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Equilibrating Dynamic [2]Rotaxanes

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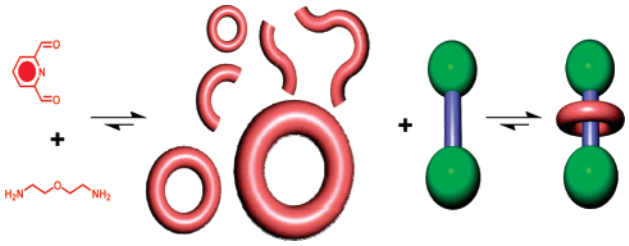

Upon mixing and dehydration, 2,6-diformylpyridine and 2,2′-oxybis(ethylamine) form a dynamic combinatorial library of at least nine members. Through hydrogen bonding and other intermolecular interactions, templating dumbbell molecules select one macrocyclic member of the library, at the expense of all the others, to create [2]rotaxanes. These rotaxanes, however, retain the dynamic character of the library, since a diformylpyridine analogue can exchange with the macrocyclic component in solution. In addition, crystallization of the mixture surprisingly furnishes only the [24]crown-8-like macrocycle on its own—evidence of a kinetic selection process occurring between phase transitions.

Introduction

In recent years, interest in rotaxanes[1] has been aroused by the fact that bistable analogues have been shown[2] to undergo switching of a mechanical nature. While bistable [2]rotaxanes, based on donor/acceptor recognition motifs, have found applications in molecular electronics[3] and in nanoelectromechanical systems[4] (NEMS) as redox-controllable switches and actuators, those[5] in which hydrogen bonding is the main source of the intercomponent recognition have given rise to linear molecular motors where the ring on the dumbbell of a [2]rotaxane is driven back and forth between two different recognition sites either by changes in pH[6] or by irradiation with light.[7]

Since the first reports of a [2]rotaxane by Harrison and Harrison[8] in 1967, the synthesis of these mechanically interlocked molecules has burgeoned, thanks to the roles that molecular recognition[9] and self-assembly[10] have played in the template-directed synthesis[11] of [2]rotaxanes. The first methods that were developed[12] under kinetic control involved either (1) threading of a rod by a ring, followed by stoppering both ends

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of the rod or (2) clipping of a ring onto an already preformed dumbbell compound. Subsequently, another approach—namely slippage[13]—became a popular thermodynamically controlled way of making rotaxanes. Then, with the advent[14] of dynamic covalent chemistry (DCC), we have seen the rapid emergence of thermodynamically controlled ways of threading-followed-by-stoppering and clipping for the efficient template-directed[11] synthesis of [2]rotaxanes. DCC relies upon the use of covalent bonds that form in a reversible manner. Common dynamic (reversible) reactions exploited in such synthesis include olefin metathesis,[15] the opening and closing of disulfide linkages,[16] and imine formation from mixtures of aldehydes and amines.[17,18] Imine formation has been reported, not only in the threading-followed-by-stoppering approach,[17] but also in the clipping approach[18] to the synthesis of [2]rotaxanes, and higher order rotaxanes. Indeed, imine formation is finding applications in chemical biology,[19] surface science,[20] and polymer chemistry,[21]

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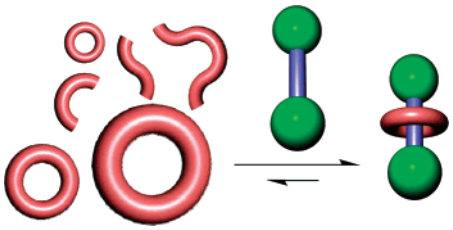
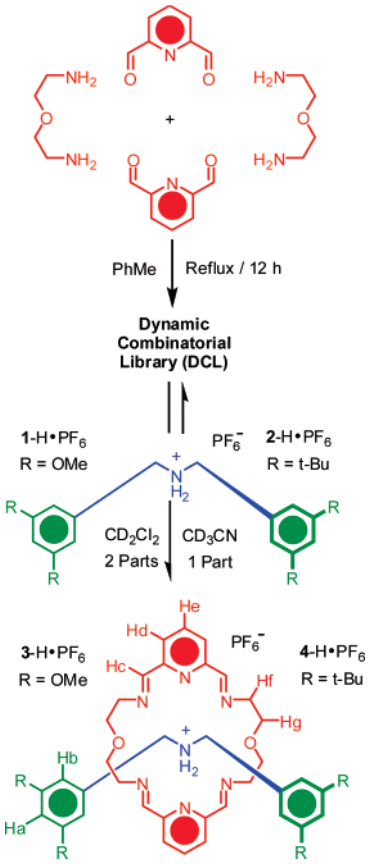
SCHEME 1. Graphical Representation of the Strategy Employed in the Template-Directed Synthesis of a [2]Rotaxane from a DCL



