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An Approach to Thermodynamically Controlled Supramolecular Assembly Possessing an Integral Locking Mechanism

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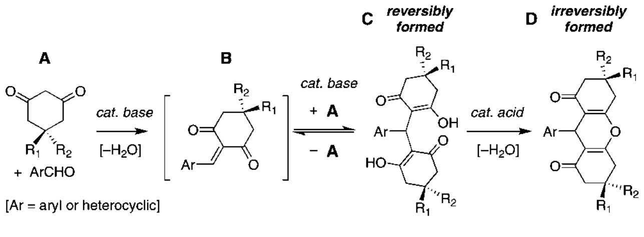
The power of template−directed synthesis under thermodynamic control has been harnessed for the efficient preparation of intricate,[1] and sometimes unexpected,[2] molecular structures. Such efficiencies are the result of the error−correcting nature of reversible covalent bond forming reactions; non−optimal bonds are cleaved and the components recycled toward an energetic structural minimum.[3] A number of reactions have been explored in establishing this field—dynamic combinatorial chemistry (DCC)[4]—arguably the most valuable of which provide a means for switching off reversibility and thereby locking-in a thermodynamically mandated structure. For example, imine exchange may be terminated via C═N reduction while processes involving olefin, disulfide, and hydrazide linkages are shut down by catalyst removal.[4] We describe here the application to a supramolecular assembly process of a reversible carbonyl chemistry-based reaction that additionally provides the facility, via a subsequent irreversible dehydration, to permanently fix an evolved molecular structure.[5] This approach, by nature of its derivation from familiar reactions and the application of simple base or acid catalysis, has potentially broad general utility.

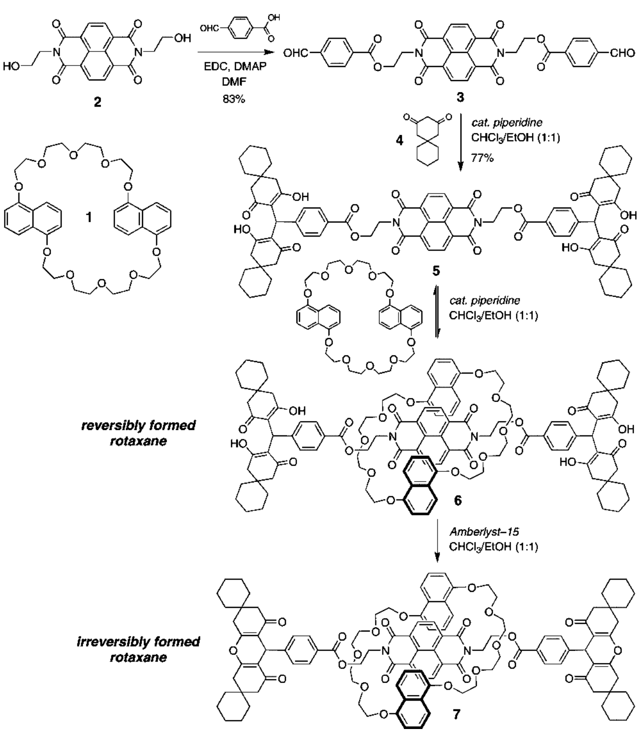
The addition of 2 equiv of a cyclic 1,3-diketone to aromatic aldehydes has been known for over 100 years[6] and has broad structural and functional tolerance (Scheme 1). From a supramolecular perspective this process offers a ready means of converting a small molecular entity (an aldehyde) into one of considerably greater bulk, an attractive overall conversion with regard to, for example, rotaxane synthesis. While the first addition of 1,3-diketone **A** is irreversible, forming, after dehydration, Michael adduct **B**, the second addition has been shown to be reversible under conditions of base catalysis.[5,7] Treatment of the resulting adducts **C**[8] with catalytic acid triggers a locking mechanism whereby a dehydrative cyclization affords adduct **D**.[5] The overall sequence of events is thus ideally suited to reversible supramolecular assembly processes: noncovalent interactions may be harnessed under conditions of base catalysis to direct formation of an energy minimized structure, with subsequent treatment with acid locking the assembled structure in place.

