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Low Temperature Capture of Pseudorotaxanes

Nurul Izzaty Hassan, Vicente del Amo, Ewen Calder, and Douglas Philp*

EaStCHEM and Centre for Biomolecular Sciences, School of Chemistry, University of St. Andrews, North Haugh, St. Andrews, Fife KY16 9ST, United Kingdom

d.philp@st-andrews.ac.uk

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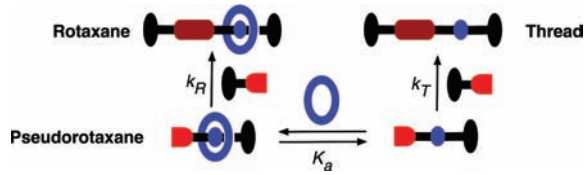
ABSTRACT



Yields of a rotaxane can be improved by employing a two-step capture protocol. Cooling a solution of the linear and macrocyclic components required for the rotaxane increases the population of the target pseudorotaxane, which is then captured by a rapid capping reaction between an azide and PPh_3. The resulting iminophosphorane rotaxane can then be manipulated synthetically at elevated temperatures.

Recent advances in supramolecular synthesis have permitted the fabrication of discrete, structurally intricate nanometer-scale objects, molecular machinery,[1] and periodic structures. Sophisticated supramolecular hierarchies of this sort can be constructed through the precise arrangement of structural subunits through algorithmic self-organization and self-assembly. Although approaches based on self-assembly are versatile, the production of the basic subunits for any assembly process currently relies upon traditional synthetic methodologies. We have become interested in applying our successful strategies for constructing reaction networks[2] based on replication processes to the synthesis of mechanically interlocked architectures such as catenanes and rotaxanes. This approach is similar in spirit to the replicable networks[3] described by Drexler. In this approach, the building blocks for the subsequent self-assembly processes are themselves capable of their own synthesis through recognition-mediated processes.

Our initial attempts[4] to integrate replication processes with mechanically interlocked architectures met with limited success. The reasons for our failure are encapsulated in Figure 1a. A plausible kinetic model for rotaxane formation, in which we are trying to maximize the amount of rotaxane formed, involves two irreversible reactions coupled to a central equilibrium. The linear component of the rotaxane **L** associates with macrocycle **M** to form the complex [**L**•**M**]. This complex is then captured irreversibly by reaction with **C** to form rotaxane **R**. If, however, the linear component **L** reacts directly with the capping reagent **C**, then product **T**, which does not contain the macrocycle, is formed. Therefore,

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(3) Drexler, K. E. *Engines of Creation*; Fourth Estate: 1990; Chapter 11, pp 171−190.

(4) Vidonne, A.; Philp, D. *Tetrahedron* **2008**, *64*, 8464–8475.

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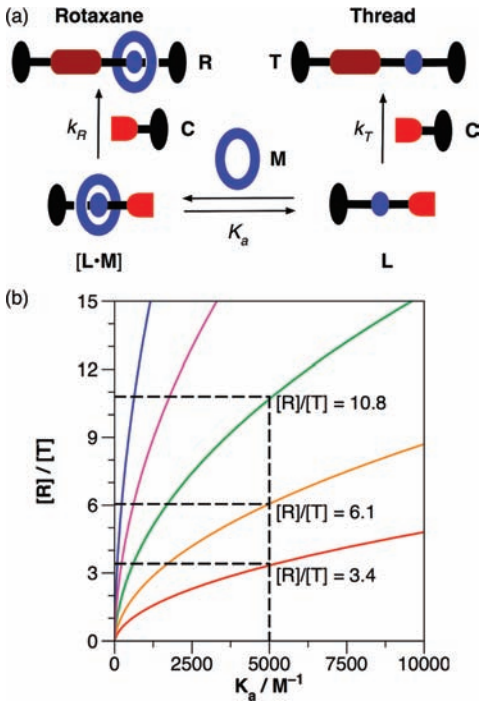


Figure 1. (a) The linear component of the rotaxane **L** associates with macrocycle **M** to form the complex [**L**•**M**]. This complex is then captured irreversibly by reaction with **C** to form rotaxane **R**. The linear component **L** can also react directly with the capping reagent **C**, forming **T**, which does not contain the macrocycle. (b) Plot of [**R**]/[**T**] against K_a for the kinetic scheme described in part (a). In the simulation, the starting concentrations of **L**, **M**, and **C** were 25 mM. Rate constant k_T was 1×10^{-3} M^{-1} s^{-1}, and k_R was varied from 4×10^{-3} M^{-1} s^{-1} (blue line) to 2.5×10^{-4} M^{-1} s^{-1} (red line), the value of k_R being halved in each step.

a key marker for the efficiency of the rotaxane-forming protocol is the ratio of **R** to **T**.

