The Influence of Constitutional Isomerism and Change on Molecular Recognition Processes

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Abstract: Three constitutionally isomeric bis(naphthylmethyl)ammonium ions, in which the two naphthyl groups are substituted 1) both at their 1-positions, 2) one at its 1-position and the other at its 2-position, and 3) both at their 2-positions, have been investigated separately in solution for their propensities to undergo spontaneous self-assembly with three different [24]crown-8 derivatives, namely, pyrido[24]crown-8 (P24C8), dipyrido[24]-crown-8 (DP24C8) and dibenzo[24]-crown-8 (DB24C8), in turn to form [2]pseudorotaxanes. The strengths of the 1:1 complexes depend on the composition of the secondary dialkylammonium ions and on the nature of the crown ether hosts; generally, as far as the guest cation is concerned, the 1/1- and 2/2-isomers form stronger complexes, as indicated by stability constant measurements, than the 1/2-isomer and, as far as the crown ethers are concerned, the more flexible P24C8 is a much more efficient host than either DP24C8 or DB24C8. The rates of formation of the [2]pseudorotaxanes are fast (i.e., taking no more than a few minutes) in solution with the exception of one case, that is, in which the crown ether host is DB24C8 and the guest cation is the 1/1-isomer, when it can take upwards of one month for the complexation–decomplexation equilibrium to be established at room temperature. In all cases, the equilibrium between complexed and uncomplexed species is slow on the NMR timescale, allowing the determination of stability constants to be made readily using the single-point method. X-ray crystallography and molecular modeling have been used to gain insight into ground and transition state interactions, respectively, in some of the [2]pseudorotaxanes. The relative stabilities of the three [2]pseudorotaxanes formed by each guest cation in the presence of the three crown ether hosts were also evaluated in solution by competition experiments that were monitored by ^{1}H NMR spectroscopy. By and large the results of the competition experiments could be predicted on the basis of the derived stability constants for the individual [2]pseudorotaxanes.

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

Introduction

The interest[1] in employing strict self-assembly processes[2] to bring together different molecular components in a highly directed manner, to produce spontaneously thermodynamically stable ensembles[3] that may be molecular or supramolecular in nature, continues to gain momentum at a remarkable pace. The impetus for this high level of research activity is no longer a quest for new forms, attractive as they may be in their own right; it is also being driven more and more by the search for functions associated with molecularly based nanoscopic devicelike systems[4–7] that might find technological applications in the not too distant future. The concept of using strict self-assembly processes[2] to construct structures and superstructures with differing aspects of interlocking and intertwining of their interactive components[8] is one that has captured the imaginations of many different researchers.[9] This trend is hardly all that suprising, since there is probably an engineer's perspective waiting to be expressed in the minds of many chemists, and particularly in those where design and synthesis, solid-state structural elucidation, and molecular modeling are some of the cornerstones of their research activities.

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For close on a decade now, one of the easiest ways to construct interlocked molecules[10,11] (including many rotaxanes but also some catenanes) and interwoven polyvalent supramolecular arrays[12] has relied upon the molecular recognition (based principally upon strong $N^+-H\cdots O$ hydrogen bonding augmented by weaker $C-H\cdots O$ interactions and occasionally some π–π stacking forces) that has been shown[8h,13] to exist between $-CH_2NH_2^+CH_2-$ centers, present in secondary dialkylammonium ions, and crown ethers based on [24]crown-8—commonly dibenzo[24]crown-8 (DB24C8)—or larger. In cases in which the secondary dialkylammonium ion is threaded through the macrocyclic polyether cavity of a DB24C8 derivative that has been functionalized on one or both catechol rings of the crown ether, symmetry-induced complications arise[14] and complicate the nature of the complexes formed and the products that can be isolated as interlocked molecular compounds.

