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A Janus [2]Rotaxane Synthesized by Using an Anion-Templated Clipping Methodology

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The construction of interlocked molecules provides the ambitious supramolecular chemist with a stimulating synthetic challenge.[1] [2]Rotaxanes and [2]catenanes are typically prepared by use of either cationic[2] or neutral[3] templation methodologies. In our laboratories we have focused on an anion-templation strategy[4] that uses appropriately functionalized components containing pyridinium[4a–f,i] and triazolium[4g,h] halide salts in combination with isophthalamide motifs to facilitate the self-assembly of orthogonal complexes that upon Grubbs'-catalyzed mediated cyclization, furnish the desired interlocked species. Meanwhile, a diverse range of interlocked higher-order molecules have also been prepared by employing cationic and neutral templates, including catenanes with up to seven interlocked rings,[5] trefoil knots,[6] suitanes,[7] and Borromean rings.[8] As part of our own program of research on anion templation we have very recently reported the preparation of a "handcuff catenane".[9]

A Janus [2]rotaxane (or alternatively a [c2]daisy chain) consists of two interlocked components each of which contains an axle covalently attached to a macrocycle, with the axle threaded through the other macrocycle of the rotaxane. Such species have been constructed by cationic and neutral templation methodologies[10] inspired in part by the possibility of generating molecules capable of controlled motion of the macrocycles along the axles of the rotaxane akin to the contraction and stretching of muscles.[11] Herein we report the preparation and characterization of the first anion-templated Janus [2]rotaxane. Importantly, a "clipping" synthetic methodology is used to trap the axle components in the formed macrocycles, making this a rare example of a Janus [2]rotaxane prepared in such a fashion (Figure 1).[12]

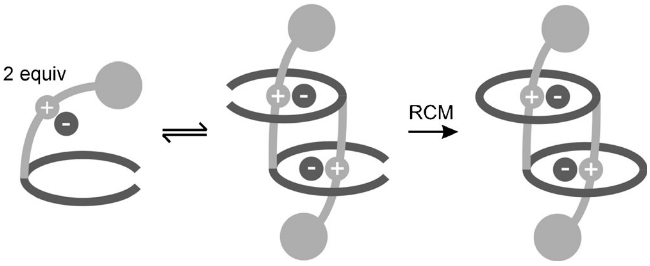

Figure 1. Schematic representation of the preparation of a pyridinium chloride/isopthalamide Janus [2]rotaxane.

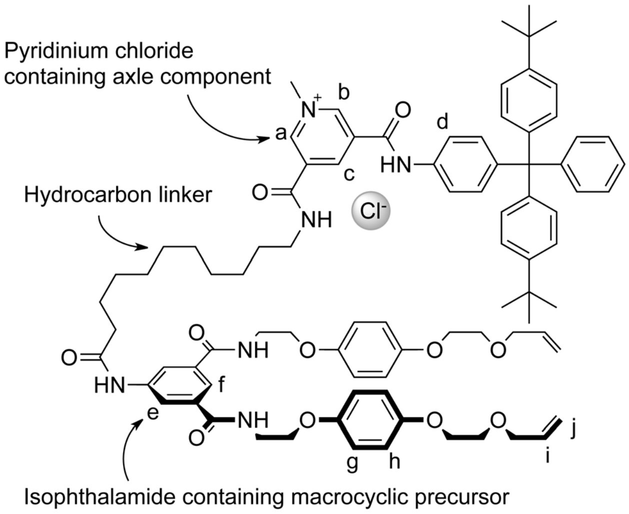

Figure 2. Design of RCM precursor **1**-Cl.