SCHEME 2. Molecular Structures and Reaction Conditions for DCL Formation and the Subsequent Template-Directed Amplification of the [2 + 2]Macrocycle To Afford, Using Templates 1-H·PF_6 and 2-H·PF_6, the Dynamic [2]Rotaxanes 3-H·PF_6 and 4-H·PF_6



as well as in the synthesis of hemicarcerands,[22] molecular Borromean rings,[23] and molecular Solomon knots[24]—compounds that are otherwise close to inaccessible by more traditional pathways.

In this paper, we describe how equilibrating dynamic [2]rotaxanes can be formed quite expeditiously by dialkylammonium ion templates being present (Scheme 1), as the incipient

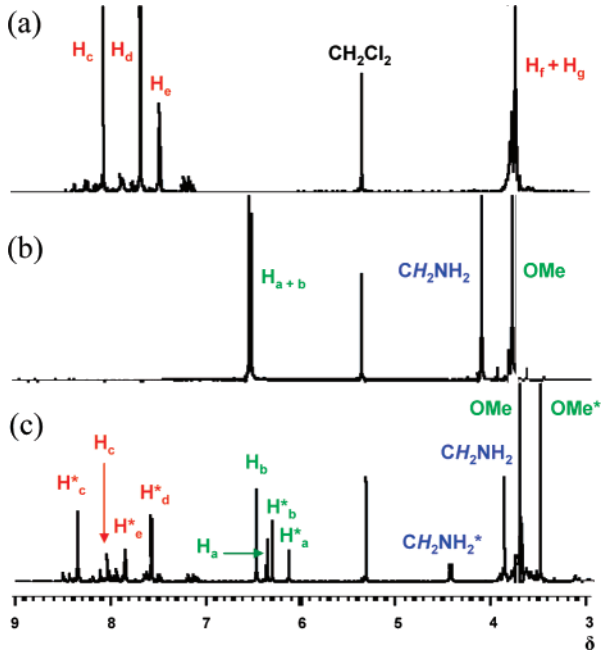


FIGURE 1. ^{1}H NMR spectra of (a) the DCL, (b) the dumbbell compound **1**-H·PF_6, and (c) the mixture containing the [2]rotaxane **3**-H·PF_6. Peaks marked with an asterisk (*) pertain to the rotaxane, whereas the others relate to signals for protons in uncomplexed species. Protons are defined in Scheme 2.

dumbbell-shaped components, in a dynamic combinatorial library (DCL) of equilibrating cyclic and acyclic oligoimines. The well-known[5b−g] [24]crown-8/dialkylammonium ion recognition motif was chosen as the driving force based on the template centrally located in the dumbbell-shaped compounds. The equilibrating dynamic [2]rotaxanes have been characterized by electrospray ion (ESI) mass spectrometry and ^{1}H NMR spectroscopy.

Results and Discussion

The DCL of equilibrating cyclic and acyclic oligoimines was established (Scheme 2) by heating 2,2′-oxybis(ethylamine) and 2,6-diformylpyridine together under reflux in PhMe for 12 h. Although, after evaporation of the solvent (PhMe), the resulting DCL afforded a deceptively simple ^{1}H NMR spectrum (Figure 1a), the ESI-MS (Figure 2a) revealed the presence in equilibrium of [2 + 2], [3 + 3], and [4 + 4] macrocycles with peaks at *m*/*z* 407.22, 610.34, and 813.46, respectively, together with evidence for at least six acyclic—hydrolyzed macrocycles—analogues of the homologous series of macrocycles. All other attempts we made to try and characterize the DCL by, for example, the separation of components by high-performance liquid chromatography were unsuccessful because of the rapid equilibration of the components of the DCL on chromatography columns.

