread.[2,3]

We recently described the synthesis of rotaxanes featuring a bifunctional macrocycle, with amide groups at one end and an oligo(ethylene glycol) chain at the other.[4] The macrocycle was designed to stabilize the charges that develop during the addition of a primary amine to a cyclic sulfate, leading to [2]rotaxane formation. A control reaction reported in that paper (Entries 3 and 4 of Table 2 in Ref 4) showed that a macrocycle missing the amide groups (which stabilize the negative charge that develops on the sulfate during ring-opening) unexpectedly still afforded rotaxane, albeit in modest (5-25 %) yield. One of us (SDPF) was sufficiently intrigued by this result to try an unlikely looking experiment:

Scheme 1. [2]Rotaxane Formation by Crown-Ether-Accelerated *N*-Alkylation of Primary Amines Showing Some Potential Stabilizing Interactions in the Proposed Transition State.



the synthesis of [2]rotaxane (**1**) by the reaction of a primary amine (**2**) and an alkyl bromide (**3**) in the presence of 24-crown-8 (**4**) (Scheme 1a). *A priori* such a reaction seems unlikely because amines are poor hydrogen bond donors,[5] binding only weakly to crown ethers,[6] while the corresponding primary ammonium salts (which could form by proton transfer from secondary and tertiary ammonium *N*-alkylation products) are excellent hydrogen bond donors[7] but have no lone pair available to act as a nucleophile. Nevertheless, the reaction in chloroform using a 5:5:1 primary amine (**2**): alkyl bromide (**3**): crown ether (**4**) ratio successfully afforded a small amount (5 %) of [2]rotaxane **1**.HBr after 24 h (Supporting Information, Table S1, entry 1). Mass spectrometry and ^{1}H NMR spectroscopy confirmed the interlocked architecture of **1** (Supporting Information).

The conversion of macrocycle to **1**.HBr could be improved to 50 % (48 % isolated yield) by using toluene, a less polar solvent. Higher temperatures increased the relative rate of the thread-forming side reaction (to give **5**) resulting in a lower yield of **1**.HBr. Reducing the relative amounts of the axle-forming components, **2** and **3**, or using more dilute conditions also lowered the yield of [2]rotaxane (see Supporting Information for details of the optimization studies).

We examined the influence of crown ether size and constitution on the rotaxane-forming reaction (Supporting Information, Table S2). Crown ethers with a 24-membered ring gave higher yields of rotaxanes than the corresponding 21- and 27- membered rings. Dibenzo-crown ethers afforded less rotaxane than all-ethylene-glycol crown ethers. This may be due to phenolic ethers being poorer hydrogen bond acceptors,[5] or the conformation of the macrocycle being less well-suited to stabilizing the reaction transition state.[8]

We also investigated the influence of the axle-forming components on rotaxane formation. Replacing alkyl amine **2** with the corresponding alcohol, thiol or ammonium salt did not generate rotaxane (Supporting Information, Table S3). Anilines were similarly unreactive. However, benzylamine **7** produced rotaxanes when using a benzylic electrophile bearing various leaving groups (Scheme 1b), the yield of rotaxane **6** decreasing (at the expense of non-interlocked thread **8**) with increasing electrophile reactivity (Supporting Information, Table S4).

Slow diffusion of hexane into an ethyl acetate solution of rotaxane **6**.HCl produced single crystals suitable for X-ray diffraction. The solid-state structure (Figure 1a) confirmed the interlocked architecture, showing two intercomponent $N^+H\cdots O$ and two $N^+CH\cdots O$ hydrogen bonds (typical of crown-ether-secondary-ammonium rotaxanes[9]), each of which likely contributes to lowering the energy of the *N*-alkylation transition state.[10]

