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Thermodynamic Synthesis of Rotaxanes by Imine Exchange

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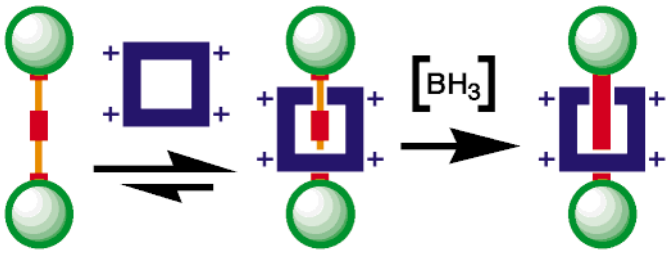
ABSTRACT



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] ($CBPQT^{4+}$), 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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(1) (a) MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383−2420. (b) Zimmerman, S. C.; Zeng, F. W.; Reichert, D. E. C.; Kolotuchin, S. V. *Science* **1996**, *271*, 1095−1098. (c) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirschberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science* **1997**, *278*, 1601−1604. (d) Jolliffe, K. A.; Timmerman, P.; Reinhoudt, D. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 933−937. (e) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278−286.

(2) Cantrill, S. J.; Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1363−1366 and references therein.

(3) Asakawa, M.; Dehaen, W.; L′abbé, G.; Menzer, S.; Nouwen, J.; Raymo, F. M.; Stoddart, J. F.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 9591−9595.

(4) In *imine-forming reactions*, it is H_2O 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 $CBPQT^{4+}$ as well as contain the appropriate imine functionality within its stoppers. The 1,5-dioxynaphthalene derivative carrying two methoxyethoxyethoxy side chains has been shown[3] to form a strong 1:1 complex with $K_a > 5000\ M^{-1}$ in MeCN at room temperature with $CBPQT{\cdot}4PF_6$, cf., $K_a = 2220 \pm 240\ M^{-1}$ for the analogous 1:1 complex in which 1,4-dioxybenzene replaces 1,5-dioxynaphthalene.