When two different templates—namely **1**-H·PF_6[18] and **2**-H·PF_6[25]—were added directly to the DCL in CD_2Cl_2/CD_3CN

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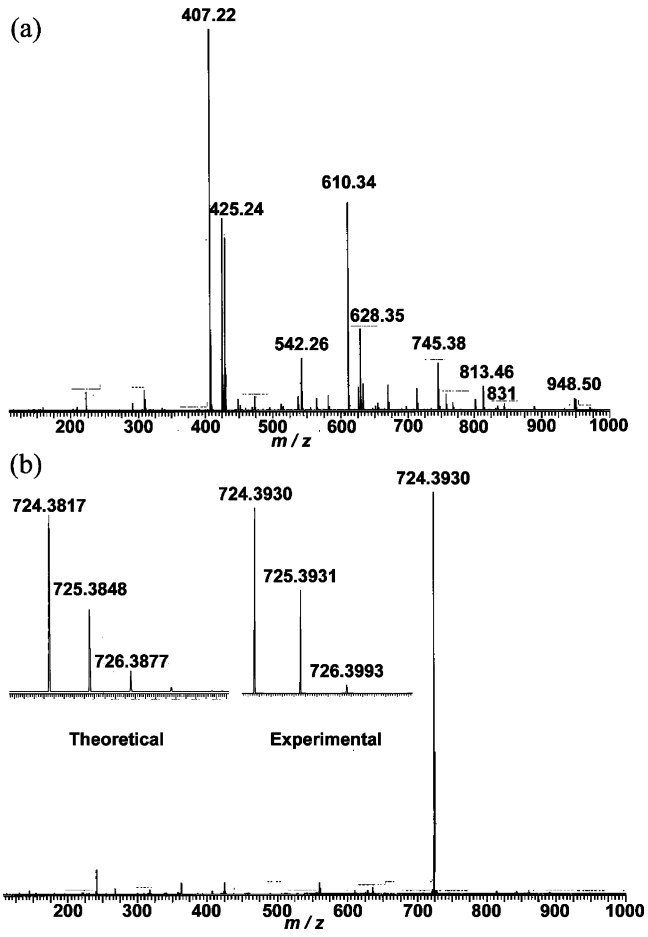
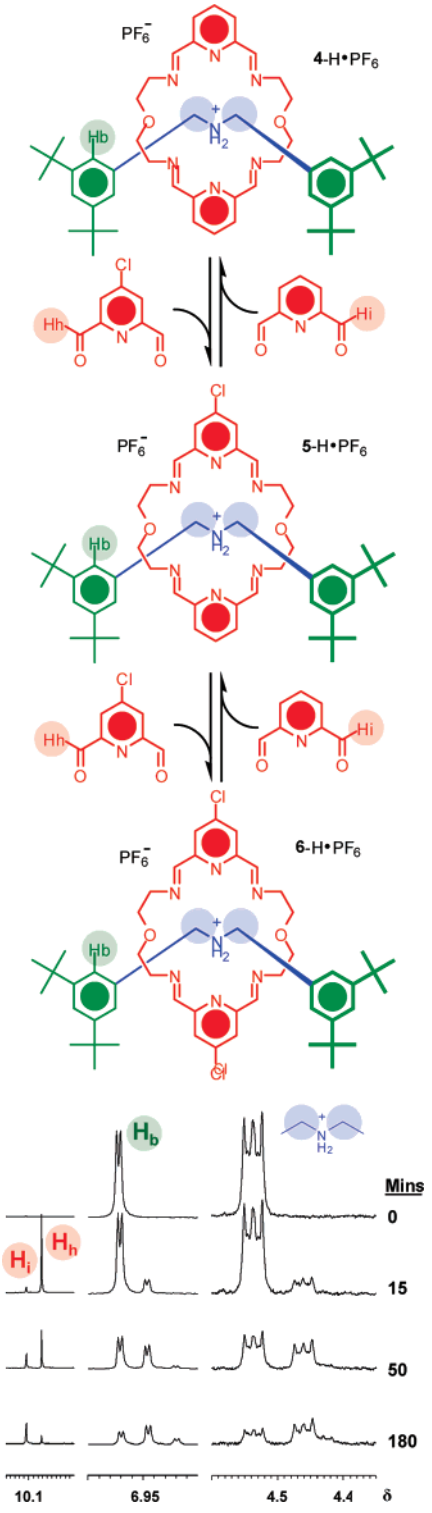


FIGURE 2. ESI mass spectra of (a) the DCL and (b) the [2]rotaxane **3**-H·PF_6. The inset shows both the theoretical and experimental isotope distributions.