The design of a precursor able to undergo ring-closing metathesis (RCM) to form the desired interlocked structure is depicted in Figure 2. Precursor **1**-Cl consists of three parts. First, a "stoppered" axle component containing the pyridinium chloride motif that will exist as a strongly associated ion pair in the CH_2Cl_2 solvent of the reaction. Second, the macrocyclic precursor consisting of an isophthalamide motif that will hydrogen bond to the chloride anion leading to the formation of the prerequisite orthogonal complex. The isophthalamide group is appended with bis-vinyl arms to allow RCM and contains hydroquinone units that will favor π–π stacking with the electron-deficient pyridinium motif. Finally, a hydrocarbon chain links together the axle and macrocyclic precursor components.

The synthesis of precursor **1**-Cl is detailed in Scheme 1. Selective reduction of the 5-nitroisophthalamide compound **2**[4c] was achieved by use of $SnCl_2$.[13] The resulting amino compound **3** was then coupled to the *tert*-butyloxycarbonyl-(Boc)-protected aminocarboxylic acid **4**[14] using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) to afford **5**. Boc deprotection by treatment with trifluoroacetic acid

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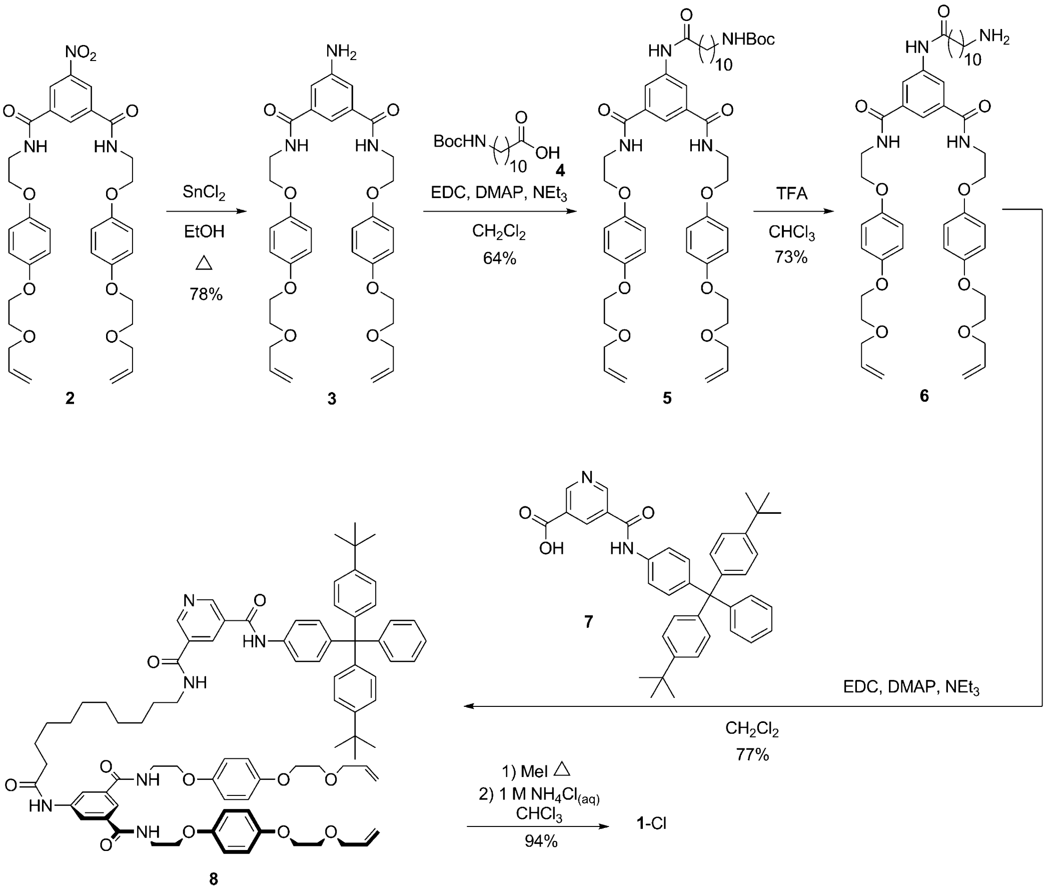


Scheme 1. Preparation of RCM precursor **1**-Cl.

