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Rotaxane Formation under Thermodynamic Control

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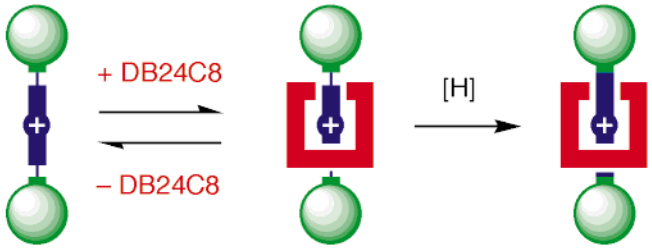
ABSTRACT



Thermodynamic control operates in the synthesis of a [2]rotaxane based upon the dibenzylammonium ion/crown ether recognition motif. When dibenzo[24]crown-8 is added to an acetonitrile solution containing a diimine dumbbell-like component, the dynamic nature of the system (i.e., imine hydrolysis/reformation) offers the ring component access to the NH_2^+ center, allowing the self-assembly of the corresponding "dynamic" [2]rotaxane to occur. The "fixing" of this [2]rotaxane can be achieved upon reduction of the imine bonds, affording a kinetically inert [2]rotaxane.

Whereas the noncovalent syntheses[1] of supermolecules (discrete complexes) and supramolecular arrays (polymeric aggregates) generally occur under thermodynamic control, the covalent syntheses of organic compounds are usually kinetically controlled. However, covalent syntheses can also be carried out within a thermodynamically controlled regime. Such reversible covalent bond-forming protocols enjoy the attributes of supramolecular processes but within a much more robust bonding framework than their noncovalent counterparts. Synthetic chemists are already exploring the opportunities presented by utilizing reversible covalent modifications, in conjunction with supramolecular assistance, to make molecular receptors[2] and interlocked molecular compounds,[3] such as catenanes and rotaxanes. To date, labile coordinative bonds, associated with certain metal−ligand interactions[4] and ring-opening/ring-closing metathesis protocols,[5] have been exploited in the self-assembly of catenanes under thermodynamically controlled conditions. However, a wide range of functionalities, including acetals,[6] esters,[7] and disulfides,[8] have also been employed in reversible processes involving wholly organic compounds. Here, we report the use of the well-known reversible imine bond-

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(2) Sanders, J. K. M. *Chem. Eur. J.* **1998**, *4*, 1378−1383.
(3) (a) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725−2828. (b) Breault, G. A.; Hunter, C. A.; Mayers, P. C. *Tetrahedron* **1999**, *55*, 5265−5293. (c) Hubin, T. J.; Kolchinski, A. G.; Vance, A. L.; Busch, D. H. In *Advances in Supramolecular Chemistry*; Gokel, G. W., Ed.; JAI Press: Stamford, CT, 1999; Vol. 10, pp 237−357.

(4) (a) Fujita, M.; Ibukuro, F.; Hagihara, H.; Ogura, K. *Nature* **1994**, *367*, 720−723. (b) Try, A. C.; Harding, M. M.; Hamilton, D. G.; Sanders, J. K. M. *Chem. Commun.* **1998**, 723−724.
(5) For an example of a [2]catenane synthesis—employing ring opening and ring closing metathesis (RORCM)—operating under thermodynamic control, see: Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599−1600. For an example of [2]catenane synthesis utilizing ring-closing metathesis (RCM), see: Mohr, B.; Weck, M.; Sauvage, J.-P.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1308−1310.
(6) For an example used in the synthesis of natural products, see: Nadin, A.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1622−1656. For comments on how ketalization under thermodynamic control can be exploited in the resolution of racemates, see: Davis, A. P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 591−594.
(7) Rowan, S. J.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 1536−1546.
(8) (a) Hioki, H.; Still W. C. *J. Org. Chem.* **1998**, *63*, 904−905. (b) Tam-Chang, S.-W.; Stehouwer, J. S.; Hao J. *J. Org. Chem.* **1999**, *64*, 334−335.