(2:1), the [2]rotaxanes **3**-H·PF_6 and **4**-H·PF_6 were formed, respectively, within minutes.[26] The high-resolution ESI-MS (Figure 2b) provides a compelling argument for the formation of **3**-H^+, since only one major peak was observed at *m*/*z* 724.3930 for its M^+ ion in the crude reaction mixture. The ^{1}H NMR spectrum, however, of this same reaction mixture indicated (Figure 1c) the presence of free template **1**-H·PF_6 and free DCL, in addition to the [2]rotaxane **3**-H·PF_6, all undergoing slow exchange with each other on the ^{1}H NMR time scale at 500 MHz. Of particular note in the spectrum are the resonances centered on δ 4.45 ppm for the benzylic methylene protons in the dumbbell-shaped component of the [2]rotaxane: they are shifted downfield by 0·35 ppm from those arising from the free dumbbell compound **1**-H·PF_6. When **2**-H·PF_6 was employed as the template in the formation of the [2]rotaxane **4**-H·PF_6, the same sequence of events occurred, as indicated by ^{1}H NMR spectroscopy performed in CD_2Cl_2/CD_3CN (2:1). When 2 equiv of 4-chloro-2,6-diformylpyridine were added to this reaction mixture, the dynamic nature of the imine bond formation and

SCHEME 3. A Dynamic Imine-Exchange Experiment with 4-Chloro-2,6-diformylpyridine and the [2]Rotaxane 4-H·PF_6[a]



[a] ^{1}H NMR spectroscopy reveals the emergence of new peaks corresponding to **5**-H·PF_6 and **6**-H·PF_6 with time.

hydrolysis became immediately evident in the ^{1}H NMR spectra (Scheme 3) with the progress of time. During a 3-h period at ambient temperature, not only did three sets of multiplets appear in the region δ 4.40−4.60, attributable to benzylic methylene protons in three different [2]rotaxanes **4**-H·PF_6−**6**-H·PF_6, but also three peaks were observed in the vicinity of δ 7.0 ppm for

(25) Nabeshima, T.; Nishida, D.; Saiki, T. *Tetrahedron* **2003**, *59*, 639−647.

(26) When **1**-H·PF_6 was added to a mixture of 2,6-diformylpyridine and 2,2′-oxybis(ethylamine), **3**-H·PF_6 was also formed according to ^{1}H NMR spectroscopy and ESI mass spectrometry. However, the results depended heavily upon the concentration of 2,2′-oxybis(ethylamine) and hence no two experiments produced exactly the same results. The diamine is basic enough to deprotonate the dumbbell, and hence turn off recognition.

