

Thermodynamic Synthesis of Rotaxanes by Imine Exchange

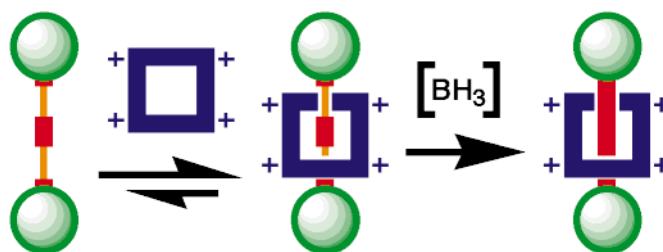
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ABSTRACT



By utilizing the dynamic nature of imine bonds, it is possible to construct [2]rotaxanes from a ring and a preformed dumbbell under thermodynamic control. These dynamic [2]rotaxanes, which exhibit reversible supramolecular-like behavior in the presence of appropriate catalysts, can be “fixed” by reduction of their imine bonds.

Although thermodynamic control dominates the chemistry of noncovalently bonded systems and allows spontaneous access to intricate supramolecular entities, with a few notable and spectacular exceptions,¹ many molecular aggregates are difficult to characterize in solution because of a lack of sufficient cooperativity between their noncovalent bonding arrays. The prospect of being able to synthesize more robust analogues of these noncovalently bonded systems is an appealing one. In a recent Letter,² we outlined the synthesis of a rotaxane utilizing thermodynamically controlled reversible covalent chemistry involving imine bond formation. In this Letter, we describe the construction of two dynamic rotaxanes in which the ring component is cyclobis(paraquat-*p*-phenylene)³ (CBPQT⁴⁺), with its π -electron-deficient bipyridinium units, and a dumbbell component which contains

either a π -electron-rich 1,5-dioxynaphthalene or 1,4-dioxybenzene ring system centrally located within a polyether chain, terminated by large aromatic stoppers containing imine bonds produced as a result of either imine formation or exchange.^{4,5} We show how these two rotaxanes can be equilibrated in the presence of an excess of the appropriate dumbbell component. Furthermore, we also demonstrated that we can “fix” the dynamic [2]rotaxanes by reduction of the imine bonds present in their dumbbell components.

The syntheses of the dynamic dumbbells 5NP/5BZ in both the 1,5-dioxynaphthalene (NP) and 1,4-dioxybenzene (BZ) series are outlined in Scheme 1. The account given here

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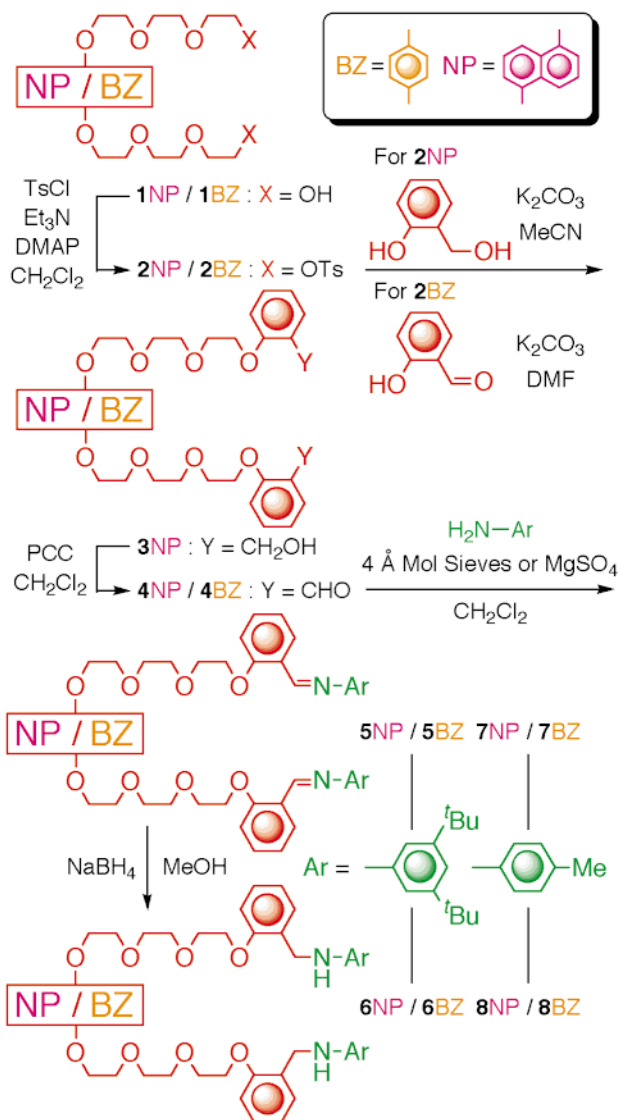
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(4) In *imine-forming reactions*, it is H₂O that is either produced or required as a nucleophile, to establish the equilibrium between the aldehyde, the amine, and the imine. In *imine-exchange reactions*, it is a “second” amine that reacts with the imine, resulting in “second” imine, thus establishing an equilibrium between two amines and two imines.