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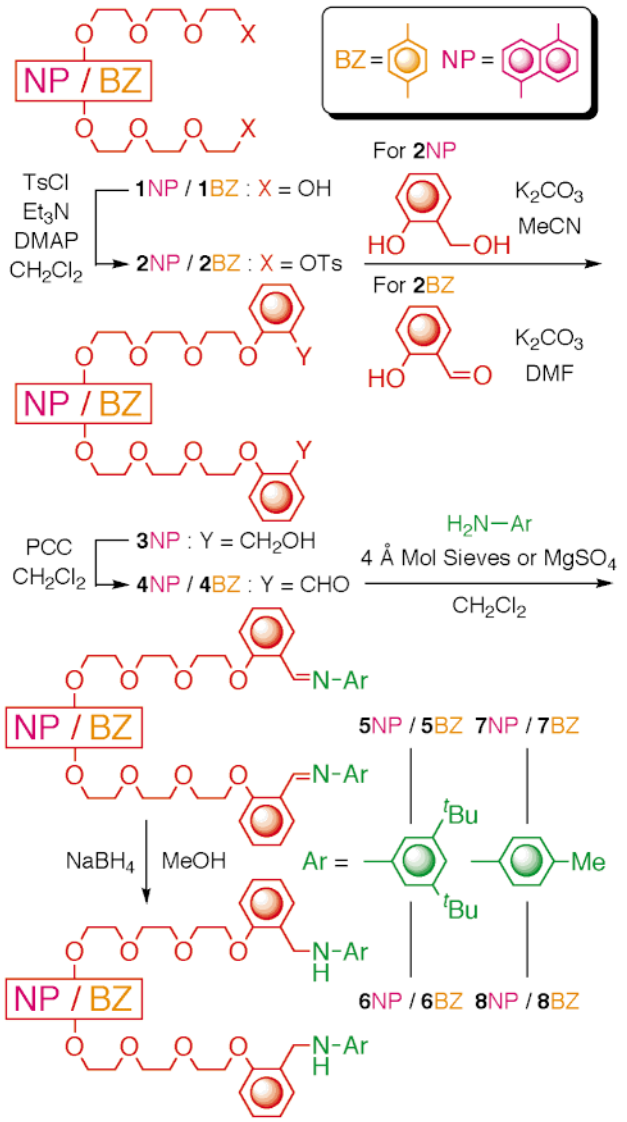
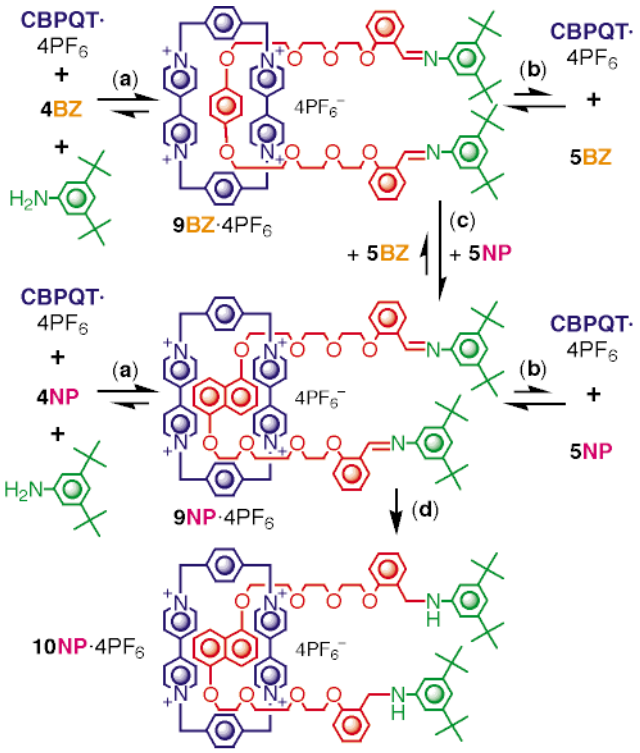
Scheme 1



relates only[6] to the NP series, starting from the known[7] diol **1**NP, which was converted ($TsCl/NEt_3$/ $DMAP/CH_2Cl_2$) into the bistosylate **2**NP in 88% yield. Reaction (K_2CO_3/MeCN) of 2-hydroxymethylphenol with **2**NP afforded (90%) **3**NP which was oxidized (PCC/CH_2Cl_2) to the dialdehyde **4**NP in 70% yield. **4**NP was shown to bind[8] to CBPQT·$4PF_6$ with a K_a value of ca. $1.7 \pm 0.4 \times 10^4$ M^{-1} for this 1:1 complex in MeCN. Treatment of **4**NP with 3,5-di-*tert*-butylaniline in the presence of either $MgSO_4$ or powdered 4 Å molecular sieves resulted in the formation of the dynamic dumbbell **5**NP in almost quantitative yield. Reduction ($NaBH_4$/MeOH) of this diimine **5**NP gave (83%) the "fixed" dumbbell **6**NP. A threadlike analogue (**7**NP) of **5**NP, in which the two 3,5-di-*tert*-butylphenyl groups in **5**NP have been replaced by two *p*-methyphenyl groups, was also prepared from **4**NP by reacting it with *p*-toluidine (*p*-$MeC_6H_4NH_2$). The [2]pseudorotaxane [**7**NP·CBPQT]·$4PF_6$ is formed spontaneously when equimolar amounts of **7**NP and CBPQT·$4PF_6$ are mixed together in MeCN.