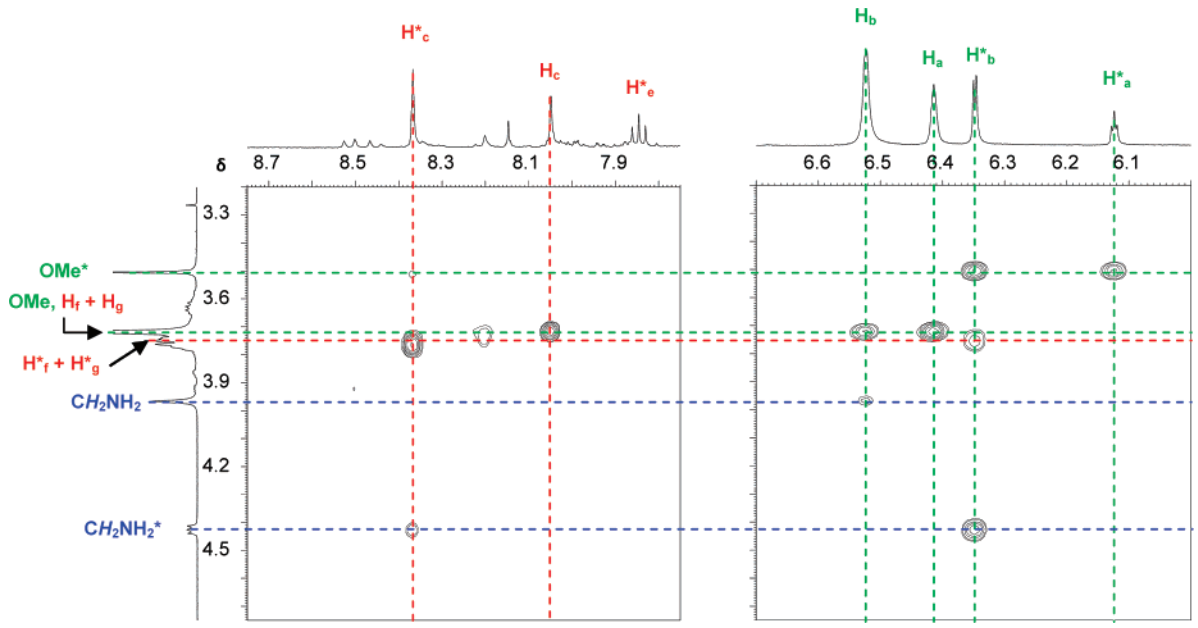


FIGURE 3. A 2D-NOESY spectrum of the crude reaction mixture containing **1**-H·PF_6, the DCL, and **3**-H·PF_6. Peaks corresponding to the [2]rotaxane **3**-H·PF_6 are labeled with an asterisk (*). All other peaks correlate with "free" species.

Hb on the dumbbell's stoppers. These observations were supported by two separate signals for formyl protons present in 4-chloro-2,6-diformylpyridine and 2,6-diformylpyrdine. The ratio of the [2]rotaxanes **4**-H·PF_6, **5**-H·PF_6, and **6**-H·PF_6 is approximately 2:3:1 at equilibrium. The results demonstrate the modularity of DCC.

Further evidence for the equilibrating dynamic [2]rotaxanes **3**-H·PF_6 and **4**-H·PF_6 was obtained from a painstaking analysis of the two-dimensional NOESY ^{1}H NMR spectra of **3**-H·PF_6 (Figure 3). Cross-peaks arising from protons in the macrocycle and dumbbell-shaped components of **3**-H·PF_6 support the fact that it is a [2]rotaxane, albeit a rather elusive dynamic one. For example, the imine protons Hc on the macrocycle show strong NOEs with the OMe and benzylic methylene protons in the dumbbell. The aromatic protons Hb in the dumbbell component also show cross-peaks with Hf and Hg in the [2 + 2]macrocycle. All protons in the "free" species show cross-peaks only with neighboring protons on the same molecules. Symmetry considerations applied to the two-dimensional NOESY ^{1}H NMR spectra are consistent with a threaded species, i.e., **3**-H·PF_6, as opposed to, for example, a face-to-face complex between **1**-H·PF_6 and the [2 + 2] macrocycle. If the species were not interlocked, the dumbbell component of the complex would no longer be in a symmetrical environment, and more peaks (and cross-peaks) would arise in the NMR spectra.

Since the [2]rotaxanes **3**-H·PF_6 and **4**-H·PF_6 exist in dynamic equilibria in solution with their "free" components, it is possible to determine effective association constants between complexed and "free" species. Integration in the ^{1}H NMR spectra of signals for probe protons associated with the [2]rotaxane **4**-H·PF_6 and its precursor dumbbell compound **2**-H·PF_6 led to the association constant (K_{eff}) for the formation of **4**-H·PF_6 from **2**-H·PF_6 and the DCL of around 340 mol^{-1} in CD_3CN solution at room temperature. This K_{eff} value is consistent with previous measurements performed on related dynamic rotaxanes. When ^{1}H NMR spectra were recorded (see the Supporting Information) over a considerable temperature range, it became evident that the equilibrium shifts gradually upon cooling toward the [2]rotaxane at the expense of the dumbbell compound and the DCL. From the calculated change in entropy (ΔS) of 29 ± 1.6 J mol^{-1} K^{-1} and the calculated change in enthalpy (ΔH) of −23 ± 1.6 kJ mol^{-1} (errors estimated from the fit of ln(K_{eff}) vs 1/T), we conclude that the formation of **4**-H·PF_6 from **2**-H·PF_6 and the DCL is an enthalpy-driven process.

