Kinetic versus Thermodynamic Control During the Formation of [2]Rotaxanes by a Dynamic Template-Directed Clipping Process

Matthias Horn, Johannes Ihringer, Peter T. Glink, and J. Fraser Stoddart*[a]

Abstract: A template-directed dynamic clipping procedure has generated a library of nine [2]rotaxanes that have been formed from three dialkylammonium salts—acting as the dumbbell-shaped components—and three dynamic, imino bond-containing, [24]crown-8-like macrocycles—acting as the ring-shaped components—which are themselves assembled from three dialdehydes and one diamine. The rates of formation of these [2]rotaxanes differ dramatically, from minutes to days depending on the choice of dialkylammonium ion and dialdehyde, as do their thermodynamic stabilities. Generally, [2]rotaxanes formed by using 2,6-diformylpyridine as the dialdehyde component, or bis(3,5-bis(trifluoromethyl)benzyl)ammonium hexafluorophosphate as the dumbbell-shaped component, assembled the most rapidly. Those rotaxanes containing this particular electron-deficient dumbbell-shaped unit, or 2,5-diformylfuran units in the macroring, were the most stable thermodynamically. The relative thermodynamic stabilities of all nine of the [2]rotaxanes were determined by competition experiments that were monitored by ^{1}H NMR spectroscopy.

Keywords: crown compounds · dynamic covalent chemistry · rotaxanes · self-assembly · supramolecular chemistry

Introduction

Of late, there has been a flurry of interest[1] in the use of a combination of directed noncovalent interactions (strict self-assembly)[2] and dynamic covalent assembly processes[3] for the preparation of thermodynamically stable complex entities, be they molecular or supramolecular in nature, with high fidelities and handsome degrees of architectural predictability. Only in recent years, however, have the syntheses[4, 5] of mechanically interlocked molecular compounds, such as rotaxanes,[6] and catenanes,[7] been investigated by using dynamic covalent chemistry.[8] Rotaxanes and catenanes are intriguing compounds to construct by this approach because, in most cases, the host–guest complexes—for exmple, pseudorotaxanes[9]—that precede their formation are themselves formed by dynamic noncovalent (i.e., strict self-assembly[2]) processes. Efficient methods for assembling interlocked molecular compounds from acyclic precursors, without the need for external reagents or catalysts, most certainly will simplify their syntheses, which often require significant amounts of tedious kinetic covalent chemistry.[10]

Recently we reported[4j] a simple and effective dynamic procedure for the template-directed synthesis[11] of a [2]rotaxane from acyclic precursors (Scheme 1). It resulted in the formation of a [2]rotaxane by clipping[12] together, through imine bond formation between a diamine and a dialdehyde, the components of its [24]crown-8-like macrocyclic unit around its dialkylammonium ion-containing dumbbell-shaped unit.[13] The NH_2^+ center of the dumbbell-shaped unit serves the dual purposes of templating (through weak acid catalysis) the formation of the imino bonds and stabilizing (through hydrogen bonding) the [2]rotaxane once it is formed. The remarkable efficiency of the process aroused our curiosity and set us on a pathway to try to discover the factors that make this dynamic clipping so effective. In this paper, we describe the effects that the constitutions of the components of the [2]rotaxane have on the kinetic and thermodynamic stabilities of these dynamic [2]rotaxanes.

Results and Discussion

We have assembled a library of [2]rotaxanes from the subunits shown in Scheme 2. The nature of the terminal benzyl stoppering groups of the dumbbell-shaped dialkylammonium ions was varied from π-electron-rich ($\mathbf{D}_{OMe}$)[14] through π-electron-neutral ($\mathbf{D}_{Me}$) to π-electron-deficient ($\mathbf{D}_{CF_3}$). The dialdehyde was varied from 2,6-diformylpyridine (**P**)[15] via isophthalaldehyde (**B**) to 2,5-diformylfuran (**F**)[16]. We chose to keep the nature of the diamine, the tetraethylene glycol

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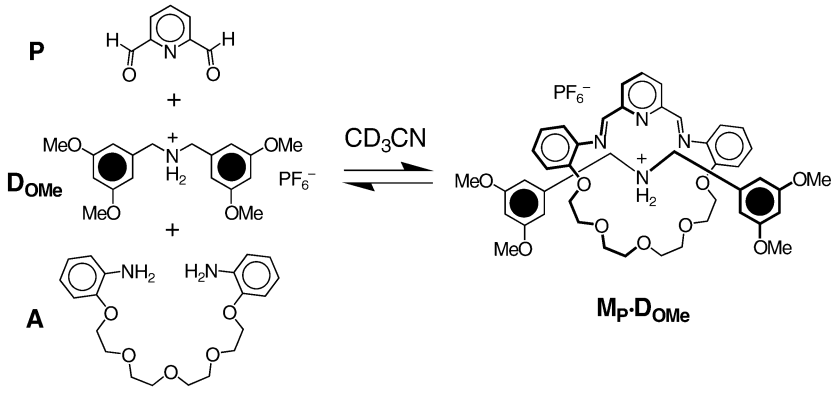
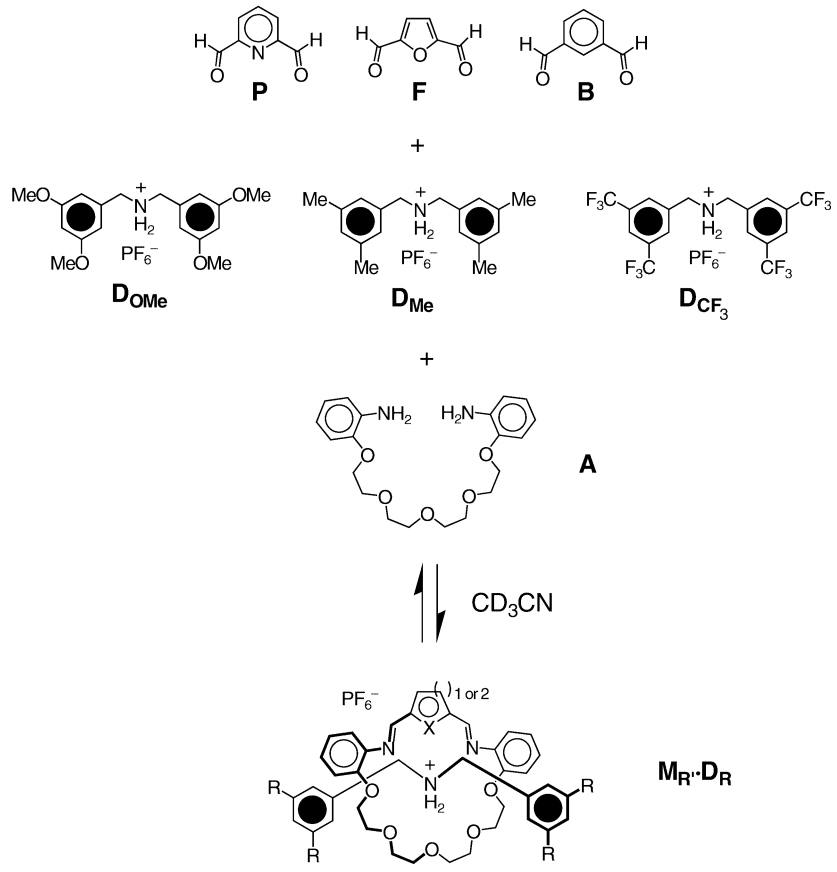


Scheme 1. Synthesis of a [2]rotaxane $\mathbf{M_P \cdot D_{OMe}}$ by clipping of the dialdehyde **P** and the diamine **A** around the dialkylammonium ion $\mathbf{D_{OMe}}$.