For a demonstration of rotaxane preparation we turned to a well established donor/acceptor supramolecular pairing: electron deficient naphthalene diimides (NDIs) and electron rich aromatic diethers.[9] A dinaphtho crown macrocycle **1**, incorporating two of the latter units, is a well-established component of numerous diimide based rotaxanes[10] and was prepared according to literature procedures.[11]

Scheme 1. Reversible and Irreversible Processes in Adduct Formation from Aromatic Aldehydes and Cyclic 1,3−Diketones



Scheme 2. Rotaxane Formation and Locking Strategy



Aromatic aldehyde termini were introduced to a suitable thread by the coupling of 4-formylbenzoic acid to an NDI-diol **2**[12] to form dialdehyde **3** (Scheme 2), while considerable thought was given to the selection of the cyclic 1,3-diketone component. Spirodiketone **4** (available in two steps from cyclohexanone[13]) was ultimately selected for its steric bulk, as the stoppered termini of thread **5** were predicted to be too large to pass through the macrocyclic cavity of crown **1**, and ability to confer excellent solubility characteristics. Stoppered thread **5** was formed in high yield from the piperidine-catalyzed reaction of **3** with 4 equiv of spirodiketone **4**.

To confirm the existence of the necessary steric barriers to rotaxane formation from the free stoppered thread **5** and crown **1** a 1:1 solution of these two components in $CDCl_3$ (10 mM in each) was maintained at 50 °C for 48 h. Comparison of the downfield regions of the ^1H NMR spectra of thread **5** (Figure 1a) and the 1:1 mixture recorded 1 h after mixing (Figure 1b) reveals negligible shifts of the key aromatic resonances. The composite nature of this spectrum was unchanged after 48 h.[14]

According to the strategy outlined in Schemes 1 and 2 addition of catalytic base to equimolar solutions of stoppered thread **5** and crown **1** should allow rotaxane formation: the driving force for assembly is provided by the energetically favorable interaction of π-rich and π-poor aromatic units, while base-catalyzed loss/addition of 1,3-diketone units from the thread will establish the equilibrium concentration of less sterically encumbered termini (form **B**) required for theading.

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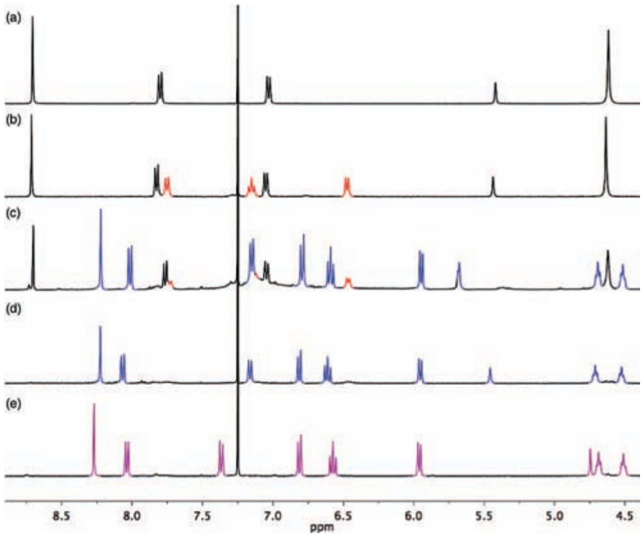

Figure 1. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$): (a) thread **5** (black); (b) 1:1 mix of crown **1** (red) and thread **5** (48 h, 50 °C); (c) 1:1 mix of crown **1** and thread **5** (48 h, cat. piperidine, 50 °C), rotaxane **6** (blue); (d) pure rotaxane **6**; (e) pure rotaxane **7** (purple).

Addition of catalytic piperidine to a 10 mM solution of **1** and **5** in $CHCl_3$/EtOH (1:1, 50 °C) prompted the gradual establishment of a red solution coloration. The ^{1}H NMR spectrum recorded after 48 h (Figure 1c) reveals features attributable to the predicted rotaxane **6**, alongside remaining crown **1** and thread **5**. Two NDI-proton resonances are now apparent, one for the free thread **5** (8.71 ppm), the other shifted upfield (8.23 ppm): integration reveals a 3:5 ratio, corresponding to a yield of rotaxane of around 60%.[15,16] The spectrum of the pure rotaxane **6** (Figure 1d), obtained in 52% isolated yield, reveals upfield shifts of the naphthalene diether protons consistent with the cofacial orientation of the aromatic platforms in the rotaxane. While the OCH_2 and NCH_2 resonances of thread **5** are coincident they are rendered distinct in the rotaxane (4.71, 4.52 ppm); small downfield shifts of the *p*-phenylene resonances of **5** are also apparent upon rotaxane formation. The signature resonance of the methine proton at the juncture of the two diketone units is essentially unchanged from thread **5** (5.42 ppm) to rotaxane **6** (5.46 ppm).[17] Integration confirms the expected 1:1 crown to thread stoichiometry, while the detection of NOEs between the OCH_2 and NCH_2 resonances of the thread and aromatic protons of the crown confirms their proximity in the rotaxane structure. Finally, heating of a $CDCl_3$ solution of rotaxane **6** at 50 °C for 4 days left the material unchanged. No dissociation into **1** and **5** was observed thereby confirming that under these conditions the stoppers are serving their designated function.[18]