In order to circumvent these symmetry-related problems, one or both of the catechol rings were replaced[15,16] with resorcinol rings, such that the macrocyclic polyethers of interest became benzo-*m*-phenylene[25]crown-8 (BMP25C8) and bis-*m*-phenylene[26]crown-8 (BMP26C8), respectively. There is a downside, however, to making these constitutional changes—namely, that the strength of the complexes, that is, pseudorotaxanes,[17] formed with secondary dialkylammonium ions, under comparable conditions,[15,16] falls considerably on going from DB24C8 to BMP25C8 and plummets in changing from BMP25C8 to BMP26C8.

Consequently, we turned our attention to replacing[18] the two catechol rings in DB24C8 by two 2,6-disubstituted pyridine rings and, as a result, synthesized in our laboratories dipyrido[24]crown-8 (DP24C8), as an alternative to DB24C8 wherein the [24]crown-8 constitution is preserved. This particular [24]crown-8 derivative not only circumvented the symmetry-related problems, but it also more than lived up to our expectations in terms of its complexation behavior by forming even more stable pseudorotaxanes[18] than DB24C8 with dibenzylammonium hexafluorophosphate in acetonitrile. Clearly, DP24C8 merits a more detailed investigation with a wider range of secondary dialkylammonium ions in order to assess its propensity to form pseudorotaxanes. It was while in pursuit of this objective that we obtained the results that are reported in this full paper.

Furthermore, although the more flexible analogue of DP24C8, that is, pyrido[24]-crown-8 (P24C8), has been known[19] for a lot longer and its complexation with guanidinium ions,[20] water,[21] malonitrile,[22] and urea[23] are all well documented, no studies, to our knowledge, have been reported on the ability of P24C8 to form pseudorotaxanes[17] with secondary dialkylammonium ions. This oversight is also addressed in this full paper.

During some investigations on the respective abilities of DB24C8, DP24C8, and P24C8 to act as encircling hosts with a range of secondary dialkylammonium guest ions, $RCH_2NH_2^+CH_2R$, in which R is either 1-naphthyl or 2-naphthyl, or a mixture of these groups, we discovered that one of the three constitutionally isomeric ions—namely, that in which both R groups are 1-naphthyls—took a much longer time than expected to reach equilibrium and form a pseudorotaxane[17] with DB24C8. This phenomenon, which we commonly refer to as slippage,[24] has been encountered by us and others previously: it provides an extremely attractive way to self-assemble rotaxanelike entities under thermodynamic control, often when other synthetic approaches are simply not viable for one reason or another.

This full paper describes the way in which three constitutionally isomeric bis(naphthylmethyl)ammonium ions behave both kinetically and thermodynamically when they come in contact with three different [24]crown-8 derivatives, namely, DB24C8, DP24C8, and P24C8, to form pseudorotaxanes[17] in solution. The 1:1 complexes, for the most part, have been fully characterized by X-ray crystallography in the solid state and their formations, singly and in competition with one another, have been investigated in solution by ^1H NMR spectroscopy.

Results and Discussion

Molecular synthesis: Of the macrocyclic hosts (Figure 1), DB24C8 is commercially available and the syntheses of DP24C8[18] and P24C8[19] have been reported previously. The four secondary dialkylammonium guest cations, namely [**1NP/1NP**-H]$^+$, [**1NP/2NP**-H]$^+$, [**2NP/2NP**-H]$^+$, and [**PIP/PIP**-H]$^+$, were all obtained as their hexafluorophosphate salts by treatment of the corresponding hydrochloride salts with saturated aqueous NH_4PF_6. The secondary amines,