Scheme 2. Dynamic syntheses of the [2]rotaxanes $\mathbf{M_{R'} \cdot D_R}$ by clipping of the dialdehydes (**P**, **F**, or **B**) and the diamine **A** around the dialkylammonium ions $\mathbf{D_{OMe}}$, $\mathbf{D_{Me}}$, or $\mathbf{D_{CF_3}}$.

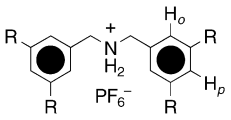
bis(2-aminophenyl)ether **A**,[17] the same in all cases. Through a combination of these three dumbbell-shaped ions, three dialdehydes, and one diamine, a total of nine [2]rotaxanes were assembled dynamically.

Two new dialkylammonium salts, bis(3,5-dimethylbenzyl)-ammonium hexafluorophosphate ($\mathbf{D_{Me}}$) and bis(3,5-bis(trifluoromethyl)benzyl)ammonium hexafluorophosphate ($\mathbf{D_{CF_3}}$) were prepared according to Scheme 3. Condensation of 3,5-dimethylbenzaldehyde with 3,5-dimethylbenzylamine, and of 3,5-bis(trifluoromethyl)-benzaldehyde with 3,5-bis(trifluoromethyl)benzylamine, followed by reduction, acid treatment, and counterion exchange, afforded the dumbbell-shaped dialkylammonium salts $\mathbf{D_{Me}}$ and $\mathbf{D_{CF_3}}$, respectively.

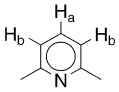
Addition of a dialkylammonium salt ($\mathbf{D_{OMe}}$, $\mathbf{D_{Me}}$, or $\mathbf{D_{CF_3}}$) to a solution of diamine **A** and a dialdehyde (**B**, **F**, or **P**) in CD_3CN (20 mM with respect to each of the three components), followed by a period of equilibration, results in [2]rotaxane formation, as evidenced by ^{1}H NMR spectroscopy and FAB mass spectrometry. New sets of signals are observed by ^{1}H NMR spectroscopy that differ significantly from those of the starting materials or the equilibrated mixture of imines. Significant shifts are observed for the signals of a number of protons of the [2]rotaxanes—relative to those of the corresponding protons of the uncomplexed dialkylammonium ions, dialdehydes, diamine, and imines—with the most characteristic signal being that for the protons of the methylene groups adjacent to the NH_2^+ centers, which appear as singlets between $\delta = 4.10$ and 4.41 when uncomplexed and as second-order multiplets between $\delta = 4.51$ and 5.18 in the rotaxanes (Table 1). Similar downfield shifts and changes in multiplicity pattern for these CH_2N^+ units are characteristic of pseudorotaxanes and rotaxanes formed from dibenzylammonium ions and DB24C8 (see, for example, ref. [13g]). That the [2]rotaxanes are formed as a result of the reaction of one diamine, one dialdehyde, and one dialkylammonium ion is confirmed by the relative intensities of the signals of selected protons on both the macrocycles $\mathbf{M_{R'}}$ and the dumbbell-shaped cations $\mathbf{D_R}$.

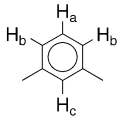
The stability and stoichiometry of the [2]rotaxanes were confirmed by FAB mass spectrometry. In all cases, a signal was observed, in some cases as the base peak, for the [2]rotaxane having lost its counterion (Table 2). No significant signals were observed for higher-order assemblies, such as

Table 1. ^{1}H NMR chemical shift data (400 MHz, CD_3CN, 298 K) for diamine **A**, three dialkylammonium ions ($\mathbf{D}_{OMe}$, $\mathbf{D}_{Me}$, and $\mathbf{D}_{CF_3}$), three dialdehydes (**P**, **F**, and **B**), and the nine [2]rotaxanes $\mathbf{M}_{R'}\cdot\mathbf{D}_R$ formed from combinations of these constituent parts.



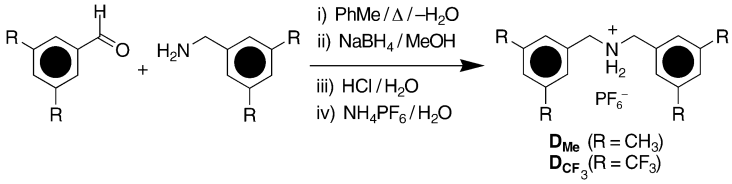
$\mathbf{M}_{R'}$





	Me	CH_2N^+	NH_2^+	H_o	H_p	α-OCH_2	CH=X[b]	H_a	H_b	H	H_a	H_b	H_c
A	–	–	–	–	–	4.06	–	–	–	–	–	–	–
$\mathbf{D}_{OMe}$	3.78	4.11	n.o.[a]	6.57	6.54	–	–	–	–	–	–	–	–
$\mathbf{D}_{Me}$	2.31	4.10	6.93	7.04	7.10	–	–	–	–	–	–	–	–
$\mathbf{D}_{CF_3}$	–	4.41	7.12	8.05	8.10	–	–	–	–	–	–	–	–
P	–	–	–	–	–	–	10.09	8.16	8.15	–	–	–	–
F	–	–	–	–	–	–	9.76	–	–	7.43	–	–	–
B	–	–	–	–	–	–	10.08	–	–	–	7.76	8.16	8.37
$\mathbf{M}_P\cdot\mathbf{D}_{OMe}$	3.34	4.57	9.94	6.43	6.03	4.47	8.41	7.99	7.65	–	–	–	–
$\mathbf{M}_P\cdot\mathbf{D}_{Me}$	1.84	4.51	9.80	6.76	6.57	3.98	8.38	7.87	7.60	–	–	–	–
$\mathbf{M}_P\cdot\mathbf{D}_{CF_3}$	–	4.88	10.63	7.87	7.66	4.44	8.41	8.05	7.70	–	–	–	–
$\mathbf{M}_F\cdot\mathbf{D}_{OMe}$	3.48	4.85	8.95	6.44	6.16	4.24	8.25	–	–	7.11	–	–	–
$\mathbf{M}_F\cdot\mathbf{D}_{Me}$	1.96	4.79	8.85	6.87	6.73	4.27	8.20	–	–	7.02	–	–	–
$\mathbf{M}_F\cdot\mathbf{D}_{CF_3}$	–	5.18	9.50	7.92	7.76	4.20	8.51	–	–	7.12	–	–	–
$\mathbf{M}_B\cdot\mathbf{D}_{OMe}$	3.52	4.77	8.65	6.40	6.16	4.13	8.54	–	–	–	7.62	7.79	n.o.[a]
$\mathbf{M}_B\cdot\mathbf{D}_{Me}$	2.02	4.71	n.o.[a]	6.80	6.73	4.12	8.53	–	–	–	7.63	7.80	n.o.[a]
$\mathbf{M}_B\cdot\mathbf{D}_{CF_3}$	–	5.14	9.22	7.88	7.66	4.15	8.51	–	–	–	7.52	7.66	7.76

[a] Not observed because of overlap with other peaks. [b] Imino or aldehydic proton.