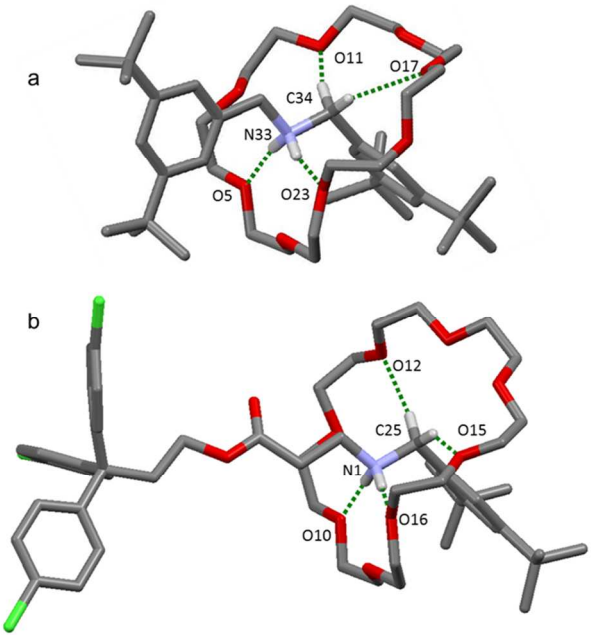
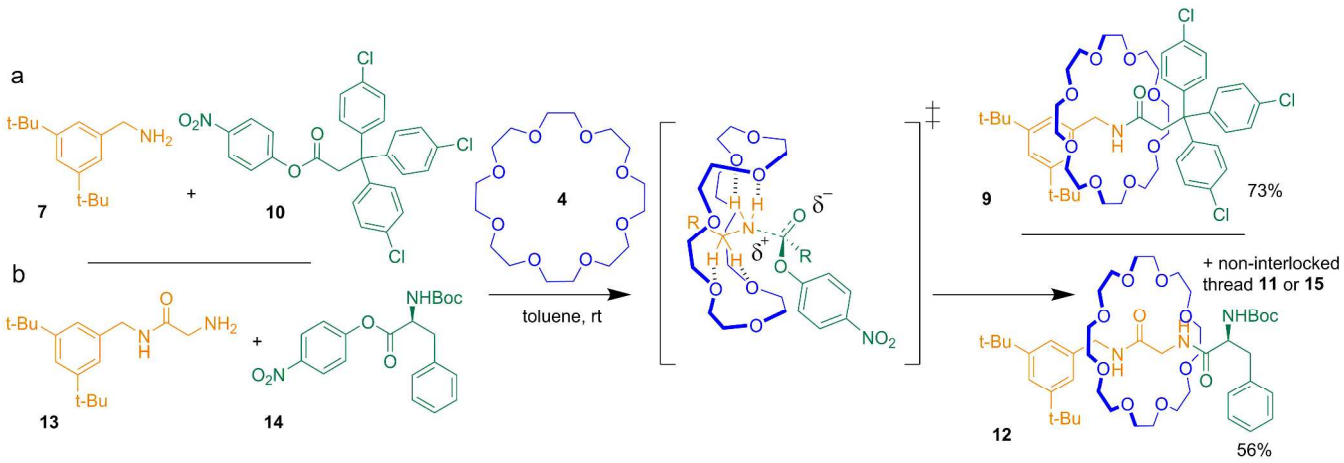


Figure 1. X-Ray crystal structures of rotaxanes formed by *N*-alkylation (scheme 1) and aza-Michael addition (scheme 3). (a) Hydrogen bond lengths [Å]: O5–H33N, 2.00; O23–H33N, 1.88; O11–H34C, 2.52; O17–H34C, 2.55. Hydrogen bond angles (°): O5–H-N33, 169.0; O23–H–N33, 164.7; O11–H–C34, 153.7; O17–H–C34, 143.4. (b) Hydrogen bond lengths [Å]: O10–H1N, 1.90; O16–H1N, 1.96; O12–H25C, 2.40; O15–H25C, 2.70. Hydrogen bond angles (°): O10–H-N1, 169.6; O16–H–N1, 164.3; O12–H–C25, 172.2; O15–H–C25, 147.4. $N^+H\cdots O$ and $N^+CH\cdots O$ hydrogen bonds shown in dark green. Solvate molecules, counterions and other hydrogen atoms omitted for clarity.

Scheme 2. [2]Rotaxane Formation by Crown-Ether-Accelerated *N*-Acylation of Primary Amines Showing Some Potential Stabilizing Interactions in the Proposed Transition State.



The experimental results obtained are consistent with the mechanism of rotaxane formation being acceleration of the S_N2-alkylation reaction through the crown ether cavity:

(i) We measured the K_a of 24C8 for amine **2** to be 32±2 M^{-1} in d_8-toluene (which is roughly two orders of magnitude less than the value for 24C8 and secondary ammonium ions used in the synthesis of similar rotaxanes by 'capping'[11]), while the K_a of 24C8 for alkyl halide **3** was below the limits we could detect by ^{1}H NMR. Accordingly, the mechanism of rotaxane formation likely starts with a crown ether bound primary amine. Hydrogen bonding to the crown ether would enhance the nucleophilicity of the amine lone pair on electronic grounds, although the environment will be more sterically hindered than the free amine.