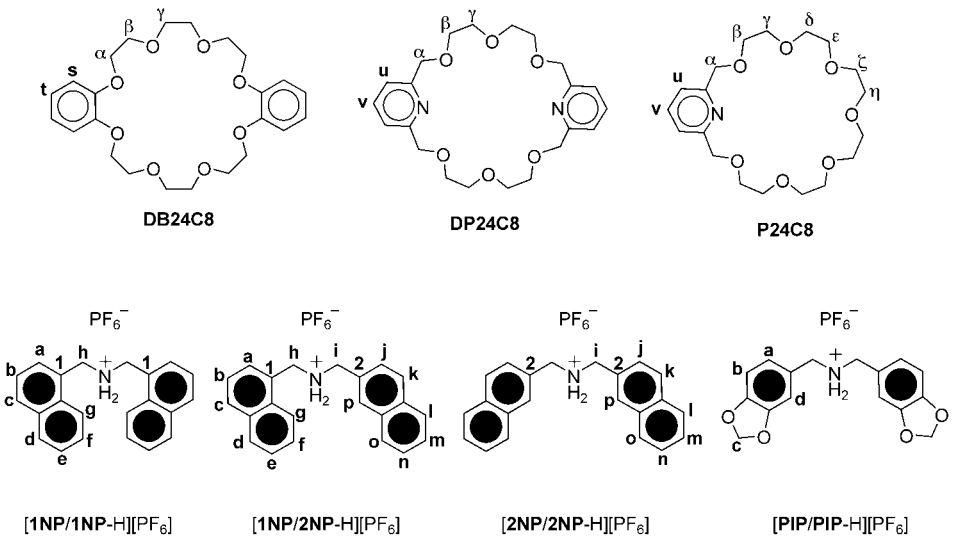

Figure 1. Structural formulas of the macrocyclic polyethers and the dialkylammonium hexafluorophosphate salts discussed in this article.

from which the hydrochloride salts were prepared (conc. HCl), were all synthesized in good yields by carrying out reductive aminations ($NaBH_4$/MeOH) on the imines, obtained from condensing appropriate aldehydes and amines by using a Dean-Stark apparatus. The four PF_6^- salts shown in Figure 1 were fully characterized by ^1H and ^{13}C NMR spectroscopy and also by high-resolution mass spectrometry.

Supramolecular synthesis: The formation in solution of the 1:1 threaded complexes, or [2]pseudorotaxanes, from equimolar amounts of the [24]crown-8 derivatives and the $[R_2NH_2][PF_6]$ salts was monitored in each case by ^1H NMR spectroscopy. The solvents in which we chose to study the self-assembly between the neutral macrocyclic hosts and the cationic guests were 1) CD_3CN, 2) CD_2Cl_2 and 3) a mixed solvent system (MSS), namely, $CDCl_3/CD_3CN$ (3:1). The first two solvents were chosen in order to investigate the strengths of the 1:1 complexes in solvents with considerably different polarities. The MSS was chosen to be able to compare stability constants (K_a values) for [2]pseudorotaxane formation with literature values for related 1:1 complexes studied previously.[24m] The complexation studies were carried out with solutions in the mM concentration range. The K_a values and derived $\Delta G°$ values are summarized in Table 1.