Scheme 3. Syntheses of dialkylammonium salts $\mathbf{D}_{Me}$ and $\mathbf{D}_{CF_3}$.

Table 2. Molecular ion data[a] obtained by FAB mass spectrometry[b] for the nine dynamic [2]rotaxanes $\mathbf{M}_{R'}\cdot\mathbf{D}_R$.

[2]Rotaxane	Formula[a]	Calcd *m/z*	Found *m/z*
$\mathbf{M}_P\cdot\mathbf{D}_{OMe}$	$C_{45}H_{53}N_4O_9$	792.3841	782.3665
$\mathbf{M}_P\cdot\mathbf{D}_{Me}$	$C_{45}H_{53}N_4O_5$	729.4030	729.4010
$\mathbf{M}_P\cdot\mathbf{D}_{CF_3}$	$C_{45}H_{41}F_{12}N_4O_5$	945.2942	945.2942
$\mathbf{M}_F\cdot\mathbf{D}_{OMe}$	$C_{44}H_{52}N_3O_{10}$	782.3665	782.3647
$\mathbf{M}_F\cdot\mathbf{D}_{Me}$	$C_{44}H_{52}N_3O_6$	718.3850	718.3850
$\mathbf{M}_F\cdot\mathbf{D}_{CF_3}$	$C_{44}H_{40}F_{12}N_3O_6$	934.2730	934.2720
$\mathbf{M}_B\cdot\mathbf{D}_{OMe}$	$C_{46}H_{54}N_3O_9$	792.3841	792.3842
$\mathbf{M}_B\cdot\mathbf{D}_{Me}$	$C_{46}H_{54}N_3O_5$	728.4073	728.4058
$\mathbf{M}_B\cdot\mathbf{D}_{CF_3}$	$C_{46}H_{42}F_{12}N_3O_5$	944.2895	944.2895

[a] Molecular ions corresponding to the [2]rotaxanes having lost their PF_6^- counterions (i.e., $[\mathbf{M}_{R'}\cdot\mathbf{D}_R - PF_6]^+$). [b] FAB mass spectra were obtained by using a ZAB-SE mass spectrometer equipped with a Kr primary atom beam utilizing a *m*-nitrobenzyl alcohol matrix.

double-stranded [3](pseudo)rotaxanes; this finding suggests that the [2]rotaxanes are by far the most stable entities in this dynamic equilibrating system.

The rates of rotaxane formation vary dramatically depending on the components used in the assembly (Table 3). For instance, equilibration of the mixture that forms $\mathbf{M}_P\cdot\mathbf{D}_{OMe}$ occurs within minutes of mixing, yet the mixture that forms $\mathbf{M}_F\cdot\mathbf{D}_{Me}$ requires three days to reach equilibrium. Figure 1 portrays the spectra for a system that reaches equilibrium slowly—that of a mixture of $\mathbf{D}_{OMe}$, **F**, and **A**. In all cases, whether equilibration has been reached rapidly or not, sharp signals in the ^{1}H NMR spectra for the [2]rotaxanes indicate that they are thermodynamically stable and relatively stable kinetically on the ^{1}H NMR timescale (360 – 500 MHz). Presumably, this stability is a result of the favorable $[N^+\text{-}H\cdots X]$ hydrogen bonds between the NH_2^+ centers and the hydrogen bond-accepting atoms (X) in the macrocycles.

The rates of rotaxane formation are affected primarily by the nature of the dialdehyde unit (Table 3). In general, the pyridyl-containing dialdehyde (**P**) results in the fastest clipping reactions with all of the three dumbbells, and the furan-containing one (**F**) results in the slowest. Clipping of isophthalaldehyde (**B**) occurs at an intermediate rate. This trend follows the electrophilicities[18] of the formyl groups, with **P** having the most electrophilic aldehyde functions and **F** the least. The nature of the dumbbell-shaped dialkylammonium ion also affects the rates of clipping. Generally, the reactions are fastest—reaching equilibria with all three dialdehydes within 4 h—with $\mathbf{D}_{CF_3}$, a situation that may be a result of i) the putative higher acidity of its NH_2^+ center relative to those of the other dumbbells and ii) the increase in the rate of imine-bond formation that results from stronger acid catalysis. Additionally, during the clipping process there are probably significantly strong aromatic – aromatic interactions occurring between the stoppering group of the dumbbell-shaped component and the aryl units (π-electron-rich units in **A** and π-electron-deficient ones in **P** and **B**) of the nascent macrocycle. When considering the π-electron density in isolation, one might predict, based on the Hunter – Sanders

Table 3. Effective stability constants (K_{eff}),[a] effective free energies of complexation (ΔG°_{eff}),[b] and times (t) required to reach equilibrium for the assembly of [2]rotaxanes $\mathbf{M}_{R'}\cdot\mathbf{D}_R$ formed from diamine **A** (20 mM), a dialdehyde (**P**, **F** or **B**; 20 mM), and a dibenzylammonium salt $\mathbf{D}_R$ (20 mM) in CD_3CN at 298 K.

	P			**F**			**B**		
$\mathbf{D}_R$	K_{eff} [M^{-1}]	ΔG°_{eff} [kcal mol^{-1}]	t [h]	K_{eff} [M^{-1}]	ΔG°_{eff} [kcal mol^{-1}]	t [h]	K_{eff} [M^{-1}]	ΔG°_{eff} [kcal mol^{-1}]	t [h]
$\mathbf{D}_{OMe}$	480 ± 190	-3.6 ± 0.3	0.1	390 ± 160	-3.5 ± 0.3	48	100 ± 40	-2.7 ± 0.3	20
$\mathbf{D}_{Me}$	340 ± 140	-3.4 ± 0.3	0.5	530 ± 210	-3.7 ± 0.3	72	90 ± 36	-2.7 ± 0.3	20
$\mathbf{D}_{CF_3}$	2900 ± 1200	-4.7 ± 0.3	3	7900 ± 3200	-5.3 ± 0.3	4	86 ± 34	-2.6 ± 0.3	3

[a] Calculated using Equation 2. [b] Calculated using the equation $\Delta G^{\circ}_{eff} = -RT\ln K_{eff}$.