Kinetic simulation (Figure 1b) reveals that this [**R**]/[**T**] ratio is sensitive to both the association constant, K_a, for the [**L**•**M**] complex and to the ratio k_R/k_T. If we assume that the K_a for the [**L**•**M**] complex is 5000 M^{-1} and $k_T = k_R$, then the [**R**]/[**T**] ratio in the final reaction mixture is 10.8 (green line, Figure 1b). However, if $k_T = 2k_R$, i.e. the [**L**•**M**] complex is less reactive than **L** itself, then a K_a for the [**L**•**M**] complex of 5000 M^{-1} results in a [**R**]/[**T**] ratio of 6.1 (orange line, Figure 1b). Such situations are relatively common in rotaxane synthesis as there are frequently remote steric effects[5] arising from the close proximity of the three species **L**, **M**, and **C** at the transition state leading to **R**. The situation deteriorates further as the k_R/k_T ratio diminishes; when $k_T = 4k_R$ the [**R**]/[**T**] ratio in the final reaction mixture is only 3.4 (red line, Figure 1b).

In our original work, the K_a for the [L•M] complex was around 100 M^{-1} and $k_T = 3k_R$. This set of parameters led to unacceptably small [**R**]/[**T**] ratios. Clearly, this situation could be addressed by a radical redesign of the recognition event that creates the [**L**•**M**] complex in order to increase the strength of this association. However, in some situations, this approach may be both difficult to implement and synthetically challenging. As an alternative strategy, we reasoned that it should be possible to manipulate the K_a for the [**L**•**M**] complex by means of a change in temperature. Lowering the temperature should increase the K_a and, therefore, lead to an increase in the population of [**L**•**M**]. Manipulating the population of [**L**•**M**] will ultimately lead to an increase in the [**R**]/[**T**] ratio. However, as the temperature decreases, the efficiency of the capping reactions between either **L** or [**L**•**M**] and **C** also decreases. It is unlikely that capping chemistry, which is rapid at room temperature, would also be fast enough at lower temperatures. In order to counteract this undesirable reduction in reactivity at lower temperatures, we have identified a new strategy (Scheme 1). In this approach, we employ the rapid reaction between a phosphine and an organic azide at low temperature as an intermediate capping step. The iminophosphorane formed in this process can then be captured permanently through reaction with an aldehyde in an aza-Wittig reaction.