(TFA), gave the aliphatic amine **6**. This compound was then coupled to asymmetric stopper **7**[15] again using EDC to achieve amide formation. After silica gel chromatography purification, pyridine **8** was isolated in 77% yield. Methylation using MeI, followed by anion exchange (by washing with NH_4Cl solution) afforded precursor **1**-Cl in almost quantitative yield from **8**.

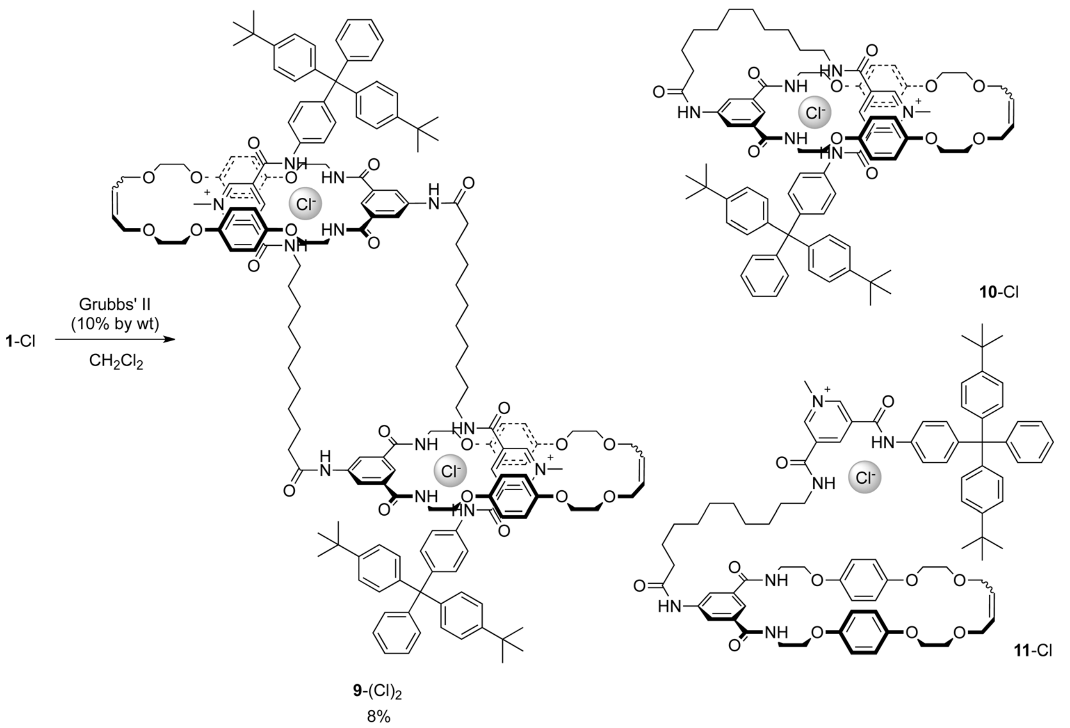
Precursor compound **1**-Cl was dissolved in dry CH_2Cl_2 and Grubbs' second-generation RCM catalyst (10% by wt) added. Notably, precipitation was observed within minutes. After stirring for 16 h, the crude reaction mixture was subjected to silica gel preparatory TLC in an attempt to separate the different species present (Scheme 2).

Two distinct bands were observed on the TLC plate. Once developed, the band with the higher R_f value proved to contain material insoluble in common organic solvents, with partial solubility being achieved in 4:1 $CDCl_3/CD_3OD$. Subsequent replating allowed pure Janus [2]rotaxane **9**-$(Cl)_2$ to be isolated in a yield of 8%. This low yield is attributed in part due to the low solubility of the compound.