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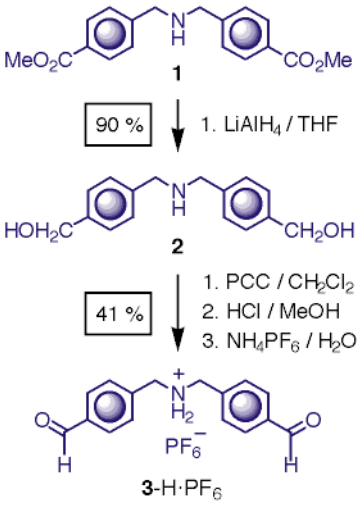
forming reaction[9] to construct a so-called dynamic [2]-rotaxane, starting from a threadlike component terminated by aldehyde functions—specifically, the bis(4-formylbenzyl)-ammonium ion—3,5-di-*tert*-butylaniline, and a complementary ring component, namely dibenzo[24]crown-8 (DB24C8).[10]

The synthesis (Scheme 1) of the threadlike component begins with the reduction ($LiAlH_4$/THF) of diester **1**,[11]

Scheme 1. Synthesis of the Dialdehyde **3**-H·PF_6



affording diol **2** which is oxidized (PCC/CH_2Cl_2) to dialdehyde **3**. Protonation (HCl/MeOH) of **3**, followed by counterion exchange (NH_4PF_6/H_2O), produces **3**-H·PF_6 in an overall yield of 37%. As expected,[12] **3**-H·PF_6 forms a strong 1:1 complex with DB24C8, both in solution and the "gas phase", as evidenced by ^{1}H NMR spectroscopy and FAB mass spectrometry, respectively. Inspection of the ^{1}H NMR spectrum (400 MHz, CD_3CN, 20 mM, 300 K) of an equimolar mixture of these two components revealed the presence of three sets of signals, corresponding to (1) the [2]pseudorotaxane [**3**-H·DB24C8]·PF_6, (2) uncomplexed **3**-H·PF_6, and (3) free DB24C8, indicating that these species are equilibrating slowly on the ^{1}H NMR time scale. As a consequence of this slow exchange, we were able to calculate a K_a value of 1600 M^{-1} ($-\Delta G° = 4.4$ kcal mol^{-1}) using the "single-point method".[13] Additionally, the base peak which was observed at $m/z = 702$ in the FAB mass spectrum of a 1:1 mixture of DB24C8 and **3**-H·PF_6 corresponds to the [2]-pseudorotaxane.

In the knowledge that the aromatic dialdehyde **3**-H·PF_6 complexes strongly in CD_3CN with DB24C8, we examined its ability to form diimine **5**-H·PF_6, via the intermediacy of the monoimine **4**-H·PF_6, on addition of 2 equiv of 3,5-di-*tert*-butylaniline. The choice of this amine relates to the fact that (1) the 3,5-di-*tert*-butylphenyl group has been shown[14] to be sufficiently large to act as a stopper toward DB24C8 and (2) the less basic aromatic amino group of the aniline will offer little competition for the proton attached to the much more basic aliphatic nitrogen atom present in **3**-H·PF_6. The reaction of **3**-H·PF_6 with 3,5-di-*tert*-butylaniline was monitored (Figure 1) by ^{1}H NMR spectroscopy.

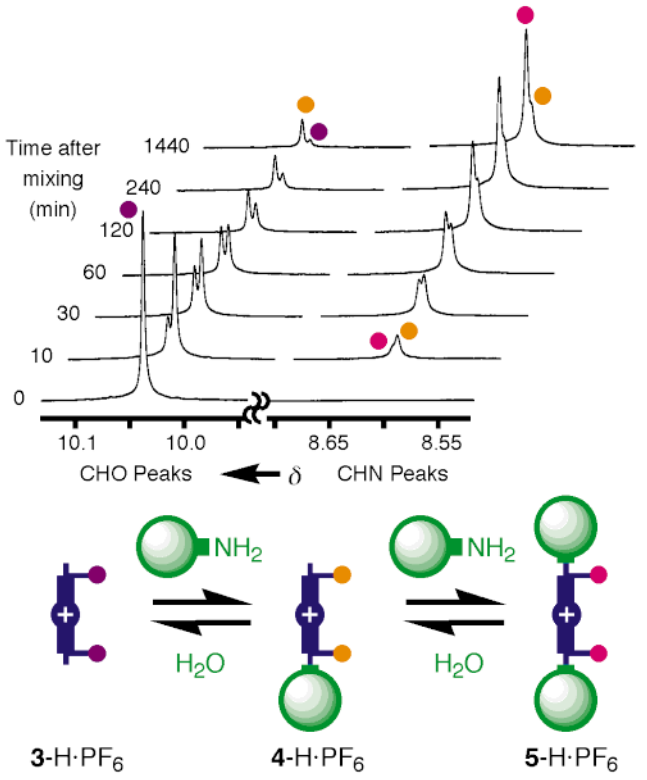


Figure 1. Top: partial ^{1}H NMR spectra (400 MHz, CD_3CN, 300 K), recorded over time, of an initial mixture of **3**-H·PF_6 (20 mM) and 3,5-di-*tert*-butylaniline (40 mM). Bottom: schematic representation of the dynamic equilibrium established in solution. The probe protons of, and the associated resonances for, the dialdehyde **3**-H·PF_6 are represented as purple dots, those of the monoaldehyde (monoimine) **4**-H·PF_6 as orange dots, and those of the diimine dumbbell **5**-H·PF_6 as magenta dots.