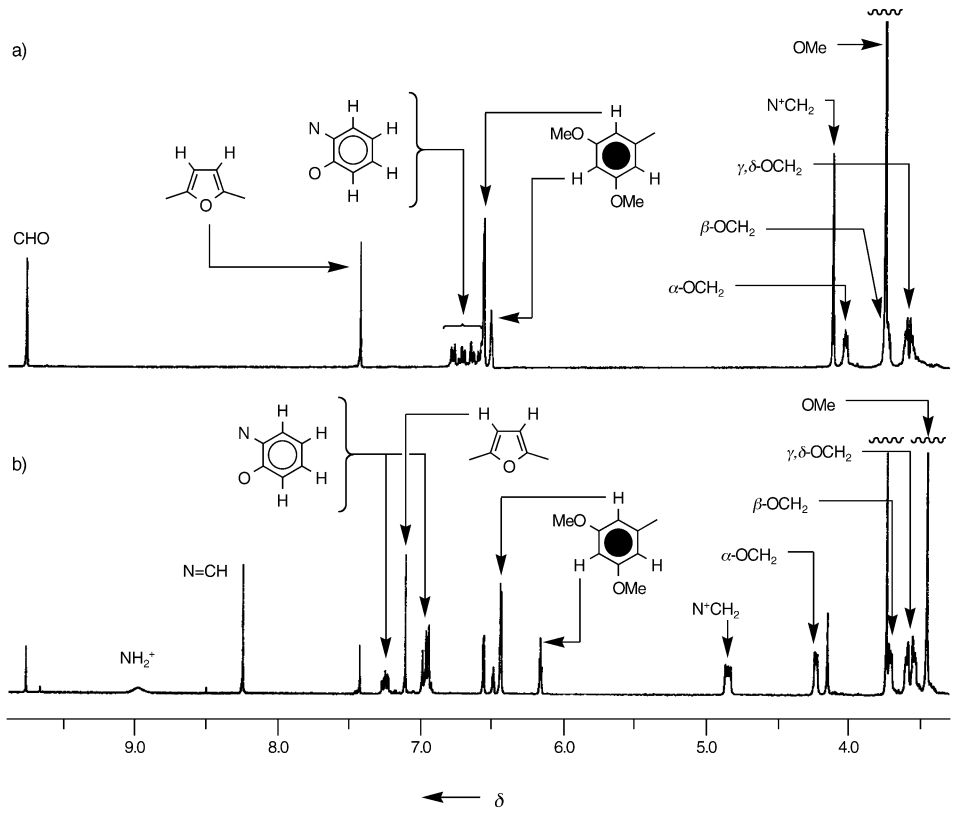


Figure 1. ^{1}H NMR spectra (360 MHz, CD_3CN, 298 K) of a 1:1:1 mixture (20 mM each) of diamine **A**, dialdehyde **F**, and dibenzylammonium salt $\mathbf{D}_{OMe}$ a) 10 min and b) 17 d after mixing them. In the upper spectrum, the signals of the free components are labeled; in the lower one, the corresponding signals for the [2]rotaxane are labeled.

model,[19] that fast clipping reactions would occur for the most π-electron-rich dumbbell with the most π-electron-deficient dialdehyde (i.e., $\mathbf{D}_{OMe}$ with **P**) and the most π-electron-deficient dumbbell with the most π-electron-rich dialdehyde (i.e., $\mathbf{D}_{CF_3}$ with **F**) as well as for pairs of π-electron-deficient dumbbells and dialdehydes (i.e., $\mathbf{D}_{CF_3}$ with **P**). By contrast, one might predict that the slowest clipping reactions would occur for the interaction of the most π-electron-rich dumbbell with the most π-electron-rich dialdehyde (i.e., $\mathbf{D}_{OMe}$ with **F**). This model appears to be a good one for explaining the rates of these dynamic reactions observed and listed in Table 1, although factors other than aromatic–aromatic interactions, such as the relatively higher acidity of $\mathbf{D}_{CF_3}$ and electrophilicity of **P**, must be considered also.

The [2]rotaxanes that form the fastest are not always the most thermodynamically stable. One would expect that the macrocycles with the largest number of hydrogen bond acceptors (i.e., $\mathbf{M}_P$ and $\mathbf{M}_F$) should bind to all of the dialkylammonium ions more strongly than the one with the least (i.e., $\mathbf{M}_B$) and indeed this is the case, as evidenced by the intensities of the signals for the [2]rotaxane in their ^{1}H NMR spectra. The overall association constant K_a for the conversion of a dialdehyde, diamine **A**, and a dialkylammonium ion $\mathbf{D}_R$ into a [2]rotaxane in given by Equation (1):

$$K_a = \frac{[\mathbf{M}_{R'}\cdot\mathbf{D}_R][H_2O]^2}{[\text{dialdehyde}][\mathbf{A}][\mathbf{D}_R]} \quad (1)$$

From single ^{1}H NMR spectra taken of each equilibrated mixture, generally we observe, and can integrate, well-resolved signals for the [2]rotaxane and its uncomplexed dumbbell (see, for example, Figure 1b). Because of difficulties in determining [**A**] and [H_2O] from these spectra, we estimate an effective association constant [K_{eff}, Eq. (2)] between a macrocycle $\mathbf{M}_{R'}$ and a dumbbell $\mathbf{D}_R$ by assuming that—in an equimolar mixture of dialdehyde, diamine, and dumbbell—all of the diamine **A** and dialdehyde (**B**, **F**, or **P**) that is not incorporated into a [2]rotaxane $\mathbf{M}_{R'}\cdot\mathbf{D}_R$ is condensed into a free macrocycle $\mathbf{M}_{R'}$ whose concentration is equal to that of the uncomplexed dumbbell $\mathbf{D}_R$ minus the concentration of the free dialdehyde. The real concentration of each free macrocycle $\mathbf{M}_{R'}$ is smaller than that,[20] but, by making this assumption, we reduce the complexity of the system down to a bimolecular self-assembly involving one macrocycle and one dialkylammonium ion.

$$K_{eff} = \frac{[\mathbf{M}_{R'}\cdot\mathbf{D}_R]}{[\mathbf{M}_{R'}]_{eff}[\mathbf{D}_R]} = \frac{[\mathbf{M}_{R'}\cdot\mathbf{D}_R]}{([\mathbf{D}_R]-[\text{dialdehyde}])[\mathbf{D}_R]} \quad (2)$$

We calculated values of K_{eff} and ΔG°_{eff} for the nine independent systems by using Equation (2) (see Table 3). While a detailed analysis of these numbers is not possible, because of the approximation made, some general trends are obvious. As expected, values of K_{eff} for [2]rotaxanes incorporating $\mathbf{M}_B$ are lower than those incorporating $\mathbf{M}_F$ and $\mathbf{M}_P$,

presumably because the latter two macrocycles bear an eighth heteroatom in their macrorings. Additionally, $\mathbf{M}_B$ features an aryl hydrogen atom—missing in both $\mathbf{M}_F$ and $\mathbf{M}_P$—that may clash sterically with dialkylammonium centers. The [2]rotaxanes $\mathbf{M}_{R'}\cdot\mathbf{D}_{CF_3}$, which incorporate the most π-electron-deficient dumbbell, seem to be the most stable, a feature that is probably a consequence of a combination of enhanced [N^+-H···X] hydrogen bonding and significant aromatic–aromatic interactions. The values of K_{eff} for [2]rotaxanes $\mathbf{M}_F\cdot\mathbf{D}_R$ and $\mathbf{M}_P\cdot\mathbf{D}_R$ are similar for each dumbbell-shaped ion and are comparable to the strengths of binding in CD_3CN of disubstituted dibenzylammonium salts with the crown ethers DB24C8[13g, 21] and dipyridyl[24]crown-8.[22]