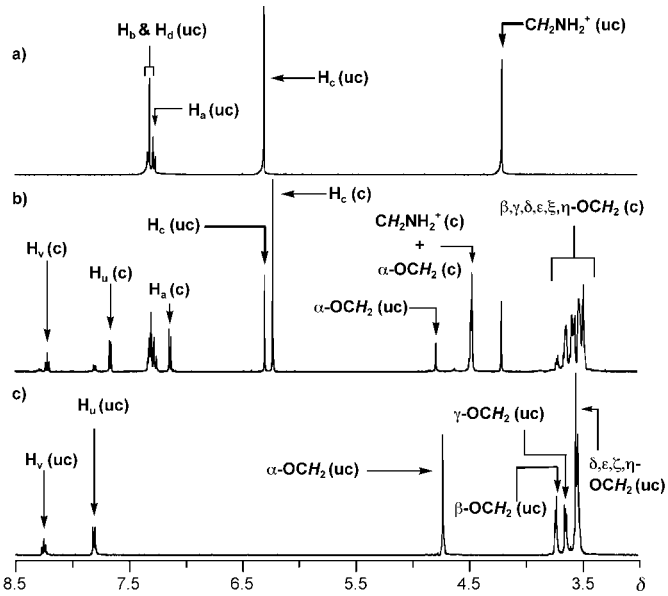

Figure 2. Partial ^1H NMR spectra recorded at 500 MHz in CD_3CN of a solution of a) [**PIP**/**PIP**-H][PF_6], b) a 1:1 mixture of [**PIP**/**PIP**-H][PF_6] and DB24C8, and c) DB24C8 at 25°C. The concentrations of the crown ether and salt were both 3 mM. Peaks associated with the uncomplexed crown ether and dialkylammonium ion are denoted by the descriptor **uc**, while those associated with the complex are denoted by the descriptor **c**.

Pseudorotaxane formation with P24C8: All four $[R_2NH_2]^+$ ions, as their PF_6^- salts shown in Figure 1, are able to form pseudorotaxanes with P24C8 in CD_3CN and CD_2Cl_2 relatively quickly, that is, equilibria are reached in the time it takes to record the ^1H NMR spectra of freshly prepared samples at room temperature, despite the fact that complexation–decomplexation is slow on the NMR timescale. When an equimolar mixture of [**PIP**/**PIP**-H][PF_6] and P24C8 in CD_3CN has its ^1H NMR spectrum recorded (Figure 2b) within 5 min of the mixing process, the result is distinctly different from the spectra (Figure 2a and c) of the free guest salt and the free crown ether, respectively. Although peaks arising from both of these uncomplexed species can be identified in Figure 2b, the major resonances present in the spectrum are for the newly formed [2]pseudorotaxane. A more than adequate separation of peaks (e.g., for the OCH_2O protons, $\mathbf{H_c}$) for the complexed and uncomplexed species renders it possible to use the single-point method[25] to determine a K_a value of $1130 \pm 60\ M^{-1}$ in CD_3CN at 298 K for a 3 mM solution. The magnitude of this stability constant demonstrates that the [2]pseudorotaxane [**PIP**/**PIP**-H⊂P24C8][PF_6] is rather stable, even in this relatively polar solvent.

Good quality crystals, suitable for X-ray analysis, were grown from a solution of [**PIP**/**PIP**-H][PF_6] and P24C8 in CH_2Cl_2 layered with iPr_2O. The X-ray structure reveals the anticipated threading of the cation through the center of the P24C8 macrocycle (Figure 3). The pseudorotaxane is stabilized by a combination of N^+–H···N (**a**), N^+–H···O (**b**), and C–H···O (**c**,**d**,**e**), hydrogen-bonding interactions. The planes of the two piperonyl ring systems are mutually inclined by approximately 82° with one unit lying close to (18°) the plane of the C-CH_2-NH_2^+-CH_2-C linking backbone, and the other oriented approximately orthogonally (82°). There are no intra- or intermolecular π–π stacking interactions; the only intermolecular interactions of note are a pair of C–H···π contacts between centrosymmetrically related pseudorotaxanes. These interactions occur between one of the polyether methylene hydrogen atoms in one pseudorotaxane and one of the benzyl rings of the cation of the other (and vice versa); the H···π distance is 2.74 Å and the C–H···π angle is 166°. There are no interactions involving the PF_6^- ion.

Although the steric bulk of the R groups in the $[R_2NH_2]^+$ ion increases on going from [**PIP**/**PIP**-H]$^+$ to the [**2NP**/**2NP**-H]$^+$, pseudorotaxane formation with P24C8 to give [**2NP**/**2NP**-H⊂P24C8]$^+$ proceeds efficiently once again. The partial ^1H NMR spectrum of this pseudorotaxane in equi-

Table 1. Stability constants (K_a) determined by using the single-point method and the derived free energies of complexation ($\Delta G°$) associated with the [2]pseudorotaxanes formed between the crown ethers P24C8, DP24C8, and DB24C8 and the salts [**1NP**/**1NP**-H][PF_6], [**1NP**/**2NP**-H][PF_6], [**2NP**/**2NP**-H][PF_6], and [**PIP**/**PIP**-H][PF_6] in CD_3CN at 25°C.[a]