Janus rotaxane **9**-$(Cl)_2$ was characterized by ^1H and ^{13}C NMR spectroscopy and high-resolution electrospray mass spectrometry. The ^1H NMR spectrum of **9**-$(Cl)_2$ (in 4:1 $CDCl_3/CD_3OD$) compared to that of precursor **1**-Cl provides evidence of the supramolecular interactions present within the interlocked structure (Figure 3). The alkene resonance *j* is not observed in the spectrum of the rotaxane, while multiplet *i* has become a broad singlet confirming cyclization has occurred. The internal pyridinium cavity proton *c* has shifted upfield, while internal isophthalamide cavity proton *f* has moved substantially downfield implying the existence of competitive hydrogen bonding to the chloride anion.[16] Crucially, there is an upfield shift and splitting of hydroquinone protons *g* and *h* that is consistent with intercalation of the electron-poor pyridinium motif between the electron-rich hydroquinones. The interpenetrated nature of the species is further corroborated by evidence from 2D ROESY NMR spectroscopy where through-space correlations are observed between the hydroquinone and alkene protons (*g*, *h*, and *i*) and protons associated with the pyridinium axle component (*a* to *d*) (Figure 4).

Proof that the isolated product was indeed the Janus rotaxane **9**-$(Cl)_2$ rather than the [1]rotaxane **10**-Cl was provided by positive electrospray mass spectrometry.[17] A peak at m/z 1367.74 with $\Delta m/z = 0.5$ is consistent with the doubly charged organic fragment $\mathbf{9}^{2+}$ (Figure 5).

[1]Rotaxane **10**-Cl was also formed in the RCM reaction, and was found in the more polar band on the prep TLC plate at an R_f identical to that of the precursor **1**-Cl. Indeed, this band was found to contain [1]rotaxane **10**-Cl, its un-



Scheme 2. Summary of products for RCM reaction of **1**-Cl.

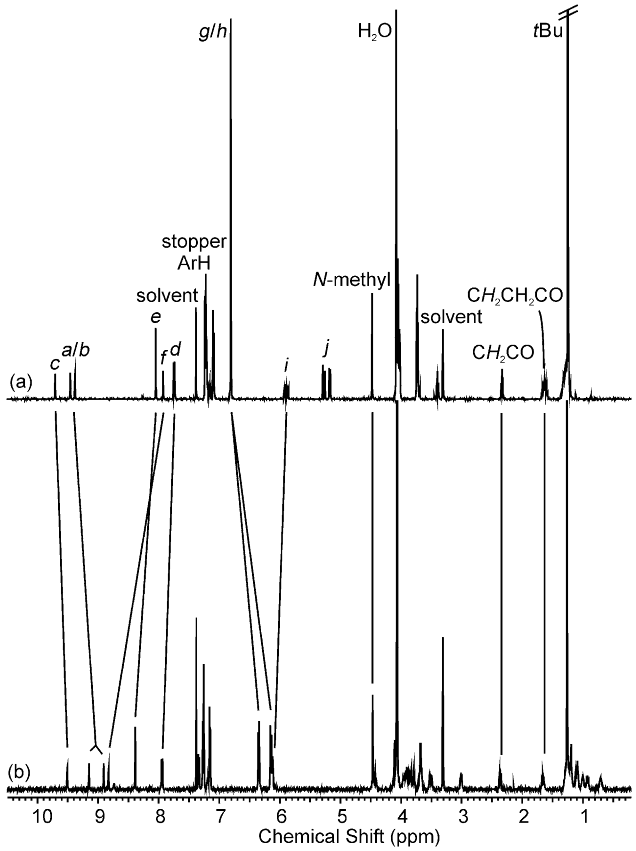


Figure 3. ^{1}H NMR spectra of a) RCM precursor **1**-Cl and b) Janus [2]rotaxane **9**-(Cl)$_2$ (solvent: 4:1 $CDCl_3/CD_3OD$, $T=293$ K). For atom labels see Figure 2.