Competition experiments, monitored by ^{1}H NMR spectroscopy (Figure 2), have allowed us to make accurate calculations of the relative stabilities of pairs of [2]rotaxanes formed from a choice of either two dialdehydes or two dumbbell-shaped components. In the case of two [2]rotaxanes assembled from one macrocycle ($\mathbf{M}_{R'}$) and having the choice of a pair of templating dumbbell-shaped units ($\mathbf{D}_1$ or $\mathbf{D}_2$), the ratio [Eq. (3)] of the values of K_a for each [2]rotaxane—each defined by Equation (1)—is dependent only on the concentrations of the [2]rotaxanes and free dumbbells, parameters that can be

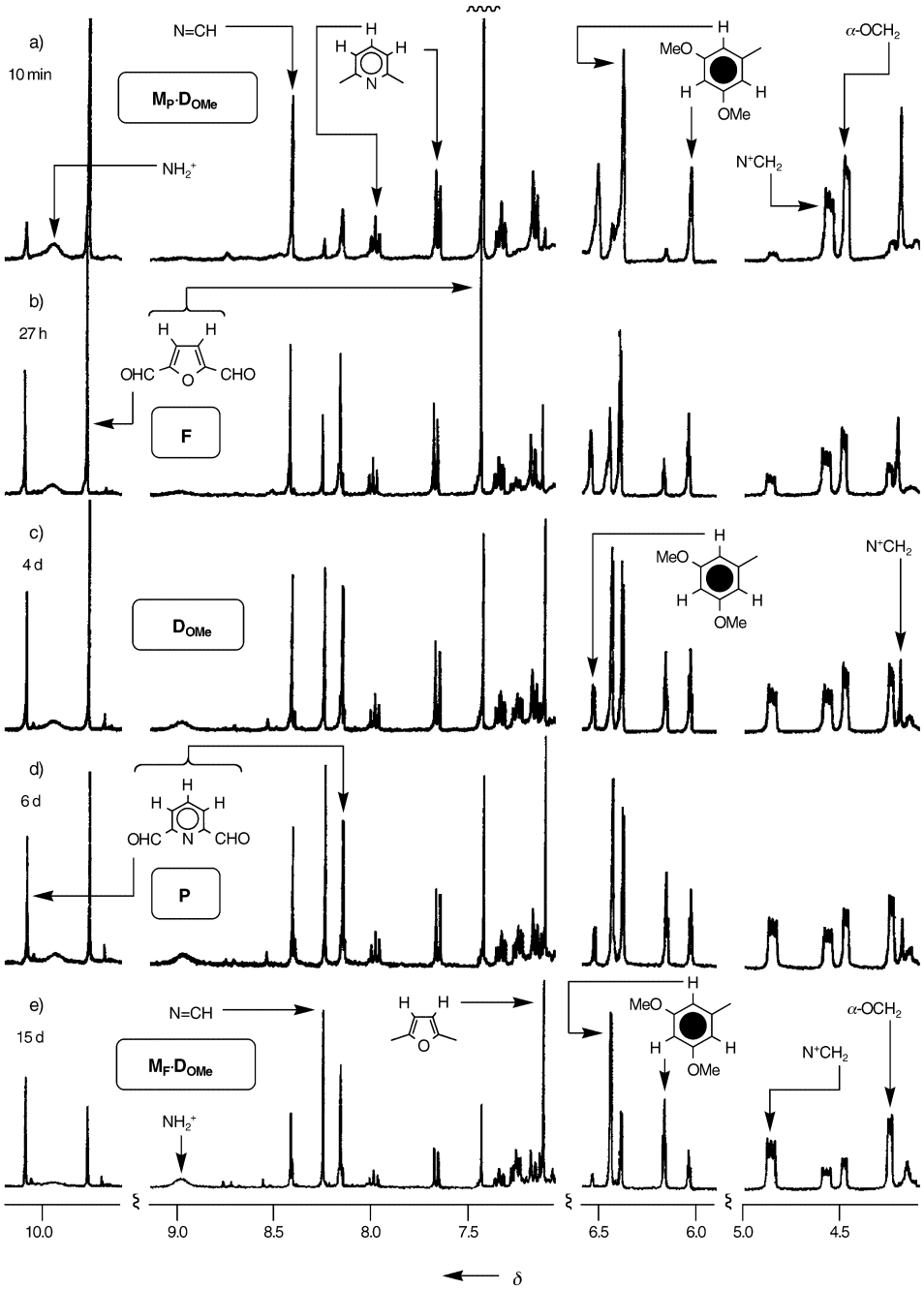


Figure 2. ^{1}H NMR spectra (360 MHz, CD_3CN, 298 K) displaying, over time, signals from a solution of diamine **A** and dibenzylammonium salt $\mathbf{D}_{OMe}$ to which dialdehydes **F** and **P** have been added simultaneously. The competition of the systems for the two dialdehydes was monitored for 30 d. The signals of the five major components of the equilibrating mixture are observed in all of these spectra and are labeled on different spectra.

Table 4. Relative stabilities[a,b] and equilibration times[c] for [2]rotaxanes formed from diamine **A** (20 mM), a dialdehyde (**B**, **F**, or **P**; 20 mM), and a choice of two dumbbell-shaped dialkylammonium ions (each 20 mM) in CD_3CN at 298 K.

		P			**F**			**B**		
Dumbbell 1	Dumbbell 2	K_1/K_2	$\Delta\Delta G^\circ_{1,2}$ [kcal mol^{-1}]	t [d]	K_1/K_2	$\Delta\Delta G^\circ_{1,2}$ [kcal mol^{-1}]	t [d]	K_1/K_2	$\Delta\Delta G^\circ_{1,2}$ [kcal mol^{-1}]	t [d]
$\mathbf{D}_{Me}$	$\mathbf{D}_{OMe}$	0.97 ± 0.19	+ 0.02 ± 0.13	14	1.10 ± 0.22	− 0.06 ± 0.14	6	1.04 ± 0.21	− 0.02 ± 0.13	6
$\mathbf{D}_{CF_3}$	$\mathbf{D}_{OMe}$	8.20 ± 1.64	− 1.24 ± 0.13	6	3.87 ± 0.77	− 0.80 ± 0.13	9	1.64 ± 0.33	− 0.29 ± 0.13	9
$\mathbf{D}_{CF_3}$[d]	$\mathbf{D}_{Me}$[d]	8.45 ± 3.38	− 1.26 ± 0.26	–	3.52 ± 1.41	− 0.74 ± 0.27	–	1.58 ± 0.63	− 0.27 ± 0.30	–