(ii) Ethylene glycol oligomers and crown ethers have been reported to accelerate amidation reactions,[12] including in Hirose's synthesis of threaded structures from a covalently-constructed 'pre-rotaxane',[12c] by the glycol units stabilizing charges in the transition state. With a crown ether, primary amine and alkyl halide, it appears that similar stabilization of the charge developing in the S_N2 transition state that forms **1**H^+ accelerates *N*-alkylation preferentially through the cavity rather than by a less congested pathway (e.g. perched on the surface of the macrocycle).

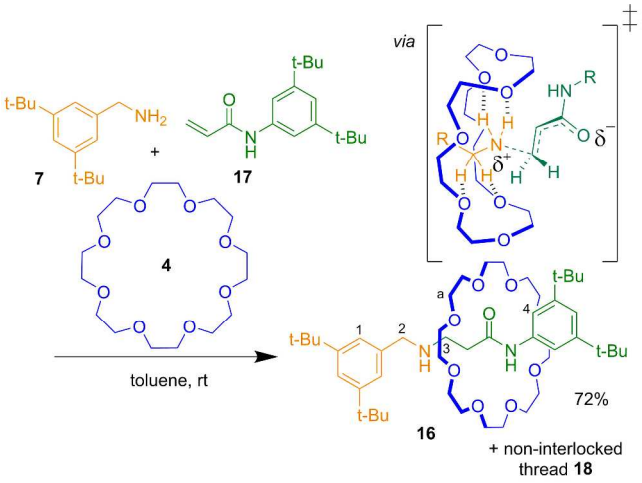
(iii) The yield of rotaxane is increased when the background reaction to produce non-interlocked thread is slow but observable (i.e. by using relatively unreactive electrophiles, Supporting Information Table S4, and/or less polar solvents, Supporting Information Table S5), i.e. in a regime that lowering the energy of the transition state (i.e. activation energy) by even a few kJ mol^{-1} can have a pronounced effect on the reaction rate.

To corroborate the proposed mechanism, and to expand the scope of the rotaxane-forming strategy, we investigated other types of reactions featuring electrophiles capable of reacting with a nucleophilic primary amine (Schemes 2 and 3). Reaction of amine **7** with nitro-phenol ester **10** in the presence of 24C8 (5:5:1 building block ratio) afforded amide [2]rotaxane **9** in 73 % yield (Scheme 2a). The threaded architecture was confirmed by ^{1}H NMR spectroscopy and mass spectrometry (see Supporting Information). In this rotaxane-forming reaction the proposed transition state stabilized by the crown ether centers on a tetrahedral carbon atom (Scheme 2). Unlike the rotaxanes formed by stabilization of S_N2 *N*-alkylation, which are isolated as their ammonium salts, rotaxane **9** was isolated as a neutral molecule, confirming that acid is unnecessary for rotaxane formation by this strategy.

Reaction rate studies using a 1:1:1 ratio of **4**:**7**:**10** showed that formation of rotaxane **9** is initially rapid: 26x faster (52 % yield after 1 h) than formation of the non-interlocked axle **11** (2 % after 1 h) over the first hour of reaction (Supporting Information, Section 6). The rate of rotaxane formation then slows (65 % rotaxane **9** after 6 days), probably due to **7**.H^+ binding to the crown ether. This retardation can likely be improved by judicious choice of leaving group or additives.

Lasso peptides such as microcin J25 feature a macrocyclic section tightly locked between adjacent peptide residues on the backbone.[13] To date such structures have eluded total synthesis, in part because the steric congestion between adjacent amino acid groups leaves little room for a conventional capping or clipping strategy. Pleasingly, treatment of glycine derivative **13** with *N*-Boc-phenylalanine 4-nitrophenol ester **14** in the presence of 24C8 (1:1:1 building block ratio) afforded [2]rotaxane **12** in 56 % yield after 2.5 h (Scheme 2b). There is clearly scope for synthesizing otherwise hard-to-access structures if this transition-state-stabilization approach can be utilized with other types of macrocycle.[14]

Scheme 3. [2]Rotaxane Formation by Crown-Ether-Accelerated Aza-Michael Addition Showing Some Potential Stabilizing Interactions in the Proposed Transition State.