The synthesis of the purple-colored dynamic [2]rotaxane **9**NP·$4PF_6$ 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 **4**NP and CBPQT·$4PF_6$ containing an excess of powdered 4 Å molecular sieves. Next, we attempted to prepare **9**NP·$4PF_6$ utilizing the reversible nature of imine bond formation (*b* in Scheme 2). Thus, addition of equimolar amounts[9] of the preformed dumbbell **5**NP to CBPQT·$4PF_6$ in CD_3CN (9.5 mM) did result in the formation of **9**NP·$4PF_6$ during a 2-week period. To confirm that it is the imine functions in **5**NP that are responsible for rotaxane

(6) In the BZ series, the bistosylate **2**BZ, prepared in 63% yield by treatment of the diol **1**BZ with $TsCl/Et_3N/DMAP$ in CH_2Cl_2, was reacted (K_2CO_3/DMF) with salicylaldehyde to yield (33%) the dialdehyde **4**BZ. The diimines—**5**BZ and **7**BZ—were prepared by reacting **4**BZ with the appropriate arylamine in the presence of $MgSO_4$. Reduction ($NaBH_4$/MeOH) of these diimines afforded the diamine dumbbells—**6**BZ and **8**BZ.

(7) Bravo, J. A.; Raymo, F. M.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Eur. J. Org. Chem.* **1998**, 2565−2571.

(8) The K_a value was determined by varying the concentration of CBPQT·$4PF_6$ in the presence of a known concentration of **4**NP and measuring the absorbance of the charge-transfer band. CBPQT·$4PF_6$ (MeCN, 10 mM) containing **4**NP (0.2 mM) was titrated with **4**NP (MeCN, 0.2 mM) until the concentration of CBPQT·$4PF_6$ 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] that CBPQT·$4PF_6$ 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 **4**NP $< 10^{-3}$ M, and starting with a large excess of CBPQT·$4PF_6$, we can estimate a value of K_a for the 1:1 complex of ca. $1.7 \pm 0.4 \times 10^4$ M^{-1}.

formation, the "inert" diamine **8**NP was added to CBPQT·$4PF_6$. Although the CD_3CN solution turned pale pink, presumably on account of some weak association of the 1,5-dioxynaphthalene ring system in **8**NP with the outside of $CBPQT^{4+}$, no binding of **8**NP inside its cavity was observed, even after addition of an acid (e.g., NH_4PF_6) or a nucleophile (e.g., *p*-$MeC_6H_4NH_2$).

The mechanism (Figure 1) of the formation of **9**NP·$4PF_6$ presumably involves imine hydrolysis, as a result of small

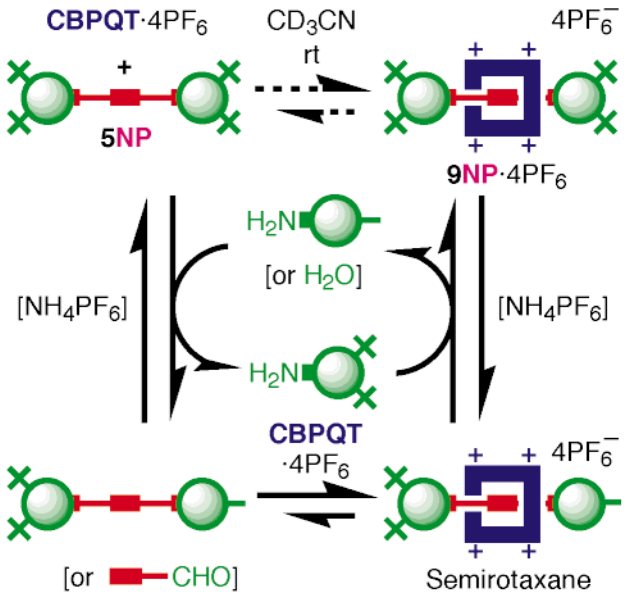


Figure 1. Formation of the [2]rotaxane **9**NP·$4PF_6$.

amounts of H_2O being present, followed by threading and then formation of the imine once again. Since acid is known[10] to catalyze imine hydrolysis and formation, the reaction was carried out in the presence of 5% of a weak acid (NH_4PF_6). 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*-$MeC_6H_4NH_2$ (5%) and NH_4PF_6 (5%) were added[9] to the dynamic dumbbell **5**NP and CBPQT·$4PF_6$. 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 pathway for the production of **9**NP·$4PF_6$. Thus, the reaction was repeated using 5% of *p*-$MeC_6H_4NH_2$ as a catalyst. Figure 2 shows the partial ^1H NMR spectrum in the region where

