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DOI:

[10.1021/jacs.7b05640](https://doi.org/10.1021/jacs.7b05640)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

De Bo, G., Dolphijn, G., McTernan, C., & Leigh, D. (2017). [2]Rotaxane Formation by Transition State Stabilization. *Journal of the American Chemical Society*. <https://doi.org/10.1021/jacs.7b05640>

Published in:

Journal of the American Chemical Society

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[2]Rotaxane Formation by Transition State Stabilization

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Supporting Information Placeholder

ABSTRACT: We report on the synthesis of [2]rotaxanes driven by stabilization of the axle-forming transition state. A bifunctional macrocycle, with hydrogen bond donors at one end and acceptors at the other, is used to stabilize the charges that develop during the addition of a primary amine to a cyclic sulfate.

Most rotaxanes are formed by exploiting permanent recognition motifs in the components that subsequently 'live on' in the interlocked product.¹ Examples of rotaxanes formed through complex-driven effective molarity increases or solvation effects have also been described,² and active template synthesis,³ in which metal ions act as both an organizing template and as a catalyst for the reaction used to covalently capture the threaded structure, enables rotaxanes to be assembled under kinetic control. Here we describe the reagent-less formation of a [2]rotaxane driven by transition state stabilization of an activated complex arising from the opening of a cyclic sulfate by a primary amine.⁴

We reasoned that an appropriate bifunctional macrocycle might be able to stabilize the charges developing during the addition of an amine to a cyclic sulfate ($\ddagger$, Scheme 1). By utilizing such a process, it seemed that a rotaxane (e.g. **1**, Scheme 1) could be assembled directly from three components, macrocycle **2** and axle building blocks **3** and **4**, without the need for additional reagents.

Macrocycle **2** contains both a hydrogen bond donor unit (pyridyl-2,6-dicarboxamide⁵) and a hydrogen bond acceptor crown ether-like region (Scheme 1). This makes it a potential receptor for dual hydrogen bond donor-acceptor guests⁶ and complementary to both the transition state and the product of nucleophile addition to a cyclic sulfate. In the presence of the macrocycle the tetrahedral geometry of

the cyclic sulfate should lead to an endotopic complex in which the axle of the building block is held perpendicular to the plane of the macrocycle. The angle of attack required for a nucleophile to open a cyclic sulfate⁷ would necessitate the amine approaching from the opposite face of the sulfate-complexed macrocycle, leading to a threaded (i.e. rotaxane) product (Scheme 1).

Scheme 1. Rotaxane formation by transition state stabilization

We were delighted by our initial finding that mixing cyclic sulfate **3**, macrocycle **2** and amine **4** in a 1:3:1 ratio in CDCl₃ led, after 7 days at room temperature, to rotaxane **1** in 24 % yield, accompanied by

some formation of the non-interlocked thread, **5** (entry 1, Table 1). Performing the reaction at higher temperature significantly increased the rate of the background thread-forming reaction (entries 2 and 3, Table 1). Increasing the reaction concentration afforded the rotaxane in higher yield with shorter reaction times (entry 4, Table 1). However, the increase in concentration is limited by the solubility of the macrocycle (~0.2 M in CDCl₃). Using a five-fold excess of the axle components relative to the macrocycle led to complete conversion of the cyclic sulfate with 50 % of the macrocycle incorporated into rotaxane **1** (entry 5, Table 1). Performing the reaction at lower temperature favors the formation of rotaxane over the free-thread (entries 6 and 7, Table 1) and, with an initial concentration of 0.7 M **3** and **4**, 70 % of macrocycle **2** is converted into rotaxane **1** after five days at 8 °C (60 % after 2 days, entry 8, Table 1).

Table 1. Variations in the Experimental Conditions and Reactants Stoichiometry for the Synthesis of [2]Rotaxane **1^a**

Entry	Equiv of 2	T (°C)	Conc of 3 (M)	Time (d)	Conv of 3 (%)	Conv to rotaxane 1 (%)
1	3	20	0.07	6	72	24
2	3	40	0.07	2	76	23
3	3	60	0.07	1	81	15
4	1.5	20	0.14	2	81	27
5	0.2	20	1.05	1.7	100	50
6	0.2	8	1.05	0.9	94	64
7	0.2	20	0.70	0.9	90	57
8	0.2	8	0.70	5	86	70

^a Reactions carried with **3** (1.0 equiv) and **4** (1.0 equiv) in CDCl₃. See Supporting Information for experimental procedure.