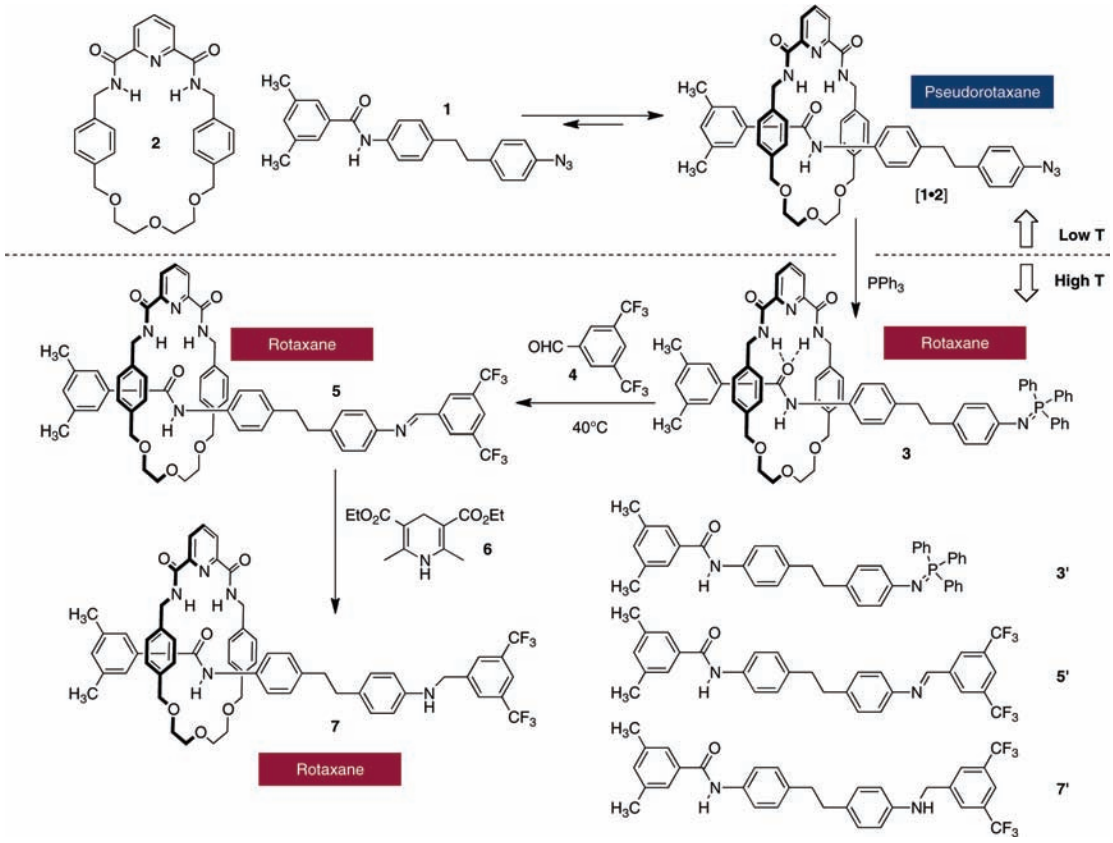
Accordingly, we designed azide **1** (Scheme 1) as a suitable linear component for incorporation within a rotaxane. Previously, we[4] and others[6] have demonstrated that diaryl amides, such as **1**, can be recognized and bound by macrocycle **2**, forming a complex, in this case [**1**•**2**] with a pseudorotaxane geometry. The small cavity size present in macrocycle **2** introduces a constrictive[7] element to the binding of diaryl amides in solvents such as $CDCl_3$. As a result, the 400 MHz ^{1}H NMR spectrum of the [**1**•**2**] complex in $CDCl_3$, recorded at 10 °C, exhibits separate resonances for free **1** and bound **1**, indicating that **1**, **2**, and [**1**•**2**] are in slow exchange on the chemical shift time scale. It was therefore possible to determine the K_a for the [**1**•**2**] complex in $CDCl_3$ directly using ^{1}H NMR data recorded at five temperatures between −10 and +10 °C. As expected, the association constant is temperature dependent. At +10 °C, the K_a for [**1**•**2**] is 67 ± 5 M^{-1} in $CDCl_3$, rising to 118 ± 6 M^{-1} at −10 °C. Fitting

(5) Altered reactivity of functional groups incorporated within mechanically interlocked structures is a well-established phenomenon. For some examples, see: (a) Leigh, D. A.; Peàez, E. M. *Chem. Commun.* **2004**, 2262–2263. (b) Zehnder, D. W.; Smithrud, D. B. *Org. Lett.* **2001**, *3*, 2485–2487. (c) Oku, T.; Furusho, Y.; Takata, T. *Org. Lett.* **2003**, *5*, 4923–4925. (d) Craig, M. R.; Hutchings, M. G.; Claridge, T. D. W.; Anderson, H. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1071–1074.