[a] Calculated by using Equation (3). [b] $\Delta\Delta G^\circ_{1,2} = \Delta G^\circ_1 - \Delta G^\circ_2 = -RT\ln(K_1/K_2)$. [c] Time taken to reach equilibrium. [d] Values in this row calculated from data in previous two rows.

determined by integration of well-resolved signals in a single ^{1}H NMR spectrum. For competition experiments in which two dialdehyde units (**Ald**$_1$ or **Ald**$_2$), but only one dumbbell-shaped unit, are used, the ratio of the values of K_a of each [2]rotaxane is given by Equation (4), and is dependent upon the concentrations of only the [2]rotaxanes and dialdehydes, parameters that also, generally speaking, are well resolved in the ^{1}H NMR spectra.

$$\frac{K_1}{K_2}=\frac{[\mathbf{M}_R\cdot\mathbf{D}_1][\mathbf{D}_2]}{[\mathbf{M}_R\cdot\mathbf{D}_2][\mathbf{D}_1]} \quad (3)$$

$$\frac{K_1}{K_2}=\frac{[\mathbf{M}_1\cdot\mathbf{D}_R][\mathbf{Ald}_2]}{[\mathbf{M}_2\cdot\mathbf{D}_R][\mathbf{Ald}_1]} \quad (4)$$

All competition experiments were carried out in CD_3CN with equimolar mixtures (20 mM) of the four components in which either a) the four components were mixed together and then equilibrated or b) the competing dumbbell or dialdehyde was added to a pre-equilibrated mixture of a single [2]rotaxane that then was monitored until re-equilibrated. Since there are two ways to perform the latter procedure, we performed each competition experiment a total of three times. Table 4 displays the data obtained from the competition experiments in which there is a choice of dialkylammonium ions. The times required for these systems to reach equilibrium are generally longer than those found for the simple experiments (Table 3); this observation suggests that the rates of macrocyclic ring opening of the [2]rotaxanes are relatively slow, when compared to their rates of clipping. The [2]rotaxanes formed by using $\mathbf{D}_{CF_3}$ were the most stable, in all cases, relative to the other two dumbbell-shaped dialkylammonium salts. The dominance of $\mathbf{D}_{CF_3}$ is particularly evident in the [2]rotaxanes incorporating the pyridyl unit, in which $\mathbf{M}_P\cdot\mathbf{D}_{CF_3}$ is about 1.2 kcal mol^{-1} more stable than either $\mathbf{M}_P\cdot\mathbf{D}_{Me}$ or $\mathbf{M}_P\cdot\mathbf{D}_{OMe}$. The difference in the stability of the [2]rotaxanes incorporating either $\mathbf{D}_{OMe}$ or $\mathbf{D}_{Me}$ is generally negligible ($\Delta\Delta G^\circ\approx\pm$ 0.15 kcal mol^{-1}). [2]Rotaxanes formed from dialdehyde **B** were less selective for the choice of dumbbell.

An example of a competition experiment in which the dialdehyde units have been varied is that in which dialdehydes **P** and **F** were added simultaneously to a solution of **A** and $\mathbf{D}_{OMe}$ in CD_3CN. The spectrum recorded after 10 min (Figure 2a) indicates that the major [2]rotaxane in solution is $\mathbf{M}_P\cdot\mathbf{D}_{OMe}$ (e.g., compare the intensities of the signals of the CH_2N^+ units of $\mathbf{M}_P\cdot\mathbf{D}_{OMe}$ at $\delta=4.57$ and of $\mathbf{M}_F\cdot\mathbf{D}_{OMe}$ at 4.85), as is expected, since the clipping of the components of $\mathbf{M}_P\cdot\mathbf{D}_{OMe}$ is much faster than that of the components of $\mathbf{M}_F\cdot\mathbf{D}_{OMe}$ (Table 3). Interestingly, over a period of a month (Figure 2b–e), the system equilibrates such that the major [2]rotaxane in solution is $\mathbf{M}_F\cdot\mathbf{D}_{OMe}$ (the ratio of $\mathbf{M}_F\cdot\mathbf{D}_{OMe}$ to $\mathbf{M}_P\cdot\mathbf{D}_{OMe}$ after 30 d is 77:23). Thus, the [2]rotaxane $\mathbf{M}_F\cdot\mathbf{D}_{OMe}$ is more stable than $\mathbf{M}_P\cdot\mathbf{D}_{OMe}$ by about 1.2 kcal mol^{-1}. Table 5 summarizes the competition experiments in which **A** and a dumbbell-shaped salt were given the choice of two dialdehydes with which to form a [2]rotaxane. In cases in which **B** was one of the dialdehydes, the [2]rotaxanes formed from **F** or **P** assembled selectively (i.e., after equilibration, no rotaxanes $\mathbf{M}_B\cdot\mathbf{D}_R$ were observed by ^{1}H NMR spectroscopy) irrespective of the nature of the dumbbell-shaped salt. Generally, [2]rotaxanes formed from **F** were more stable than those from **P** by over 0.5 kcal mol^{-1}.

The values of $\Delta\Delta G^\circ$, determined by competition experiments for the [2]rotaxanes, mirror, to some degree, the relative values of ΔG°_{eff} given in Table 3, but are far more reliable numbers.[23] We combined the data from Tables 4 and 5 to get a sequence of relative stabilities for the nine [2]rotaxanes. From the graphical representation in Figure 3,

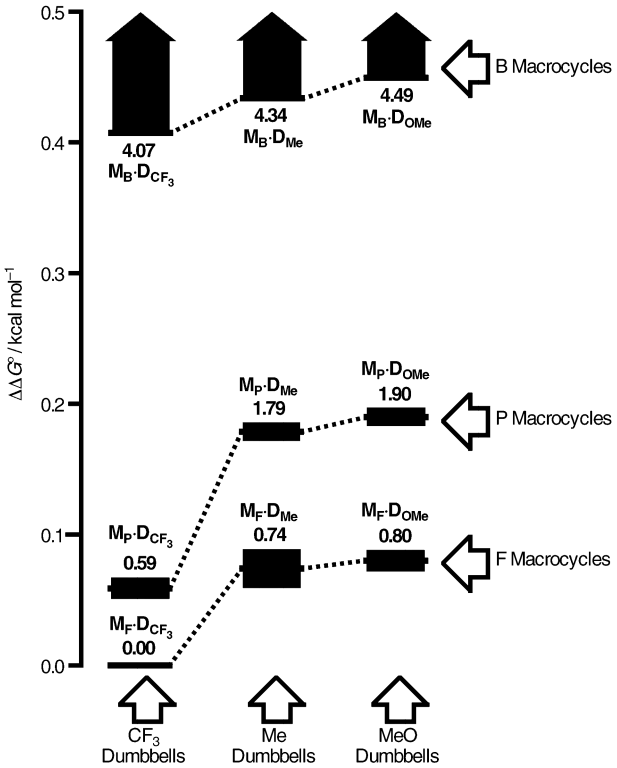


Figure 3. The stabilities of the nine [2]rotaxanes investigated in this study relative to the stability of [2]rotaxane $\mathbf{M}_F\cdot\mathbf{D}_{CF_3}$, which is designated as zero. The thickness of each black bar indicates the error associated with each measurement. The relative energy levels of the [2]rotaxanes incorporating the dialdehyde **B** are indicated as their lower limits.