	K_a [M^{-1}]			$-\Delta G°$ [kcal mol^{-1}][b]		
	P24C8	DP24C8	DB24C8	P24C8	DP24C8	DB24C8
[**1NP**/**1NP**-H][PF_6]	2230 ± 60	720 ± 40	760 ± 40	4.62 ± 0.01	3.92 ± 0.03	3.95 ± 0.04
[**1NP**/**2NP**-H][PF_6]	1100 ± 55	890 ± 50	370 ± 30	4.17 ± 0.03	4.05 ± 0.04	3.53 ± 0.04
[**2NP**/**2NP**-H][PF_6]	2270 ± 60	940 ± 50	900 ± 50	4.61 ± 0.01	4.08 ± 0.03	4.06 ± 0.04
[**PIP**/**PIP**-H][PF_6]	1130 ± 60	710 ± 40	520 ± 30	4.19 ± 0.04	3.91 ± 0.04	3.73 ± 0.04

[a] The spectra were obtained at 25°C on a Bruker Avance 500 spectrometer with the deuterated solvent as the lock and the residual solvent as internal reference. [b] The free energies of association ($-\Delta G°$) were calculated from the K_a values by using the expression $\Delta G° = -RT \ln K_a$.

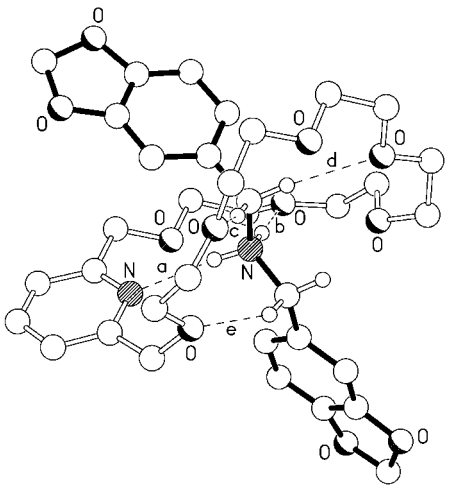

Figure 3. The solid-state superstructure of [**PIP**/**PIP**-H⊂P24C8]$^+$. The geometries of the X–H···Y hydrogen bonds are X···Y, H···Y [Å], X–H···Y [°]: **a**) 3.07, 2.17, 174; **b**) 2.92, 2.02, 175; **c**) 3.25, 2.30, 166; **d**) 3.34, 2.38, 172; **e**) 3.14, 2.27, 149.

librium with its free components in CD_3CN at 298 K is shown in Figure 4a, recorded just 5 min after mixing [**2NP**/**2NP**-H][PF_6] and P24C8. Well separated from each other

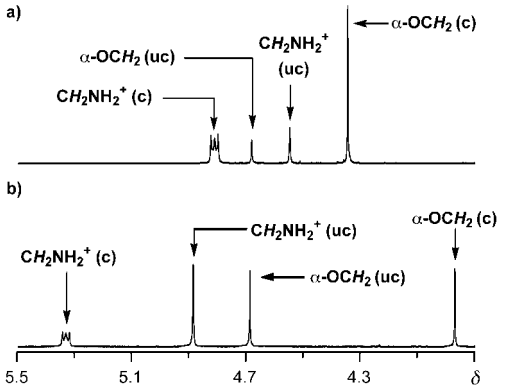

Figure 4. Partial ^{1}H NMR spectra of the [2]pseudorotaxane formation for P24C8 with a) [**2NP**/**2NP**-H][PF_6] and b) [**1NP**/**1NP**-H][PF_6] in CD_3CN at 25 °C. Peaks associated with the uncomplexed crown ether and dialkylammonium ion are denoted by the descriptor **uc**, while those associated with the complex are denoted by the descriptor **c**. The initial concentrations of the crown ether and the salt were both 3 mM.