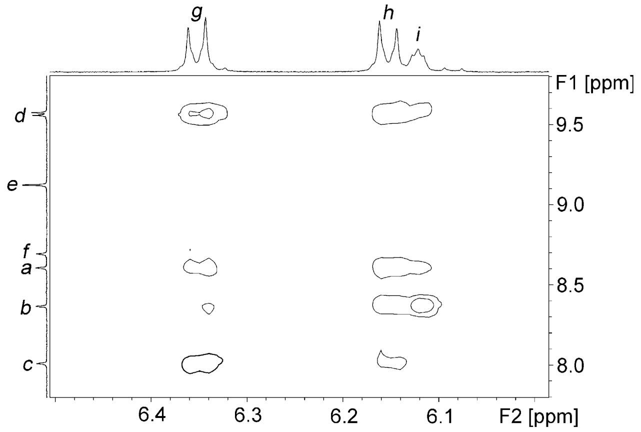


Figure 4. Section of ^{1}H ROESY NMR spectrum of Janus [2]rotaxane **9**-(Cl)$_2$ (solvent: 4:1 $CDCl_3/CD_3OD$, $T=293$ K). For atom labels see Figure 2.

threaded isomer **11**-Cl and trace amounts of unreacted starting material **1**-Cl. Despite repeated attempts, in our hands, it proved impossible to separate these components.

To test whether the formation of the Janus [2]rotaxane was chloride anion-templated, the non-coordinating hexafluorophosphate salt of **1**-PF_6 was prepared and submitted to the same RCM conditions as **1**-Cl. In this case, no precipitation of material was observed, however a ^{1}H NMR spectrum of the crude reaction mixture recorded after 16 h revealed that cyclization had occurred. Attempted purification by silica gel preparative TLC proved exceedingly difficult due to the generation of multiple poorly separated bands on

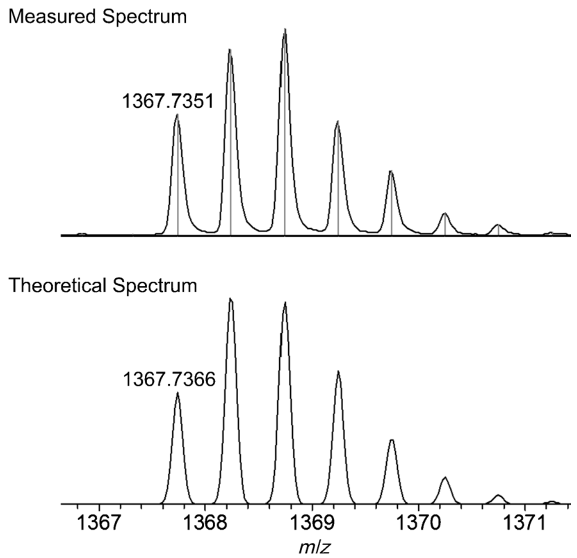


Figure 5. HR electrospray MS of Janus [2]rotaxane **9**-(Cl)$_2$. (The isotope pattern observed is consistent with the molecular ion fragment $\mathbf{9}^{2+}$).

the TLC plate; none of these bands, however, contained the doubly charged Janus [2]rotaxane, as determined by electrospray MS. This observation suggests the intermolecular reaction to form the Janus [2]rotaxane is chloride anion-templated. It is noteworthy that a band was developed which contained, through a combination of ^{1}H NMR and electrospray MS evidence, the threaded [1]rotaxane **10**-PF$_6$, but isolated in low yield due to the very challenging purification (see the Supporting Information).

In summary, the first anion-templated Janus [2]rotaxane has been prepared consisting of pyridinium chloride axle and isophthalamide macrocyclic components. Its synthesis by a Grubbs'-catalyzed RCM clipping reaction is an unusual method to use for the construction of a Janus rotaxane. The synthesis of further "higher-order" interlocked molecules by anion-templation strategies are continuing in our laboratories

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Keywords: anions · rotaxanes · supramolecular chemistry · template synthesis

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