(5) In order that the equilibrium is driven toward rotaxane formation, the dumbbell component has to interact strongly with CBPQT⁴⁺ as well as contain the appropriate imine functionality within its stoppers. The 1,5-dioxynaphthalene derivative carrying two methoxyethoxyethoxy side chains has been shown³ to form a strong 1:1 complex with $K_a > 5000 \text{ M}^{-1}$ in MeCN at room temperature with CBPQT⁴⁺PF₆⁻, cf., $K_a = 2220 \pm 240 \text{ M}^{-1}$ for the analogous 1:1 complex in which 1,4-dioxybenzene replaces 1,5-dioxynaphthalene.

Scheme 1



relates only⁶ to the NP series, starting from the known⁷ diol **1NP**, which was converted (TsCl/NEt₃/DMAP/CH₂Cl₂) into the bis(OTs) **2NP** in 88% yield. Reaction (K₂CO₃/MeCN) of 2-hydroxymethylphenol with **2NP** afforded (90%) **3NP** which was oxidized (PCC/CH₂Cl₂) to the dialdehyde **4NP** in 70% yield. **4NP** was shown to bind⁸ to CBPQT·4PF₆ with a K_a value of ca. $1.7 \pm 0.4 \times 10^4 \text{ M}^{-1}$ for this 1:1 complex

(6) In the BZ series, the bis(OTs) **2BZ**, prepared in 63% yield by treatment of the diol **1BZ** with TsCl/Et₃N/DMAP in CH₂Cl₂, was reacted (K₂CO₃/DMF) with salicylaldehyde to yield (33%) the dialdehyde **4BZ**. The diimines—**5BZ** and **7BZ**—were prepared by reacting **4BZ** with the appropriate arylamine in the presence of MgSO₄. Reduction (NaBH₄/MeOH) of these diimines afforded the diamine dumbbells—**6BZ** and **8BZ**.

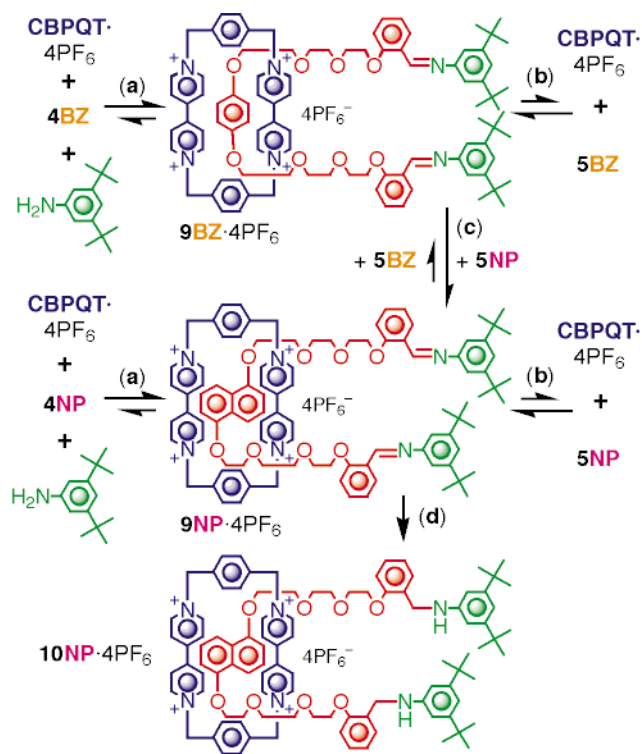
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(8) The K_a value was determined by varying the concentration of CBPQT·4PF₆ in the presence of a known concentration of **4NP** and measuring the absorbance of the charge-transfer band. CBPQT·4PF₆ (MeCN, 10 mM) containing **4NP** (0.2 mM) was titrated with **4NP** (MeCN, 0.2 mM) until the concentration of CBPQT·4PF₆ reached 0.1 mM. The binding constant was obtained by curve fitting the experimental absorbance values using the ULTRAFIT 2.11 program [see: Connors, K. A. *Binding Constants*; Wiley: New York, 1987; Chapter 4]. Previously, we had shown [ref 3]