are the characteristic multiplet, centered on $\delta = 4.8$ ppm, for the methylene protons adjacent to an NH_2^+ center encircled by a macrocycle and the singlet for the same methylene protons in the free cation, which resonate just below $\delta =$ 4.5 ppm. Likewise, signals can also be identified for the α-OCH_2 protons in the complexed and free P24C8 at approximately $\delta = 4.3$ and 4.7 ppm, respectively. On this occasion, a single-point determination[25] of the stability constant in CD_3CN at 298 K yielded a K_a value of $2270 \pm 60\,M^{-1}$. This value is almost exactly twice that obtained previously for the [**PIP**/**PIP**-H⊂P24C8][PF_6] complex, suggesting that two 2-naphthyl groups, either directly through increased π–π stacking interactions or by some indirect influence on the N^+–H···O hydrogen bonds and C–H···O interactions, are more stabilizing within the 1:1 complex than are two piperonyl groups.

Next we investigated pseudorotaxane formation between P24C8 and the [**1NP**/**1NP**-H]$^+$ ion in which the constitutions of both naphthyl rings have been changed from being linked through their 2-positions to being linked through their 1-positions. A ^{1}H NMR spectrum was recorded 5 min after the mixing of [**1NP**/**1NP**-H][PF_6] and P24C8 in equimolar amounts in CD_3CN at 298 K. Its features did not change on standing. The partial ^{1}H NMR spectrum (Figure 4b) reveals sharp signals belonging to both free and complexed species present in the solution. When compared with the analogous partial spectrum (Figure 4a) for the [**2NP**/**2NP**-H⊂P24C8]$^+$ ion, we note that the differences in the chemical shifts between the methylene protons adjacent to the NH_2^+ center in a threaded cation and the α-OCH_2 protons in the complexed P24C8 differ substantially. In the [**2NP**/**2NP**-H⊂P24C8]$^+$ ion, the signal for the complexed guest protons ($CH_2NH_2^+$) are to be found 0.55 ppm downfield of the complexed host protons (α-OCH_2), whereas for the [**1NP**/**1NP**-H⊂P24C8]$^+$ ion, there is a difference of ~1.3 ppm between the complexed host protons (α-OCH_2) and the complexed guest protons ($CH_2NH_2^+$). These differences probably reflect the existence in solution of dissimilar co-conformations adopted by the two pseudorotaxanes, in addition to variations in the conformations exhibited by the crown ether component and the constitutionally isomeric cations. Nonetheless, the stability constant of $2230 \pm 60\,M^{-1}$ obtained by the single-point method[25] for the 1:1 complex formed between [**1NP**/**1NP**-H][PF_6] and P24C8 in CD_3CN at 298 K, is almost the same as that calculated for the [**2NP**/**2NP**-H⊂P24C8]$^+$ ion.

The ^{1}H NMR spectrum of [**1NP**/**2NP**-H][PF_6] recorded in CD_3CN at 298 K is shown in Figure 5a. After addition of equimolar amounts of P24C8, the complexation/decomplexation equilibrium was established inside 5 min. An interesting feature in the ^{1}H NMR spectrum (Figure 5b) of [**1NP**/**2NP**-H⊂P24C8][PF_6] is the diastereotopicity observed[10f,15b] for the α-OCH_2 protons, in keeping with the constitutionally asymmetric guest cation being in slow exchange on the ^{1}H NMR timescale with the host crown ether, namely P24C8. On this occasion, the single-point method[25] for obtaining stability constants delivered a K_a value of $1100 \pm 60\,M^{-1}$ for the 1:1 complex formed between P24C8 and the "mixed" cation, [**1NP**/**2NP**-H]$^+$, at 298 K in CD_3CN. Clearly, this constitutionally asymmetrical cation is bound less strongly by P24C8 than are the two constitutionally symmetrical cations. The reason for this difference in binding is not immediately apparent.