A 20 mM solution of **3**-H·PF_6 in CD_3CN was prepared and, after recording its ^{1}H NMR spectrum ($t = 0$ min), 2 equiv of the aniline was added and the ^{1}H NMR spectrum was recorded at appropriate time intervals.

After 10 min, two singlets are observed for the CHO protons: the more intense singlet corresponds to unreacted

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(14) Martínez-Díaz, M.-V.; Spencer, N.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1904−1907.

3-H·PF_6, while the smaller resonance arises from **4**-H·PF_6. Two singlets, one each for **4**-H·PF_6 and **5**-H·PF_6, are also observed in the CHN region of the spectrum. During the course of the reaction, both CHO signals decrease in their intensities, concomitant with the increasing intensities observed for the CHN peaks. Moreover, comparison of the spectra shows that, although initially intermediate monoaldehyde/monoimine **4**-H·PF_6 is the major product, eventually, after 60 min, diimine **5**-H·PF_6 starts to predominate. At equilibrium (1440 min = 1 day), integration of the CHO/CHN signals allows the product distribution, dialdehyde **3**-H·PF_6 (4%), monoaldehyde/monoimine **4**-H·PF_6 (23%), and diimine dumbbell **5**-H·PF_6 (73%), to be calculated.[15]

The implication of this equilibrium composition is that, on addition of 1 equiv of DB24C8 to the equilibrated mixture, no more than 27% of it can be rotaxanated unless thermodynamic control is operating. The results are recorded in Figure 2. At $t = 0$ min, with no crown ether present, the

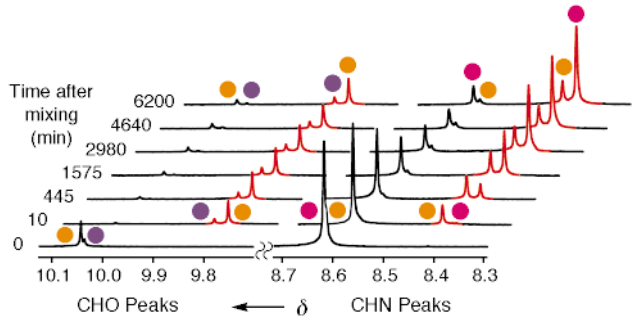

Figure 2. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 300 K), recorded over time, of an initial mixture of **3**-H·PF_6 (20 mM) and 3,5-di-*tert*-butylaniline (40 mM), which was allowed to reach equilibrium (spectrum at $t = 0$ min) prior to the addition of DB24C8 (20 mM). Peaks corresponding to species containing an NH_2^+ center not bound/occupied by a DB24C8 ring are represented in black while those which are bound/occupied are represented in red. The resonances associated with the dialdehyde, monoaldehyde, and diimine probe protons are highlighted as described in Figure 1.

spectrum is identical with the one recorded in Figure 1 at equilibrium ($t = 1440$ min). Upon addition of DB24C8, any species with an aldehyde group at either of its termini (i.e., **3**-H·PF_6 and **4**-H·PF_6) is capable of threading through the crown ether's macrocyclic cavity, generating the corresponding [2]pseudorotaxane—i.e., [**3**-H·DB24C8]·PF_6 and [**4**-H·DB24C8]·PF_6, respectively. This effect is seen immediately ($t = 10$ min) and, subsequently, resonances corresponding to **3**-H·PF_6, **4**-H·PF_6, [**3**-H·DB24C8]·PF_6, and [**4**-H·DB24C8]·PF_6 remain substantially unchanged throughout the course of the experiment. By far the most predominant change observed in the spectra is the decrease in intensity of the peak at $\delta = 8.62$ ppm (diimine dumbbell **5**-H·PF_6) and the corresponding growth of a new resonance at $\delta = 8.37$ ppm (diimine [2]rotaxane [**5**-H·DB24C8]·PF_6). It is apparent, therefore, that since the diimine dumbbell **5**-H·PF_6 *cannot* thread through the cavity of DB24C8, the [2]rotaxane is being generated via a process in which consumption of **5**-H·PF_6 results in the formation of either a monoaldehyde/monoimine (**4**-H·PF_6) or dialdehyde (**3**-H·PF_6) thread which, in turn, *can* pass through the cavity of the macrocyclic polyether and subsequently react to form the diimine [2]-rotaxane [**5**-H·DB24C8]·PF_6. At equilibrium ($t = 6200$ min = ca. 4.5 days), the product distribution is [**5**-H·DB24C8]·PF_6 (47%), **5**-H·PF_6 (16%); [**4**-H·DB24C8]·PF_6 (26%), **4**-H·PF_6 (6%); [**3**-H·DB24C8]·PF_6 (4%), **3**-H·PF_6 (1%).