in MeCN. Treatment of **4NP** with 3,5-di-*tert*-butylaniline in the presence of either MgSO₄ or powdered 4 Å molecular sieves resulted in the formation of the dynamic dumbbell **5NP** in almost quantitative yield. Reduction (NaBH₄/MeOH) of this diimine **5NP** gave (83%) the “fixed” dumbbell **6NP**. A threadlike analogue (**7NP**) of **5NP**, in which the two 3,5-di-*tert*-butylphenyl groups in **5NP** have been replaced by two *p*-methylphenyl groups, was also prepared from **4NP** by reacting it with *p*-toluidine (*p*-MeC₆H₄NH₂). The [2]pseudo-rotaxane [7NP·CBPQT]·4PF₆ is formed spontaneously when equimolar amounts of **7NP** and CBPQT·4PF₆ are mixed together in MeCN.

The synthesis of the purple-colored dynamic [2]rotaxane **9NP**·4PF₆ in ca. 90% yield was performed initially using a threading, followed-by-stoppering approach (*a* in Scheme 2),

Scheme 2



whereby 3,5-di-*tert*-butylaniline was added to a 10 mM MeCN solution of **4NP** and CBPQT·4PF₆ containing an excess of powdered 4 Å molecular sieves. Next, we attempted to prepare **9NP**·4PF₆ utilizing the reversible nature of imine bond formation (*b* in Scheme 2). Thus, addition of equimolar amounts⁹ of the preformed dumbbell **5NP** to CBPQT·4PF₆ in CD₃CN (9.5 mM) did result in the formation of **9NP**·4PF₆ during a 2-week period. To confirm that it is the imine functions in **5NP** that are responsible for rotaxane

that CBPQT·4PF₆ can bind a 1,5-dioxynaphthalene derivative carrying two methoxyethoxyethoxy side chains in a 1:2 ratio at concentrations >10⁻³ M and in a 1:1 ratio at concentrations <10⁻³ M. By keeping the concentration of **4NP** <10⁻³ M, and starting with a large excess of CBPQT·4PF₆, we can estimate a value of K_a for the 1:1 complex of ca. $1.7 \pm 0.4 \times 10^4 \text{ M}^{-1}$.

formation, the “inert” diamine **8NP** was added to **CBPQT**·**4PF₆**. Although the **CD₃CN** solution turned pale pink, presumably on account of some weak association of the 1,5-dioxynaphthalene ring system in **8NP** with the outside of **CBPQT⁴⁺**, no binding of **8NP** inside its cavity was observed, even after addition of an acid (e.g., **NH₄PF₆**) or a nucleophile (e.g., *p*-**MeC₆H₄NH₂**).