Pseudorotaxane formation with DP24C8: In common with P24C8, the formation of pseudorotaxanes by DP24C8 is rapid in CD_3CN and CD_2Cl_2 solutions with all four $[R_2NH_2]^+$ ions as their PF_6^- salts (Figure 1) on the laboratory timescale; that is, the self-assembly of all four pseudorotaxanes is complete within 5 min at 298 K. Close inspection of the ^{1}H NMR spectra (Figure 5c and 6) for all four of these pseudorotaxanes in equilibria with their free counterparts reveal that the signals are somewhat broader in all in-

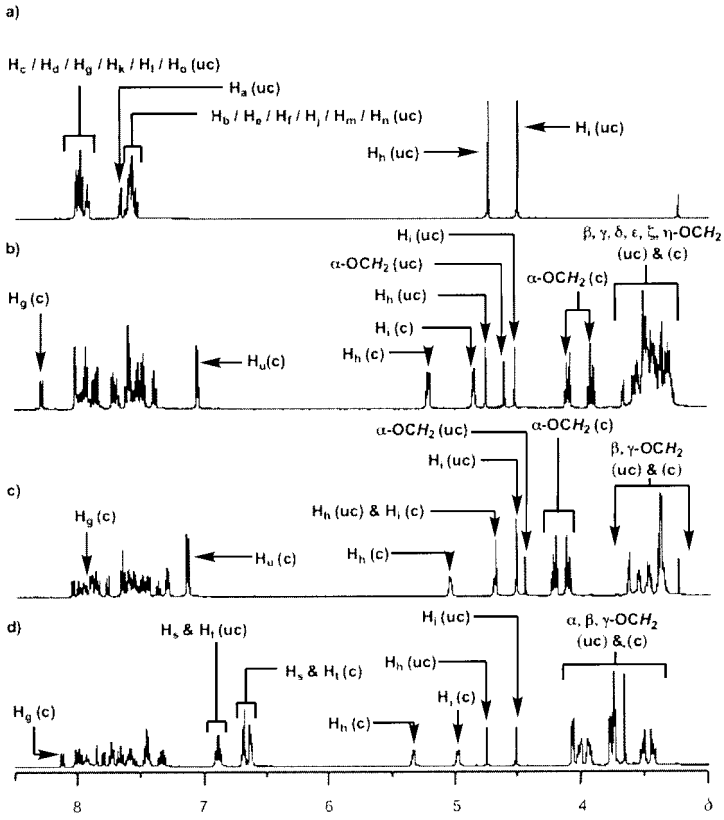

Figure 5. ^{1}H NMR spectra (500 MHz, 298 K) of a) free [**1NP/2NP**-H][PF_6], b) a 1:1 mixture of [**1NP/2NP**-H][PF_6] and P24C8, c) a 1:1 mixture of [**1NP/2NP**-H][PF_6] and DP24C8, and d) a 1:1 mixture of [**1NP/2NP**-H][PF_6] and DB24C8 in CD_3CN showing the formation of the [2]pseudorotaxanes. The initial concentrations of the crown ethers and salts were 3 mM.