Yet another observation sheds light on the nature of these equilibrating dynamic [2]rotaxanes. When an attempt was made to crystallize **3**-H·PF_6 by slow vapor diffusion of *i*-Pr_2O into the crude, equilibrating mixture of the [2]rotaxane, **3**-H·PF_6, and the DCL dissolved in CH_2Cl_2/MeOH (2:1), the crystals that were isolated did not contain the dumbbell component of the [2]rotaxane, but rather the free [24]crown-8 macrocycle, as indicated by a single-crystal X-ray diffraction analysis.[27,28] The crystalline product (Figure 4) turned out to be that of the free [24]crown-8 derivative with no solvent trapped inside the macrocycle. Beyond the molecule itself, no hydrogen bonding or $\pi-\pi$ stacking interactions were evident. The free macrocycle exhibits C_{2h} symmetry with a length of over 10.9 Å and a plane-to-plane separation between the two pyridine rings of just under 5.33 Å. All efforts to crystallize any component of the DCL without the presence of a template were unsuccessful. In essence, this outcome is suggestive of the fact that the dialkylammonium

(27) Crystal data for $C_{22}H_{26}N_6O_2$: monoclinic, a = 7.3056(14) Å, b = 9.6015(18) Å, c = 15.749(3) Å, β = 101.937(3)°, V = 1080.8(4) Å^3, space group $P2_1/c$, Z = 2, ρ_{calcd} = 1.249 g cm^{-3}, μ(Mo Kα) = 0.084 mm^{-1}, F(000) = 432, T = 100(2) K, 5317 reflections measured ($2\theta_{max}$ = 52.82°), 2166 unique. Final R factors: R_1 = 0.0677, wR_2 = 0.1122 for all reflections and 136 parameters.

(28) Single crystals of $C_{22}H_{26}N_6O_2$, suitable for X-ray crystallography, were obtained by vapor diffusion of (*i*-Pr)$_2$O into the crude reaction mixture of the DCL, **1**-H·PF_6, and **3**-H·PF_6. The crystals were mounted in inert oil and the diffraction data were collected at low temperature on a CCD X-ray diffractometer. CCDC-635863 contains the supplementary crystallographic data for this crystalline compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

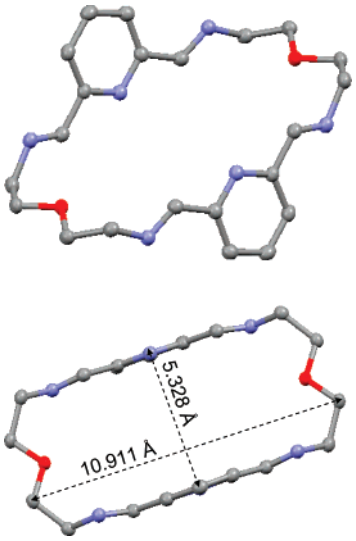


FIGURE 4. Solid-state structure of the [2 + 2] macrocyclic member of the DCL.

ion serves to amplify the production of the macrocycle before departing the scene during the kinetically controlled crystallization process.[29] The vagaries of obtaining X-ray quality single crystals from a thermodynamically equilibrating mixture of species in solution is certainly a phenomenon that continues to provide surprises, insofar as it is often a minor component present in the solution that chooses to crystallize.

Conclusions

The synthesis of a couple of equilibrating dynamic [2]-rotaxanes from a DCL of acyclic and cyclic components, from which one particular macrocyclic component is amplified in the presence of dumbbell components, is not in dispute as judged by mass spectrometry and ^{1}H NMR spectroscopy. Nonetheless, these [2]rotaxanes are willing, on account of the four imine bonds present in their macrocyclic components, to witness this component swap one dialdehyde building block in the macrocycle for another in solution and cast off the macrocycle altogether during the crystallization process. The solution state provides an environment where thermodynamic traps operate whereas entry from the solution into the solid state can and does introduce a kinetic trap. The combination of a dynamic combinatorial library with DCC renders synthesis a highly adaptive pursuit wherein the environment surrounding the chemistry dictates the eventual outcome in a reasonably predictive manner, as long as phase changes are avoided. The challenge remains for the synthetic chemist to be able to predict and control the nature of the product(s) when a phase change occurs in relation to an equilibrium situation. Nonequilibrium states, such as this one, require further fundamental and intensive investigation.