The mechanism (Figure 1) of the formation of **9NP**·**4PF₆** presumably involves imine hydrolysis, as a result of small

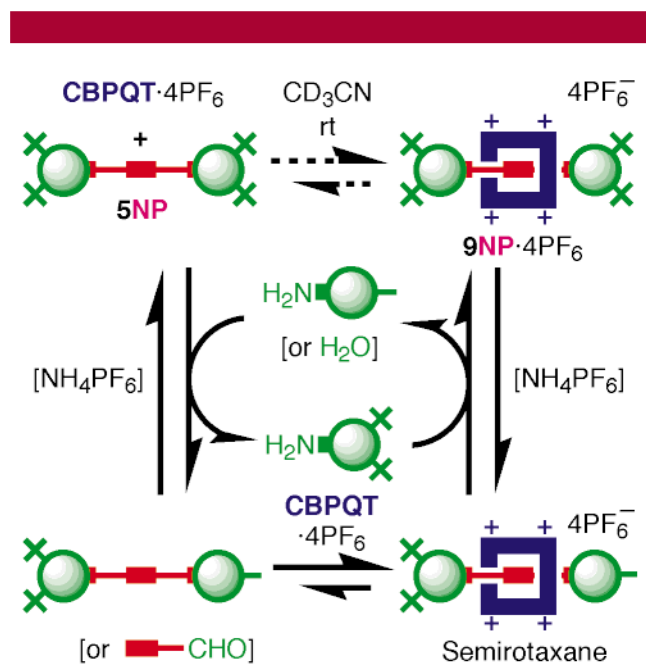


Figure 1. Formation of the [2]rotaxane **9NP**·**4PF₆**.

amounts of **H₂O** being present, followed by threading and then formation of the imine once again. Since acid is known¹⁰ to catalyze imine hydrolysis and formation, the reaction was carried out in the presence of 5% of a weak acid (**NH₄PF₆**). This modification resulted in an increase in the rate of formation of the [2]rotaxane, such that equilibrium was reached inside 3 h.

Next, it was decided to try and establish if a similar result could be obtained during an imine exchange process. And so, *p*-**MeC₆H₄NH₂** (5%) and **NH₄PF₆** (5%) were added⁹ to the dynamic dumbbell **5NP** and **CBPQT**·**4PF₆**. Addition of both the acid and the nucleophile increased the rate of [2]-rotaxane formation such that equilibrium was attained inside 2 h. This observation, however, does not rule out the possibility of imine hydrolysis/formation being the major

(9) In the formation of the **9NP**·**4PF₆**, via the dynamic process, stock solutions (20 mM) of **CBPQT**·**4PF₆** and **5NP** in **CD₃CN** were prepared and partially dried with freshly activated 4 Å molecular sieves. **CBPQT**·**4PF₆** (300 μL) and **5NP** (300 μL) were added to an NMR tube (note that the resulting concentration of the reactants at this point is 10 mM). Catalyst (if any) (15 μL, 5%) was then added to the NMR tube from 20 mM stock solutions of either **NH₄PF₆** or *p*-**MeC₆H₄NH₂** in **CD₃CN**. In the case where no—or only one—catalyst was used, then an extra 30 μL (or 15 μL) of **CD₃CN** was added to the NMR tube in order to make the concentration of all the samples 9.5 mM. ¹H NMR spectroscopy was then used to follow the reactions at room temperature.

(10) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489–510.

pathway for the production of **9NP**·**4PF₆**. Thus, the reaction was repeated using 5% of *p*-**MeC₆H₄NH₂** as a catalyst. Figure 2 shows the partial ¹H NMR spectrum in the region where

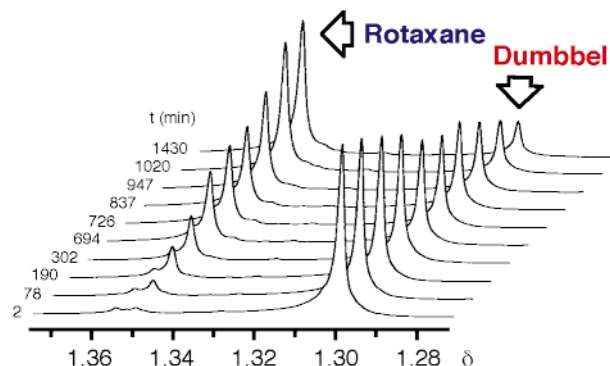


Figure 2. Partial ¹H NMR (400 MHz, **CD₃CN**) spectra of the *t*-Bu region during the dynamic [2]rotaxane **9NP**·**4PF₆** formation. This reaction was carried out at 9.5 mM using 5% *p*-**MeC₆H₄NH₂** as catalyst. The small peak observed downfield of the rotaxane peak is believed to correspond to a semirotaxane wherein one end of the “dumbbell” carries a 3,5-di-*tert*-butylaryl group and the other end is occupied by either an aldehyde or a *p*-methylaryl group.