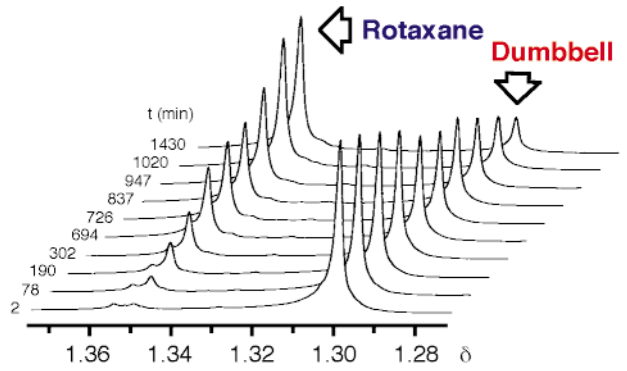


Figure 2. Partial ^1H NMR (400 MHz, CD_3CN) spectra of the *t*-Bu region during the dynamic [2]rotaxane **9**NP·$4PF_6$ formation. This reaction was carried out at 9.5 mM using 5% *p*-$MeC_6H_4NH_2$ as catalyst. The small peak observed downfield of the rotaxane peak is believed to correspond to a semirotaxane 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 **9**BZ·$4PF_6$ utilizing the stoppering methodology in a manner analogous to that used to obtain **9**NP·$4PF_6$ (*a* in Scheme 2). The yield (65%) of **9**BZ·$4PF_6$ was lower compared with that (90%) of **9**NP·$4PF_6$, reflecting the weaker association ($K_a = 1.8 \pm 0.4 \times 10^3\ M^{-1}$) of **4**BZ with CBPQT·$4PF_6$. 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 **9**BZ·$4PF_6$ into **9**NP·$4PF_6$ under thermodynamic control. This objective was achieved by adding 1 equiv[11] of **5**NP to a CD_3CN solution containing 65% of the BZ-dynamic [2]rotaxane **9**BZ·$4PF_6$ and 35% of free CBPQT·$4PF_6$ and **5**BZ.

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 NH_4PF_6 and *p*-$MeC_6H_4NH_2$, the proportion of **9**NP·$4PF_6$ increased gradually at the expense of **9**BZ·$4PF_6$ until an

(9) In the formation of the **9**NP·$4PF_6$, via the dynamic process, stock solutions (20 mM) of CBPQT·$4PF_6$ and **5**NP in CD_3CN were prepared and partially dried with freshly activated 4 Å molecular sieves. CBPQT·$4PF_6$ (300 μL) and **5**NP (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 NH_4PF_6 or *p*-$MeC_6H_4NH_2$ in CD_3CN. In the case where no—or only one—catalyst was used, then an extra 30 μL (or 15 μL) of CD_3CN 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.

(11) The exchange reaction was carried out by addition of **5**NP in CD_3CN (300 μL, 20 mM) to a CD_3CN (300 μL, 20 mM) solution containing the [2]rotaxane **9**BZ·$4PF_6$ (65%) and free CBPQT·$4PF_6$ and **5**BZ (35%). Then 15 μL of the catalyst *p*-$MeC_6H_4NH_2/NH_4PF_6$ (20 mM of each in CD_3CN) was added to the reaction mixture (final concentration 9.8 mM) and the reaction monitored by ^1H NMR spectroscopy.