Table 5. Relative stabilities[a,b] and equilibration times[c] of [2]rotaxanes formed from diamine **A** (20 mM), a dumbbell-shaped dialkylammonium ion ($\mathbf{D}_{Me}$, $\mathbf{D}_{OMe}$, or $\mathbf{D}_{CF_3}$; 20 mM), and a choice of two dialdehydes (each 20 mM) in CD_3CN at 298 K.

		$\mathbf{D}_{Me}$			$\mathbf{D}_{CF_3}$			$\mathbf{D}_{OMe}$		
Ald$_1$	**Ald**$_2$	K_1/K_2	$\Delta\Delta G^\circ_{1,2}$ [kcal mol^{-1}]	t [d]	K_1/K_2	$\Delta\Delta G^\circ_{1,2}$ [kcal mol^{-1}]	t [d]	K_1/K_2	$\Delta\Delta G^\circ_{1,2}$ [kcal mol^{-1}]	t [d]
F	**P**	3.60 ± 0.72	-0.76 ± 0.13	14	2.71 ± 0.54	-0.59 ± 0.13	6	8.29 ± 1.66	-1.25 ± 0.13	30
F	**B**	>100	<-2.7	6	>100	<-2.7	15	>100	<-2.7	23
P	**B**	>100	<-2.7	30	>100	<-2.7	15	>100	<-2.7	23

[a] Calculated by using Equation (4). [b] $\Delta\Delta G^\circ_{1,2}=\Delta G^\circ_1-\Delta G^\circ_2=-RT\ln(K_1/K_2)$. [c] Time allowed for system to reach equilibrium.

it is quite evident that i) **B** forms the least stable [2]rotaxanes, ii) there is little difference in stability between $\mathbf{D}_{OMe}$- and $\mathbf{D}_{Me}$-containing [2]rotaxanes, and iii) the **F**- and $\mathbf{D}_{CF_3}$-containing [2]rotaxanes are the most stable.

The question of why a furan ring in a macrocycle gives rise to more stable [2]rotaxanes than a pyridyl one is not a simple one to explain. One would expect that a pyridyl unit, being more basic than the furan one, would form the stronger hydrogen bonds. This basicity seems not to be the major factor determining the [2]rotaxanes' relative stabilities. It seems that, in order to explain the greater hydrogen-bonding ability of $\mathbf{M}_F$ over $\mathbf{M}_P$, we must consider the basicities of their imino nitrogen atoms as well.[24] Any partial positive charge that these groups receive upon hydrogen bonding to an NH_2^+ center is better stabilized by the furan ring than by a pyridyl one, by virtue of the former's greater π-electron density. The pyridyl unit may be expected to also withdraw a significant amount of electron density mesomerically from the phenolic ether oxygen atoms of $\mathbf{M}_P$. Thus, although the furan ring, when compared with the pyridyl ring, is not as capable of accepting a hydrogen bond directly, the enhanced basicity of its neighboring imino and phenoxy units, relative to those in $\mathbf{M}_P$, results in a more strongly coordinating macrocycle.[25]

Conclusion

We have demonstrated the generality of the dynamic clipping of imine-containing macrocycles around dialkylammonium ions to form [2]rotaxanes. This approach is remarkably sensitive to small structural changes in the constitutions of the macrocyclic and dumbbell-shaped components, which, in turn, have dramatic effects on the kinetics and thermodynamics of the assemblies. We have found that furan-containing macrocycles and π-electron-deficient dumbbell-shaped ions are the components of choice for forming the thermodynamically most-stable [2]rotaxanes, even though pyridine-containing macrocycles form [2]rotaxanes that are more kinetically stable.

Experimental Section

General methods: Dialkylammonium salt $\mathbf{D}_{OMe}$,[14] diamine **A**,[17] and dialdehydes **P**[15] and **F**,[16] were prepared according to established procedures. Deuterated solvents were purchased from Cambridge Isotope Laboratories, solvents were purchased from EM Sciences and Fisher, and all other chemicals were purchased from Aldrich, Lancaster, or Fluka and used as received, unless indicated otherwise. CD_3CN was dried over activated 4 Å molecular sieves. Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker ARX400 and AC360 spectrometers with residual solvent as the internal standard. All chemical shifts are quoted on the δ scale, and all coupling constants are expressed in Hertz (Hz). Fast atom bombardment (FAB) mass spectra were obtained by using a ZAB-SE mass spectrometer equipped with a krypton primary atom beam, utilizing a *m*-nitrobenzyl alcohol matrix. Cesium iodide or poly(ethylene glycol) was employed as the reference compound.

Bis(3,5-dimethylbenzyl)ammonium hexafluorophosphate ($\mathbf{D}_{Me}$): A solution of 3,5-dimethylbenzylamine (1.0 g, 7.32 mmol) and 3,5-dimethylbenzaldehyde (1.2 g, 9.0 mmol) in toluene (50 mL) was evaporated to dryness under reduced pressure. The residue was dissolved in toluene (50 mL) and evaporated to dryness. [^1H NMR (CD_3CN) $\delta = 2.32$ (s, 6H; CH_3), 2.35 (s, 6H; CH_3), 4.74 (s, 2H; CH_2), 6.91 (s, 1H; ArH), 6.95 (s, 2H; ArH), 7.08 (s, 1H; ArH), 7.42 (s, 2H; ArH), 8.33 (s, 1H; N=CH)]. The Schiff's base was dissolved in anhydrous EtOH and stirred vigorously under Ar while $NaBH_4$ (0.79 g, 21.0 mmol) was added carefully in portions. The resulting solution was stirred at ambient temperature for 3 h. Aqueous HCl was added until the suspension became slightly acidic, and then the EtOH was evaporated in vacuo. CH_2Cl_2 (50 mL) was added to the mixture, and then the aqueous layer was separated and extracted again with CH_2Cl_2 (50 mL). The combined organic extracts were washed with NaOH (1N, 50 mL), dried ($MgSO_4$), filtered, concentrated under reduced pressure, and then dried under high vacuum to afford a colorless residue. This residue was dissolved in EtOAc (100 mL) and washed with HCl (1N, 100 mL). The white precipitate that formed at the organic/aqueous interface was filtered off and dissolved in boiling H_2O. A saturated aqueous solution of NH_4PF_6 was added to the hot solution, and a white solid precipitated instantly. The mixture was cooled to ambient temperature, and the white solid was filtered, dried, and recrystallized from *n*PrOH to afford the title compound as a white crystalline material (2.08 g, 72%). M.p. 231.5 °C; ^1H NMR (CD_3CN) $\delta = 2.32$ (s, 12H; CH_3), 4.11 (s, 4H; CH_2), 7.05 (s, 4H; ArH), 7.11 (s, 2H; ArH); ^{13}C NMR (CD_3CN) $\delta = 20.2$, 51.3, 127.7, 130.2, 131.1, 138.9; FABMS *m/z* (%) = 254.1895 (100) [$M^+ - PF_6$] ($C_{18}H_{24}N$ requires 254.1909).