the protons on the *tert*-butyl groups resonate. Monitoring the reaction using these signals indicated that equilibrium was reached within 2 days (cf. 2 weeks with no amine catalyst present), implying that, in this particular reaction, the major pathway to the formation of the dynamic [2]rotaxane is imine exchange.

To exploit the reversible nature of imine exchange even further, we have assembled the BZ-dynamic [2]rotaxane **9BZ**·**4PF₆** utilizing the stoppering methodology in a manner analogous to that used to obtain **9NP**·**4PF₆** (*a* in Scheme 2). The yield (65%) of **9BZ**·**4PF₆** was lower compared with that (90%) of **9NP**·**4PF₆**, reflecting the weaker association ($K_a = 1.8 \pm 0.4 \times 10^3 \text{ M}^{-1}$) of **4BZ** with **CBPQT**·**4PF₆**. On account of the differences in the noncovalent bonding interactions between the dumbbell and the ring components of these two [2]rotaxanes, we decided to see if we could exchange (*c* in Scheme 2) the BZ dumbbell for the NP dumbbell and so convert **9BZ**·**4PF₆** into **9NP**·**4PF₆** under thermodynamic control. This objective was achieved by adding 1 equiv¹¹ of **5NP** to a **CD₃CN** solution containing 65% of the BZ-dynamic [2]rotaxane **9BZ**·**4PF₆** and 35% of free **CBPQT**·**4PF₆** and **5BZ**.

The reaction was followed (Figure 3) by monitoring the relative intensities of signals for the *tert*-butyl protons in the various different species. On addition of 5% of both **NH₄PF₆** and *p*-**MeC₆H₄NH₂**, the proportion of **9NP**·**4PF₆** increased gradually at the expense of **9BZ**·**4PF₆** until an

(11) The exchange reaction was carried out by addition of **5NP** in **CD₃CN** (300 μL, 20 mM) to a **CD₃CN** (300 μL, 20 mM) solution containing the [2]rotaxane **9BZ**·**4PF₆** (65%) and free **CBPQT**·**4PF₆** and **5BZ** (35%). Then 15 μL of the catalyst *p*-**MeC₆H₄NH₂**/**NH₄PF₆** (20 mM of each in **CD₃CN**) was added to the reaction mixture (final concentration 9.8 mM) and the reaction monitored by ¹H NMR spectroscopy.