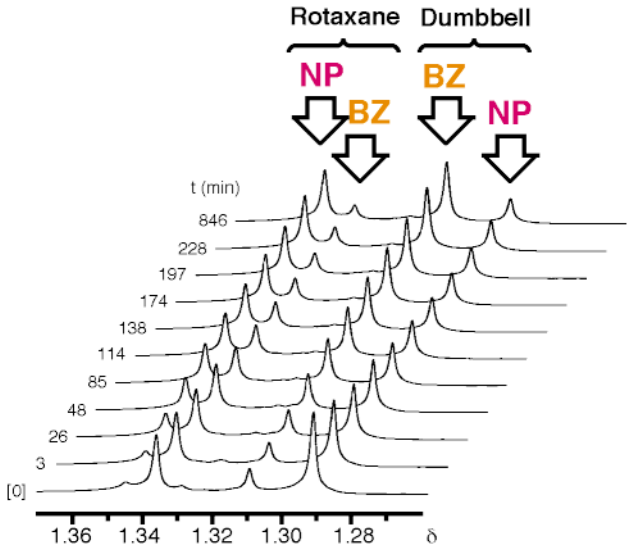


Figure 3. Partial ^{1}H NMR (400 MHz, CD_3CN) spectra of the *t*-Bu region during the exchange reaction of **9**NP·4PF_6 with **9**BZ·4PF_6. This reaction was carried out at 9.8 mM using 5% *p*-$MeC_6H_4NH_2$/NH_4PF_6 as catalysts. Time = [0] indicates the ^{1}H NMR spectrum taken before any catalyst 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-di-*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**NP·4PF_6:**9**BZ·4PF_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 control[13] 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 (*d* in Scheme 2). Eventually, we discovered that reduction of **9**NP·4PF_6 can be achieved by using the BH_3·2,6-lutidine complex, followed by hydrolysis, to afford the "fixed" [2]-rotaxane **10**NP·4PF_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 methodology[15] 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 **1**NP−**10**NP and **4**BZ−**5**BZ. ^{1}H NMR spectra for **4**NP−**8**NP, **10**NP·4PF_6, **4**BZ, and **5**BZ. ^{1}H NMR spectra of the reaction mixtures formed in the synthesis of **9**NP·4PF_6 and **9**BZ·4PF_6 and VT ^{1}H NMR of these two compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The increased reaction time reflects the fact that there are now an increased number of reactions that are required to occur before **5**NP can exchange with **5**BZ in the [2]rotaxane. The first step in the process is presumably imine exchange (or hydrolysis) of **9**BZ·4PF_6, resulting in a semirotaxane (Figure 1) which can then undergo decomplexation of the BZ thread component revealing "free" CBPQT·4PF_6. This "free" cyclophane can then form **9**NP·4PF_6 with **5**NP by means of the process depicted by *b* in Scheme 2.

(13) (a) Rowan, S. J.; Sanders, J. K. M. *Chem. Commun*. **1997**, 1407−1408. (b) Hamilton, D. G.; Feeder, N.; Teat, S. J.; Sanders, J. K. M. *New. J. Chem*. **1998**, 1019−1021. (c) Sanders, J. K. M. *Chem. Eur. J*. **1998**, *4*, 1378−1383. (d) Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc*. **1999**, *121*, 1599−1600. (e) Tam-Chang, S.-W.; Stehouwer, J. S.; Hao, J. *J. Org. Chem*. **1999**, *64*, 334−335. (f) Ipaktschi, J.; Hosseinzadeh, R.; Schalf, P. *Angew. Chem. Int. Ed*. **1999**, *38*, 1658−1660. (g) Weck, M.; Mohr, B.; Sauvage, J.-P.; Grubbs, R. H. *J. Org. Chem*. **1999**, *64*, 5463−5471. (h) Fujita, M. *Acc. Chem. Res*. **1999**, *32*, 53−61. (i) Cousins, G. R. L.; Poulsen, S.-A.; Sanders, J. K. M. *Chem. Commun*. **1999**, 1575−1576.

(14) The yield is based on the assumption that the starting material consists of only 90% **9**NP·4PF_6.

(15) Raymo, F. M.; Houk, K. N.; Stoddart, J. F. *J. Am. Chem. Soc*. **1998**, *120*, 9318−9322.