The same equilibrium proportions of these six species can be reached—but much more quickly—in 2125 min (Figure 3) when DB24C8 is present in the reaction mixture from

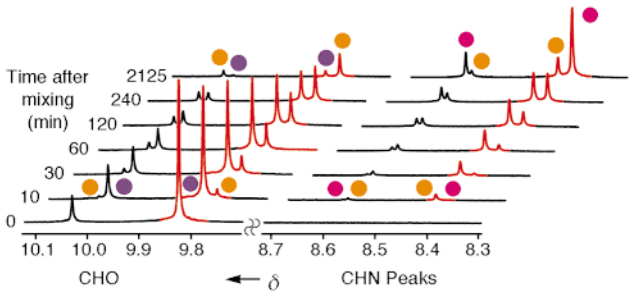

Figure 3. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 300 K), recorded over time, of an initial mixture of **3**-H·PF_6 (20 mM), 3,5-di-*tert*-butylaniline (40 mM), and DB24C8 (20 mM). Peaks corresponding to species containing an NH_2^+ center not bound/occupied by a DB24C8 ring are represented in black while those which are bound/occupied are represented in red. The resonances associated with the dialdehyde, monoaldehyde, and diimine probe protons are highlighted as described in Figure 1.

the outset. This observation is yet another indication that thermodynamic control is operating in this system, as the same equilibrium composition is being reached, irrespective of the starting point of the reaction. By utilizing the secondary dialkylammonium ion/crown ether recognition motif to bring about the noncovalent synthesis of a [2]-pseudorotaxane, in conjunction with reversible imine bond formation to stopper covalently the [2]pseudorotaxane and produce a dynamic [2]rotaxane, we have demonstrated that thermodynamic control can be used in the construction of interlocked molecular compounds that are wholly organic in nature. A high degree of control of superstructure and structure can be envisaged in such "slowly" equilibrating systems. For example, in Scheme 2, by judiciously altering solvent polarities,[16] the equilibria in the "vertical" direction

(15) Although by no means quantitative, the positive-ion FAB mass spectrum of this equilibrium mixture tallies approximately with the ratios of the components observed by ^{1}H NMR spectroscopy in solution. The intensities of the signals in the mass spectrum, corresponding to [**5**-H·DB24C8]$^+$:**5**-H^+:[**4**-H·DB24C8]$^+$:**4**-H^+, occur in the ratio 100:32:11:5. Signals are not observed for the minor solution components, namely [**3**-H·DB24C8]$^+$ and **3**-H^+, respectively.

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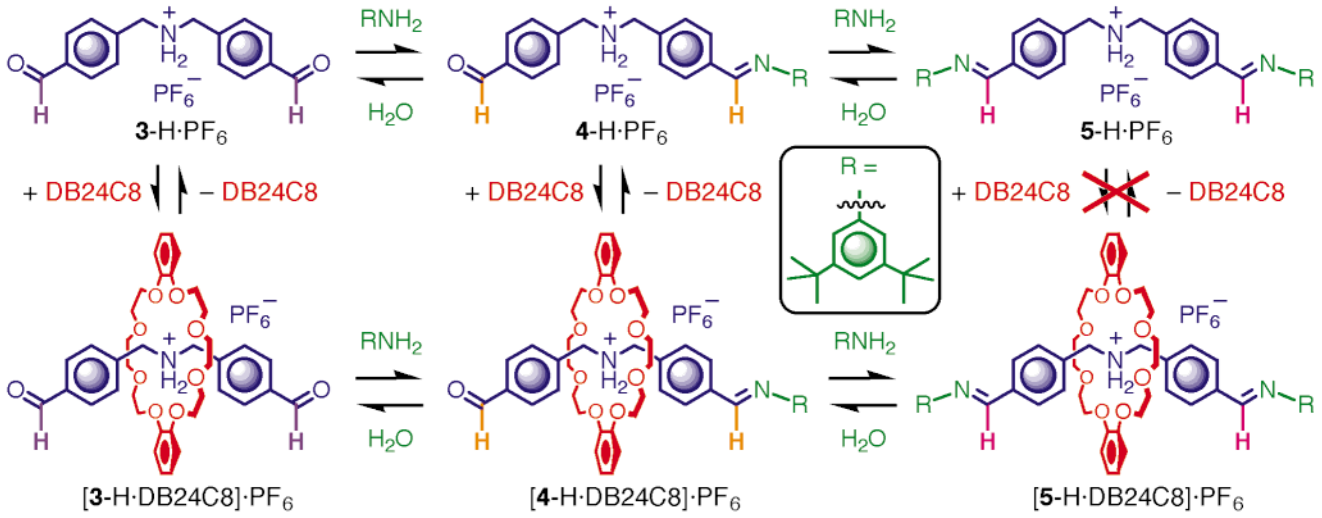
Scheme 2 Dynamic Equilibrium Established upon Dissolution of a 1:2:1 Ratio (20:40:20 mM) of **3**-H·PF_6, 3,5-Di-*tert*-butylaniline, and DB24C8 in CD_3CN