Finally, we investigated the formation of rotaxanes through aza-Michael addition. Reaction of amine **7** and α,β-unsaturated anilide **17** in the presence of 24C8 (**4**) (5:5:1 building block ratio) afforded rotaxane **16** in 72 % yield after 16 days (Scheme 3). Once again the threaded structure of the rotaxane was characterized by ^{1}H NMR spectroscopy and mass spectrometry (see Supporting Information). In the ^{1}H NMR spectrum of the crude reaction mixture the diagnostic signal for rotaxane protons adjacent to an ammonium group is not present (Figure 2a), indicating that the ammonium site in the initially formed ammonium-enolate zwitterionic intermediate quickly rearranges to the amine-amide tautomer despite stabilization of the ammonium group by the crown ether. Slow diffusion of pentane into an ethyl acetate solution of an analog of rotaxane **16**.HCl produced colorless crystals suitable for single crystal X-ray diffraction (Figure 1b).

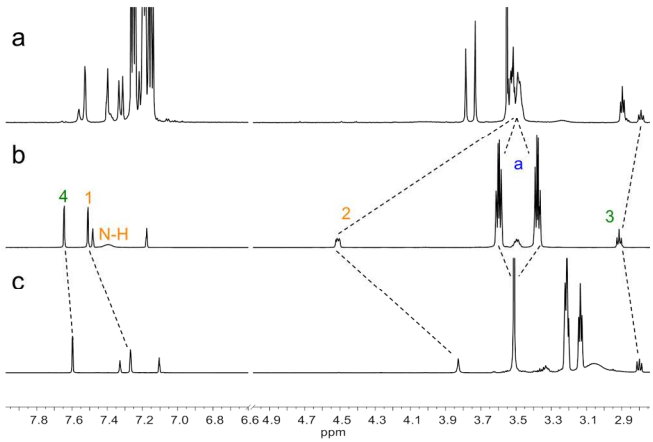


Figure 2. Partial ^{1}H NMR spectra (600 MHz, CD_3CN, 298 K) of a rotaxane assembled by aza-Michael addition. (a) Reaction mixture following assembly of **16**. (b) Rotaxane **16**.HCl isolated following acidic workup. (c) **16**, formed by deprotonation of **16**.HCl with 5 eq. DBU. The assignments correspond to the lettering shown in Scheme 3. For full assignment of **16**.HCl see Supporting Information.

Rotaxane **16**/**16**.HCl acts as a stimuli-responsive molecular shuttle (Supplementary Information, Section 6).[1] In the ammonium form (**16**.HCl) the ^{1}H NMR spectrum in CD3CN shows that the macrocycle binds to the ammonium group of the thread (H_2 δ4.5; H_1 δ7.5; Figure 2b). In amine **16** the ring resides primarily on the axle amide group (H_2 δ3.8; H_1 δ7.25; Figure 2c). Switching between **16**.HCl and **16** is achieved in one direction with 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) (**16**.HCl to **16**) and in the other by addition of HCl (**16** to **16**.HCl).

In conclusion, crown-ether-dialkylammonium rotaxanes, one of the most extensively studied rotaxane systems,[1,15] can be assembled directly from primary amines and alkyl or benzyl halides (or other leaving groups). The approach circumvents the classic two-step clipping and capping strategies used for rotaxane synthesis, and negates the need for additional reagents or the incorporation into the rotaxane design of additional functionality for covalent capture. Rotaxane formation is accomplished by transition state stabilization of the axle-forming reaction by the macrocycle, a form of metal-free active template[2] synthesis. Other electrophiles can also be used, demonstrating that different transition states can be stabilized, leading to amide (through *N*-acylation) or 3-aminopropanamide (through aza-Michael addition) rotaxanes. Rotaxane formation by aza-Michael addition leads directly to pH-switchable molecular shuttles; *N*-acylation of amino acids generates crown-ether-peptide rotaxanes. The rotaxane yields in these first generation systems range from modest-to-good (25-73 %) and, although in some cases initially rapid, require relatively long reaction times to go to completion (typically >2 days). Both should improve with macrocycle and leaving group designs specifically tailored[4] to suit the axle-forming reaction.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxxxx. Detailed descriptions of synthetic procedures; characterization of new compounds; spectroscopic data (PDF).

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ACKNOWLEDGMENT

This research was funded by the Engineering and Physical Sciences Research Council (EP/P027067/1). We thank Dr Simon Halstead for preliminary modeling studies on the mechanism of rotaxane formation and Dr George Whitehead for assistance with the X-ray crystallographic analysis. We are grateful to the EPSRC National Mass Spectrometry Facility at Swansea University for high resolution mass spectrometry, Diamond Light Source for time on the I19 beamline, and the Xunta de Galicia and European Social Fund for a predoctoral fellowship to BP-S. DAL is a Royal Society Research Professor.

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