Though stable in neutral solution rotaxane **6** remains a system amenable to thermodynamic equilibration in the presence of base.[19] To remove the capacity for base-catalyzed equilibration the final "locking" step in Scheme 2 is necessary. Treatment of a solution of rotaxane **6** in 1:1 $CHCl_3$/EtOH with Amberlyst-15 acid beads (50 °C, 4 h) gave a near quantitative yield of locked rotaxane **7**.[20] Unsurprisingly, rotaxane **7** is spectroscopically similar to the parent **6** (Figure 1e). The sole notable change is the diagnostic shift of the stopper methine proton (from 5.46 to 4.75 ppm).[5] As observed for its thermodynamically assembled precursor, rotaxane **7** is quite stable with respect to dissociation into its component parts. No measureable dissociation to the free thread and crown components was observed after 7 days in neutral, mildly basic, or mildly acidic solution ($CDCl_3$, 20 °C).[21]

The chemistry presented in this communication facilitates the thermodynamic assembly of substantial structures in rapid, highly modular, and adaptable fashion. For example, the tuning of stopper dimensions that would be required for other macrocycle/thread pairings could be accomplished through the use of alternatively substituted 1,3-diketones. Alternatively, one could imagine employing this addition chemistry as a macrocyclization reaction, or as a means to establish libraries of adducts from a pool of aldehydes and diketones.[22] Finally, the dehydrative locking chemistry may be conducted in the presence of amines to form, in high yield, fluorescent acridone diones.[5,20] The inclusion of linear diamines here would thus open a route to polymeric systems, including polyrotaxanes. These and other avenues are under investigation.

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Supporting Information Available: Preparative procedures and spectroscopic details for **3**, **5**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Nor did the solution of **5** and **1** exhibit the red color that is the hallmark of inclusion complex formation between these π-rich/poor aromatic cores. Such colors, resulting from the presence of a charge transfer absorption, are ubiquitous features of systems that establish stable cofacial arrangements of these components (see refs 9−11).
(15) This yield is in accord with those for related systems (see ref 10a and references therein) and did not increase with extended reaction times.
(16) A comparable yield of rotaxane **6** was also obtained via thermodynamic assembly of a 1:1:4 ratio of crown **1**, thread **3**, and spirodiketone **4** ($CHCl_3$/EtOH, cat. piperidine, 50 °C, 48 h).
(17) The downfield shifts of the thread **5** and rotaxane **6** methine protons (Figure 1c) are the result of the presence of catalytic base (see Supporting information).
(18) This experiment is the reverse of that detailed in Figure 1b. Neither of these experiments precludes the possibility of association/dissociation at far higher temperatures or over far longer time periods.
(19) Accordingly, treatment of a solution of **6** in $CDCl_3$/C_2D_5OD (10mM, 1:1) with piperidine re-established (50 °C, 48 h), within the limits provided by ^{1}H NMR signal integration, the equilibrium concentrations of rotaxane **6** (approx 60%) and free components **1** and **5** (approx 40%).
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(21) Partial dissociation was detected after heating for 3 days at higher temperature ($CDCl_3$, 50 °C) with ^{1}H NMR signal integration indicating around 10% loss of the interlocked rotaxane structure. Irreversibly formed adducts of form **D** (Scheme 1) are around 8% smaller (in their longest dimension) than the parent (reversibly formed) adducts **C** (ref 5) and this change is sufficient to allow partial dissociation of **7** versus **6**.
(22) Libraries of macrocycles (hosts) and guests could thus be established, both of which should prove amenable to templating effects: for macrocycles, their ability to bind to a static guest, for guests, their ability to adapt their shape to a static host.

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