(6) The syntheses of similar macrocycles have been reported: (a) Furusho, Y.; Matsuyama, T.; Takata, T.; Moriuchi, T.; Hirao, T. *Tetrahedron Lett.* **2004**, *45*, 9593–9597. (b) Leigh, D. A.; Thomson, A. R. *Org. Lett.* **2006**, *8*, 5377–5379. (c) Huang, Y.-L.; Hung, W.-C.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6629–6633. For some recent examples of the use of amides for the construction of rotaxane, see: (d) Aucagne, V.; Leigh, D. A.; Lock, J. S.; Thomson, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 1784–1785. (e) Kishan, M. R.; Parham, A.; Schelhase, F.; Yoneva, A.; Silva, G.; Chen, X.; Okamoto, Y.; Vögtle, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 7296–7299. (f) Chatterjee, M. N.; Kay, E. R.; Leigh, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 4058–4073. (g) Berna, J.; Brouwer, A. M.; Fazio, S. M.; Haraszkiewicz, N.; Leigh, D. A.; Lennon, C. M. *Chem. Commun.* **2007**, 1910–1912. (h) Serreli, V.; Lee, C.-F.; Kay, E. R.; Leigh, D. A. *Nature* **2007**, *445*, 523–527. (i) Fioravanti, G.; Haraszkiewicz, N.; Kay, E. R.; Mendoza, S. M.; Bruno, C.; Marcaccio, M.; Wiering, P. G.; Paolucci, F.; Rudolf, P.; Brouwer, A. M.; Leigh, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 2593–2601. (j) Alvarez-Perez, M.; Goldup, S. M.; Leigh, D. A.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2008**, *130*, 1836–1838.

(7) For a discussion of slippage and constrictive binding, see: Fyfe, M. C. T.; Raymo, F. M.; Stoddart, J. F. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds.; VCH: Weinheim, 2000; pp 211−220.

Scheme 1



of the experimental binding data to the van't Hoff equation gives an excellent fit (see Supporting Information) and affords values of ΔH and ΔS of binding for [**1**•**2**] of −17.2 kJ mol^{-1} and −25.7 J mol^{-1} K^{-1}, respectively. Having established the relationship between temperature and the stability of the [**1**•**2**] complex, we next sought to trap this pseudorotaxane by capping. To this end, we reacted a solution of **1** and **2**, each at a concentration of 20 mM, with PPh_3 at a series of temperatures from +10 to −10 °C. The result was rapid conversion of the pseudorotaxane [**1**•**2**] into rotaxane **3**. The progress of this reaction could be monitored readily by ^{31}P NMR spectroscopy; the formation of the iminophosphorane results in the emergence of a new broad resonance at around δ +5.5.

Gratifyingly, the ratio of rotaxane **3** to capped linear component **3′** mirrored exactly the ratio of **1** and **2** to [**1**•**2**] before the addition of PPh_3 to the solution. Further, this ratio did not change upon heating the solution, indicating that **3** was, indeed, a rotaxane and that the iminophosphorane capping group was robust.

Once macrocycle **2** had been incorporated as a component of rotaxane **3**, we were able to manipulate this rotaxane structure further by virtue of its reactive iminophosphorane capping group. Hence, the addition of aldehyde **4** and 1 equiv[8] of 4-bromophenylacetic acid, to a solution containing a mixture of iminophosphoranes **3** and **3′** in $CHCl_3$ followed by heating at 40 °C for 48 h effected an aza-Wittig reaction affording[9] a mixture of imines **5** and **5′**. These imines could be reduced readily by treament with dihydropyridine **6** in $CHCl_3$ for 48 h at room temperature affording a mixture of the secondary amines **7** and **7′**, which could be separated readily by column chromatography (25% and 11% respectively after purification, over three steps from **1** and **2**). The 400 MHz ^1H NMR spectrum of **7**, recorded in $CDCl_3$ at room temperature (Figure 3), shows the characteristic pattern of chemical shift changes associated with the coconformation of the macrocycle and linear component within the rotaxane. In particular, the amide NH resonance (**A**, Figure 2) exhibits a downfield shift of more than 1.3 ppm, consistent with its participation in a hydrogen bond with the carbonyl oxygen atom of the diarylamide unit. The resonances associated with the pyridine ring (**B**, Figure 2) in the macrocyclic component of **7** experience strong downfield shifts of up to 0.4 ppm as a result of their location within the deshielding region of the aromatic rings associated with the diarylamide in the linear component of **7** (**D**, Figure 2). The resonances arising from the diarylamide (**D**, Figure 2) are themselves shielded significantly by their proximity to the *para*-disubstituted aromatic rings (**C**, Figure 2). The location of the macrocycle at the diarylamide end of the structure is supported by the fact that the aromatic proton

(8) The aza-Wittig reaction in these systems requires the presence of 1 equiv of a carboxylic acid. See: del Amo, V.; Philp, D. *Org. Lett.* **2009**, *11*, 301–304.