Bis(3,5-bis(trifluoromethyl)benzyl)ammonium hexafluorophosphate ($\mathbf{D}_{CF_3}$): A solution of 3,5-bis(trifluoromethyl)benzylamine (2.42 g, 10.0 mmol) and 3,5-bis(trifluoromethyl)benzaldehyde (2.43 g, 10.0 mmol) in toluene (100 mL) was evaporated to dryness under reduced pressure. The residue was dissolved in toluene (100 mL), evaporated to dryness under reduced pressure, and then dried under high vacuum. [^1H NMR ($CDCl_3$) $\delta = 4.94$ (s, 2H; CH_2), 7.83 (s, 2H; ArH), 7.97 (s, 1H; ArH), 8.25 (s, 2H; ArH), 8.35 (s, 1H; ArH), 8.55 (s, 1H; N=CH)]. The Schiff's base was dissolved in anhydrous EtOH (50 mL) and stirred vigorously under Ar while $NaBH_4$ (0.79 g, 21.0 mmol) was added carefully in portions. The resulting solution was stirred at ambient temperature for 3 h. Aqueous HCl was added until the suspension became slightly acidic, and then the EtOH was evaporated in vacuo. CH_2Cl_2 (50 mL) was added to the mixture, and the aqueous layer was separated and extracted again with CH_2Cl_2 (50 mL). The combined organic extracts were washed with NaOH (1N, 50 mL), dried ($MgSO_4$), filtered, concentrated under reduced pressure, and then dried under high vacuum to afford a white solid. This solid was dissolved in EtOAc (100 mL) and washed with HCl (1N, 100 mL). The organic phase was separated, dried, filtered, and evaporated to dryness. The white solid was suspended in a 1:1 mixture of acetone and H_2O, and then a saturated aqueous solution of NH_4PF_6 was added until dissolution occurred. The mixture was filtered, and then H_2O was added to cause a white solid to precipitate. The white solid was filtered, dried, and recrystallized from *n*PrOH to afford the title compound as a white crystalline material (4.64 g, 75%). M.p. 130.5 °C; ^1H NMR (CD_3CN) $\delta = 4.27$ (s, 4H; CH_2), 8.05 (s, 4H; ArH), 8.11 (s, 2H; ArH); ^{13}C NMR (CD_3CN) $\delta = 50.25$, 121.89, 124.53, 131.45, 131.79, 132.98; FABMS *m/z* (%) = 470.0788 (100) [$M^+ - PF_6$] ($C_{18}H_{12}F_{12}N$ requires 470.0778).

General procedure for the synthesis of a dynamic [2]rotaxane: Diamine **A** (7.5 mg, 20 μmol) was dissolved in a solution of a dibenzylammonium salt ($\mathbf{D}_{Me}$, $\mathbf{D}_{OMe}$, or $\mathbf{D}_{CF_3}$: 20 μmol) and a dialdehyde (**P**, **F**, or **B**: 20 μmol) in dry CD_3CN (1.00 mL). The solution was transferred to an NMR tube and the dynamic equilibrium was monitored by ^1H NMR spectroscopy until equilibrium was reached.

General procedures for the competition experiments leading to the formation of two dynamic [2]rotaxanes

Dynamic synthesis with two dialdehydes: Method A: Diamine **A** (7.5 mg, 20 μmol) was dissolved in a solution of a dibenzylammonium salt ($\mathbf{D}_{Me}$, $\mathbf{D}_{OMe}$, or $\mathbf{D}_{CF_3}$: 20 μmol) and two dialdehydes (a pair chosen from **P**, **F**, and **B**: 20 μmol) in dry CD_3CN (1.00 mL). The solution was transferred to an NMR tube and the dynamic system was monitored by ^1H NMR spectroscopy until equilibrium was reached.

Method B: Diamine **A** (7.5 mg, 20 μmol) was dissolved in a solution of a dibenzylammonium salt ($\mathbf{D}_{Me}$, $\mathbf{D}_{OMe}$, or $\mathbf{D}_{CF_3}$: 20 μmol) and a first dialdehyde (**P**, **F**, or **B**: 20 μmol) in dry CD_3CN (1.00 mL). The solution was transferred to an NMR tube and the dynamic equilibrium was monitored by ^1H NMR spectroscopy until equilibrium was reached. A second, different dialdehyde (**P**, **F**, or **B**: 20 μmol) was then dissolved in this

solution, and the new dynamic system monitored by ^{1}H NMR spectroscopy until it had reached a new equilibrium.

Dynamic synthesis with two dibenzylammonium ions: Method A: Diamine **A** (7.5 mg, 20 μmol) was dissolved in a solution of two dibenzylammonium salts (a pair chosen from $\mathbf{D}_{Me}$, $\mathbf{D}_{OMe}$, and $\mathbf{D}_{CF_3}$: 20 μmol) and a dialdehyde (**P**, **F**, or **B**: 20 μmol) in dry CD_3CN (1.00 mL). The solution was transferred to an NMR tube and the dynamic system was monitored by ^{1}H NMR spectroscopy until equilibrium was reached.

Method B: Diamine **A** (7.5 mg, 20 μmol) was dissolved in a solution of a first dibenzylammonium salt ($\mathbf{D}_{Me}$, $\mathbf{D}_{OMe}$, or $\mathbf{D}_{CF_3}$: 20 μmol) and a dialdehyde (**P**, **F**, or **B**: 20 μmol) in dry CD_3CN (1.00 mL). The solution was transferred to an NMR tube and the dynamic equilibrium was monitored by ^{1}H NMR spectroscopy until equilibrium was reached. A second, different dialkylammonium salt ($\mathbf{D}_{Me}$, $\mathbf{D}_{OMe}$, or $\mathbf{D}_{CF_3}$: 20 μmol) was then dissolved in this solution, and the new dynamic system monitored by ^{1}H NMR spectroscopy until it had reached a new equilibrium.

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[24] The solid-state structure of a reduced form of $\mathbf{M}_P \cdot \mathbf{D}_{OMe}$ suggests that the aminophenyl nitrogen atoms are important for hydrogen bonding with the NH_2^+ center. See ref. [4j].

[25] Inspection of molecular models (Chem3D) suggests that the bite angle of a 2,5-diiminofuryl unit (N···O···N angle of ca. 144°) is somewhat larger than that of a corresponding pyridyl unit (N···N···N angle of ca. 125°). This larger bite angle suggests that any NH_2^+ unit that hydrogen bonds to the two imino nitrogen atoms of these subunits will be positioned about 0.4 Å closer to the furan oxygen atom than to the pyridine nitrogen atom. This small structural effect may result in more favorable electrostatic interactions and help to explain the stability of [2]rotaxanes incorporating $\mathbf{M}_F$.

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