(29) In several attempts to kinetically trap the [2]rotaxanes in a different way, namely, reduction, the only products successfully isolated were the non-interlocked dumbbell and reduced [24]crown-8-like macrocycle. Spectroscopic evidence indicates that borohydride reducing agents deprotonate the dumbbell, destroying the recognition element and hence the [2]rotaxane architecture. Unfortunately, non-basic reducing agents did not react with the substrate.

Experimental Section

General. All commercial reagents and starting materials were used without further purification. Dumbbells **1**-H·PF_6[18] and **2**-H·PF_6[25] were synthesized according to literature procedures. Deuterated solvents for NMR spectroscopic analyses were used as received. Unless otherwise noted, all NMR spectra were recorded at room temperature in a 2:1 mixture of CD_2Cl_2:CD_3CN on a 500 MHz spectrometer, with a working frequency of 500.13 MHz for ^{1}H nuclei. The residual solvent peak for CD_3CN at 1.93 ppm was taken as a reference. High-resolution ESI mass spectra were recorded on a 7T FTICR instrument.

Synthesis of the Dynamic Combinatorial Library (DCL). 2,6-Diformylpyridine (973 mg, 7.20 mmol) and 2,2′-oxybis-(ethylamine) (750 mg, 7.20 mmol) were heated under reflux in 150 mL of PhMe under Dean−Stark conditions overnight. The crude reaction mixture was cooled and filtered and the solvent was evaporated to furnish 1.456 g (99%) of the DCL as a brown solid that was used directly in the synthesis of [2]rotaxanes without further purification. The ^{1}H NMR spectrum is shown in Figure 2a. The high-resolution ESI mass spectrum is shown in Figure 3a.

General Synthesis of Rotaxanes. An appropriate dumbbell compound (0.01 mmol) in CD_2Cl_2 (0.30 mL) and CD_3CN (0.15 mL) was added to the DCL (0.01 mmol) in CD_2Cl_2 (0.30 mL) and CD_3CN (0.15 mL). The reaction was followed by ^{1}H NMR spectroscopy.

3-H·PF_6: The ^{1}H NMR spectrum recorded from a mixture that also included the DCL and **1**-H·PF_6: δ 9.92−9.84 (br s, 2H), 8.37 (s, 4H), 7.88 (t, J = 7.8 Hz, 2H), 7.60 (d, J = 7.8 Hz, 4H), 6.32 (d, J = 2.3 Hz, 4H), 6.15 (t, J = 2.3 Hz, 2H), 4.45 (m, 4H), 3.80−3.69 (m, 16H), 3.51 (s, 12 H); MS(ESI) m/z calcd for $C_{40}H_{50}N_7O_6$ $[M - PF_6]^+$ 724.3823, found 724.3844.

4-H·PF_6: The ^{1}H NMR spectrum recorded from a mixture that also included the DCL and **2**-H·PF_6: δ 9.95−9.84 (br s, 2H), 8.40 (s, 4H), 7.88 (t, J = 7.8 Hz, 2H), 7.62 (d, J = 7.8 Hz, 4H), 7.17 (t, J = 1.8 Hz, 2H), 6.97 (d, J = 1.8 Hz, 4H), 4.54 (m, 4H), 3.69 (m, 8H), 3.64 (m, 8H), 1.06 (s, 32 H); MS(ESI) m/z calcd for $C_{52}H_{74}N_7O_2$ $[M - PF_6]^+$ 828.5904, found 828.6018.

Acknowledgment. This work was supported through the National Science Foundation. Special thanks to Ivan Aprahamian for his help with 2D ^{1}H NMR spectroscopy.

Supporting Information Available: Experimental details and spectral characterization data of all new compounds, as well as crystal packing and VT ^{1}H NMR spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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