(9) The ratio of rotaxane to thread in **5** and **5′**, as determined by ^1H NMR spectroscopy, was the same as that for **3** and **3′**, indicating that there was no decomplexation during the aza-Wittig step. This observation is consistent with the concerted nature of the aza-Wittig reaction.

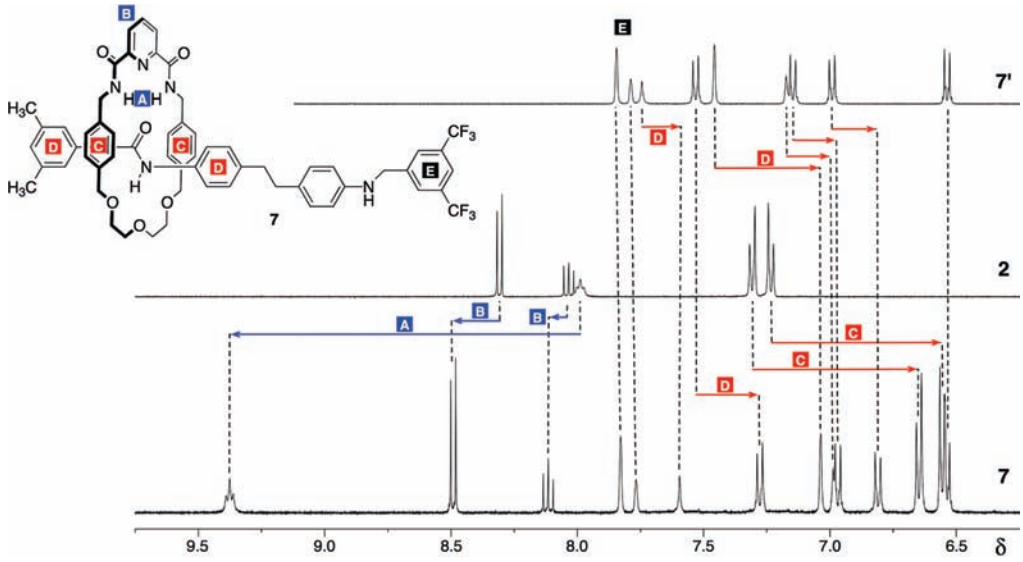


Figure 2. Partial 400.1 MHz ^{1}H NMR spectrum of rotaxane **7** (bottom) recorded in $CDCl_3$ at room temperature. The same chemical shift region is also shown for free macrocycle **2** (middle) and secondary amine **7′** for comparison. Downfield chemical shift changes on rotaxane formation are marked with blue arrows and upfield chemical shift changes on rotaxane formation are marked with red arrows.

resonances associated with the CF_3-containing ring show no chemical shift changes on rotaxane formation.

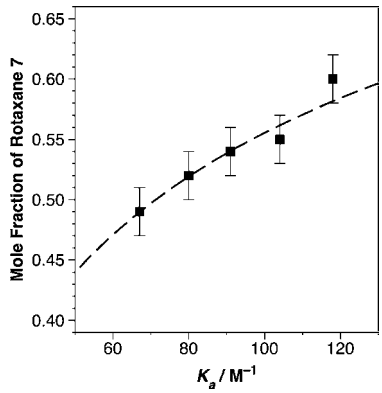


Figure 3. Mole fraction of rotaxane **7**, assayed by 400.1 MHz ^{1}H NMR spectroscopy (see Supporting Information), as a function of the K_a for [**1**•**2**] complex. Filled squares represent experimental data, and the dashed line represents the relationship expected based on the kinetic model shown in Figure 1 with $k_T = 1.7k_R$.

Satisfyingly, there is an excellent fit (Figure 3) of the mole fraction of rotaxane **7**, synthesized through the process shown in Scheme 1, to the behavior expected from the kinetic model (Figure 1) on which the process is based. Thus, transiently raising the K_a for pseudorotaxane formation by lowering the temperature results, ultimately, in an increased yield of rotaxane. We are currently exploiting the methodology described here in more complex systems such as mechanically interlocked architectures that are capable of replication.

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Supporting Information Available: Synthetic procedures and characterization for compounds **1**, **7**, and **7′**. Experimental details of kinetic simulation and van't Hoff analysis of the stability of [**1**•**2**]. This material is available free of charge via the Internet at http://pubs.acs.org.

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