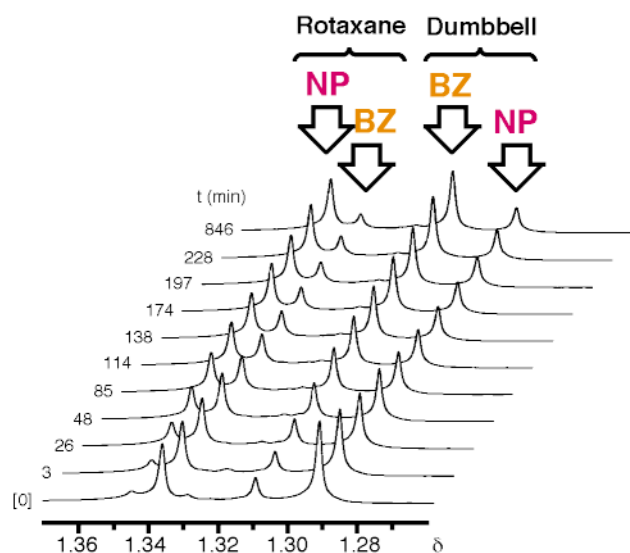


Figure 3. Partial ^1H NMR (400 MHz, CD_3CN) spectra of the *t*-Bu region during the exchange reaction of $9\text{NP}\cdot 4\text{PF}_6$ with $9\text{BZ}\cdot 4\text{PF}_6$. This reaction was carried out at 9.8 mM using 5% *p*- $\text{MeC}_6\text{H}_4\text{NH}_2/\text{NH}_4\text{PF}_6$ as catalysts. Time = [0] indicates the ^1H NMR spectrum taken before any catalyst was added. The small peak observed just upfield of the rotaxane peaks is believed to correspond to the semirotaxane wherein one end of the “dumbbell” carries a 3,5-*tert*-butylaryl group and the other end is occupied by either an aldehyde or the *p*-methylaryl group.

equilibrium was reached after 14 h, i.e., the equilibrium takes a lot longer to reach than in the previous experiments involving only one dumbbell at a time. This difference in time scale is not unexpected.¹² The ratio of the dynamic rotaxanes $9\text{NP}\cdot 4\text{PF}_6:9\text{BZ}\cdot 4\text{PF}_6$, at equilibrium, is ca. 6:1, reflecting the stronger binding of the naphthalene-derived components over the benzene derivatives. Thus, this experiment reveals all the subtlety and attractions of using thermodynamic control¹³ exclusively in the self-assembly of interlocked molecular compounds.

One challenge remained. It was to show that the imine functions in the dynamic [2]rotaxanes can be reduced without losing the interlocking between their dumbbells and rings

(12) The increased reaction time reflects the fact that there are now an increased number of reactions that are required to occur before 5NP can exchange with 5BZ in the [2]rotaxane. The first step in the process is presumably imine exchange (or hydrolysis) of $9\text{BZ}\cdot 4\text{PF}_6$, resulting in a semirotaxane (Figure 1) which can then undergo decomplexation of the BZ thread component revealing “free” $\text{CBPQT}\cdot 4\text{PF}_6$. This “free” cyclophane can then form $9\text{NP}\cdot 4\text{PF}_6$ with 5NP by means of the process depicted by *b* in Scheme 2.

(*d* in Scheme 2). Eventually, we discovered that reduction of $9\text{NP}\cdot 4\text{PF}_6$ can be achieved by using the $\text{BH}_3\cdot 2,6$ -lutidine complex, followed by hydrolysis, to afford the “fixed” [2]-rotaxane $10\text{NP}\cdot 4\text{PF}_6$ in 40% yield.¹⁴

The research reported here has shown how [2]rotaxanes with dynamic structures can be assembled under equilibrium control. These dynamic species represent a halfway house between rotaxanes and pseudorotaxanes. Although their components are covalent in nature, under certain conditions, e.g., in the presence of a small nucleophile and/or an acid catalyst, they can equilibrate and exchange their components as if they were their supramolecular counterparts, namely, the pseudorotaxanes. In this respect, dynamic rotaxanes have some of the hallmarks of the “rotaxanes” which have been obtained using the slippage methodology¹⁵ where, in nonpolar solvents at low temperatures, they behave like rotaxanes while, at higher temperatures in more highly solvating polar solvents, they assume the characteristics of pseudorotaxanes. In the case of the dynamic rotaxanes, it is the presence of the appropriate catalyst which imparts upon them their pseudorotaxane characteristics. These new dynamic rotaxanes, however, have the added advantage that they can be transported out of a thermodynamic regime and transferred into a kinetic one, simply by reduction of their imine bonds.

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Supporting Information Available: Experimental procedures and characterization data for 1NP – 10NP and 4BZ – 5BZ . ^1H NMR spectra for 4NP – 8NP , $10\text{NP}\cdot 4\text{PF}_6$, 4BZ , and 5BZ . ^1H NMR spectra of the reaction mixtures formed in the synthesis of $9\text{NP}\cdot 4\text{PF}_6$ and $9\text{BZ}\cdot 4\text{PF}_6$ and VT ^1H NMR of these two compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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