The ¹H NMR spectra (Figure 1) of the macrocycle (**2**), thread (**5**) and rotaxane (**1**) confirms the interlocked architecture, and that the macrocycle binds to both the sulfate and the ammonium moieties in the interlocked product. The downfield shift of the H_e amide protons in the rotaxane compared to the parent macrocycle ($\Delta\delta H_e = 1.04$ ppm) and the shifts of the protons on the central region of the polyether chain ($\Delta\delta H_l = -0.16$ ppm; $\Delta\delta H_{m,n} = -0.07$ ppm) are indicative of hydrogen bonding between the macrocycle and the sulfate anion and the ammonium cation, respectively. Protons of the backbone of the thread are shifted upfield in the rotaxane ($\Delta\delta H_{12} = -0.45$ ppm; $\Delta\delta H_{13} = -0.38$ ppm; $\Delta\delta H_{15} = -0.60$ ppm; $\Delta\delta H_{16} = -0.66$ ppm; $\Delta\delta H_{17} = -0.82$ ppm) due to the

shielding effect of aromatic rings of the macrocycle. Diastereotopic splitting of macrocycle protons H_f and H_k occur in the rotaxane as a result of the asymmetry of the threaded axle.

Figure 1. ¹H NMR spectra (600 MHz, CDCl₃, 298 K) of (a) thread **5**, (b) [2]rotaxane **1**, (c) macrocycle **2**. The assignments correspond to the lettering shown in Scheme 1.

The DFT energy-minimized structure of rotaxane **1** (Figure 2, see Supporting Information for details) shows an excellent fit between the macrocycle and the aminoethyl sulfate unit, and confirms the hydrogen bond interactions between the pyridyl-2,6-dicarboxamide and the sulfate anion, and the crown ether and the ammonium group.

Figure 2. Energy-minimized (DFT B3LYP/6-31G*) structure of [2]rotaxane **1**.

Macrocycle **2** forms only weak complexes with either of the other reaction partners (K_a 25 M⁻¹ with **4**, no detectable binding to **3**; see Supporting Information), meaning that a classical ‘passive template’ process for rotaxane formation cannot operate. Instead rotaxane formation likely proceeds via the formation of an initially weak complex between **2** and **4** that progressively strengthens during nucleo-

phile addition to **3** as the macrocycle stabilizes both positive and negative charges developing during the course of the reaction. Hence the macrocycle acts as both a template, preorganizing one (or both) component(s) in a reactive co-conformation, and as a catalyst, stabilizing the transition state of the reaction, in a manner reminiscent of active template synthesis.^{3b}

This mechanism is supported by the observation that only free-thread **5** is produced when using macrocycle **6** bearing an alkyl chain instead of the crown-ether region (entries 1 and 2, Table 2). Macrocycle **7**, lacking the hydrogen bond donor motif, does produce rotaxane (**9**) in an analogous reaction (entries 3 and 4, Table 2) but in much lower yield than macrocycle **2** (entries 5 and 6, Table 2). The results demonstrate the importance of the bifunctional structure of the macrocycle used to promote rotaxane formation.

Table 2. Influence of Macrocycle Structure on Rotaxane Formation

Entry	Mac	Equiv of 3 and 4	Time (h)	Conv of 3 (%)	Conv to rotaxane (%)
1	6	0.6	26	36	0
2		5	26	75	0
3	7	0.6	26	32	5
4		5	26	77	25
5	2	0.6	48	81	27
6		5	22	90	57

The reagent-free synthesis of rotaxanes via transition state stabilization complements existing strategies for the assembly of mechanically interlocked architectures.¹ The concept may be applicable to a variety of reactions that feature polar transition states.

ASSOCIATED CONTENT

Supporting Information. Detailed descriptions of synthetic procedures, characterization of new compounds, and spec-

troscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ACKNOWLEDGMENTS

This research was funded by the Engineering and Physical Sciences Research Council (UK). We thank the EPSRC National Mass Spectrometry Centre (Swansea, UK) for high resolution mass spectrometry, Euticals GmbH for a generous donation of n-propanephosphonic acid anhydride, and the Royal Society for a University Research Fellowship (to G.D.B.) and Research Professorship (to D.A.L.).

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