could be controlled, while removal of water from the reaction mixture should shift the equilibria in the "horizontal" direction toward diimine formation. Thereafter, a "fast" reduction of the imine bonds would give kinetically stable products and, in so doing, "fix" the [2]rotaxane. Indeed, initial investigations on the "fixing" of this system—involving reduction of the imine functions—are encouraging. Treatment of an equilibrated mixture of **3**-H·PF_6, 3,5-di-*tert*-butylaniline, and DB24C8 in a CH_2Cl_2 solution with PhSeH[17] affords[18] the "fixed" [2]rotaxane **6**-H·PF_6.

Although kinetic approaches[19] have so far dominated the syntheses of interlocked molecular compounds with wholly organic constitutions, strategies involving thermodynamic control[20] are now set to challenge that domination. Such a seed change in synthetic strategy is one that could lead to much more efficient routes, not only to rotaxanes and catenanes but also to their macromolecular counterparts.[21]

Acknowledgment. We thank UCLA for generous financial support.

Supporting Information Available: Experimental procedures for **2** and **3**-H·PF_6 and ^{1}H and ^{13}C NMR spectroscopic and FAB mass spectrometric data for **2**, **3**-H·PF_6, and **6**-H·PF_6. This material is available free of charge via the Internet at http://pubs.acs.org.

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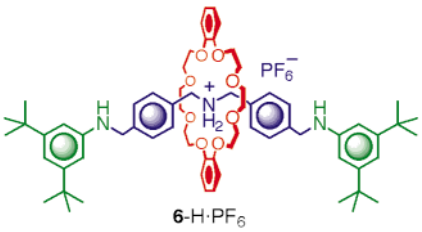
(17) Fujimori, K.; Yoshimoto, H.; Oae, S. *Tetrahedron Lett.* **1980**, *21*, 3385−3388.

(18) An excess of PhSeH (1.0 g, 6.4 mmol) was added to an equilibrated (ca. 3 d stirring under ambient conditions) mixture of **3**-H·PF_6 (0.25 g, 0.6 mmol), DB24C8 (0.56 g, 1.3 mmol) and 3,5-di-*tert*-butylaniline in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred for 4 d under ambient conditions, before being poured into Et_2O (500 mL). A white solid was recovered upon filtration and subjected to column chromatography (SiO_2: CH_2Cl_2, then CH_2Cl_2/MeOH, 99:1). Although fractions containing the "fixed" [2]rotaxane as the major product were collected, DB24C8 coelutes from the column with this compound, accounting for ∼10% (by mass) of the isolated white solid, as determined by ^{1}H NMR spectroscopy. On the basis of the ^{1}H NMR spectrum, the yield for the conversion of **3**-H·PF_6 into **6**-H·PF_6 was calculated to be 18%.



Selected data for **6**-H·PF_6: ^{1}H NMR (400 MHz, CD_2Cl_2, 300 K) δ = 1.25 (s, 36H), 3.48 (s, 8H), 3.73−3.77 (m, 8H), 4.04−4.09 (m, 8H), 4.25 (s, 4H), 4.60−4, 65 (m, 4H), 6.45 (d, J = 1.6 Hz, 4H), 6.75−6.80 (m, 6H), 6.88−6.94 (m, 4H), 7.22 (AA′ of AA′BB′ system, J = 8.0 Hz, 4H), 7.29 (BB′ of AA′BB′ system, J = 8.0 Hz, 4H), 7.57 (br s, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2, 300 K) δ = 31.7, 35.2, 48.3, 52.9, 68.6, 70.8, 71.3, 108.1, 112.7, 113.2, 118.1, 122.1, 128.2, 129.9, 131.0, 142.1, 148.1, 152.3; MS (FAB) m/z = 1081 [M − PF_6]$^+$.

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(21) Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, 99, 1643−1663.