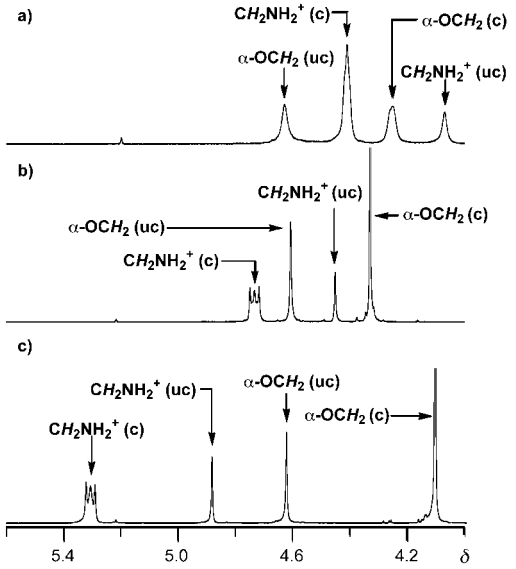

Figure 6. Partial ^{1}H NMR spectra of the free species and the [2]pseudorotaxanes formed between DP24C8 and a) [**PIP/PIP**-H][PF_6], b) [**2NP/2NP**-H][PF_6], and c) [**1NP/1NP**-H][PF_6]. The spectra were recorded at 500 MHz in CD_3CN at 25 °C. Peaks associated with the uncomplexed crown ether and dialkylammonium ion are denoted by the descriptor **uc**, while those associated with the complex are denoted by the descriptor **c**. The initial concentrations of the crown ether and the salt were both 3 mM.

stances than was observed when P24C8 is the crown ether host. This peak broadening is particularly marked in the partial spectrum (Figure 6a) of an equimolar mixture of [**PIP/PIP**-H][PF_6] and DP24C8 in CD_3CN at 298 K. Despite this fact, however, peaks belonging to both the complexed and uncomplexed species were easily distinguishable and so it was possible to deduce a K_a value of $710 \pm 40\,M^{-1}$ for [**PIP/PIP**-H⊂DP24C8][PF_6] by using the single-point method.[25] This value is slightly less than that ($1130 \pm 60\,M^{-1}$) for the same guest ion binding with the more flexible P24C8 host, an observation which suggests that no advantage in terms of binding is to be gained from increasing macrocyclic ring rigidity by introducing a second pyrido unit into it. The same downward trend in K_a values on going from P24C8 to DP24C8 as host with the guest ions [**2NP/2NP**-H]$^+$ and [**1NP/1NP**-H]$^+$ has been observed (Table 1) with values of $940 \pm 50\,M^{-1}$ and $720 \pm 40\,M^{-1}$ being obtained from the partial ^{1}H NMR spectra reproduced in Figure 6b and c, respectively. As far as chemical shifts are concerned, there is a remarkable similarity in patterns between these two spectra and those displayed in Figure 4a and b, respectively, for P24C8 and its 1:1 complexes with [**2NP/2NP**-H][PF_6] and [**1NP/1NP**-H][PF_6].

It proved possible to grow, from a solution of [**1NP/1NP**-H][PF_6] and DP24C8 in CH_2Cl_2 layered with iPr_2O, single crystals of [**1NP/1NP**-H⊂DP24C8][PF_6] that were amenable to X-ray crystallography. The solid-state superstructure is illustrated in Figure 7. The cation is threaded through the

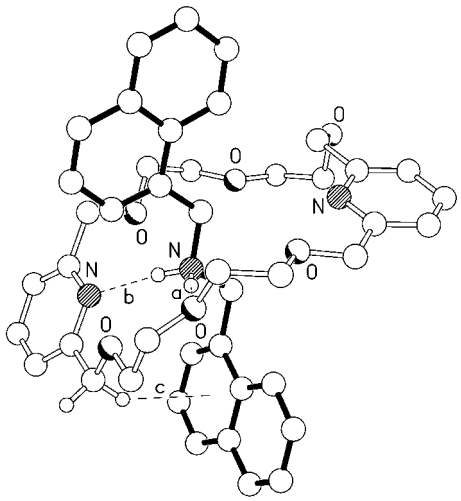

Figure 7. The solid-state superstructure of [**1NP/1NP**-H⊂DP24C8]$^+$. The hydrogen bonding geometries are, X···Y, H···Y [Å], X–H···Y [°]: **a**) 2.88, 1.99, 169; **b**) 2.96, 2.07, 170. The C–H···π interaction **c**) has H···π = 2.62 Å, C–H···π = 147°.

center of the DP24C8 macrocycle and anchored by N^+–H···O (**a**), and N^+–H···N (**b**) hydrogen bonds, and by a C–H···π interaction (**c**). There are no interactions involving either of the methylene groups adjacent to the ammonium center. The geometry of the cation is very similar to that observed for its analogue in the superstructure of [**PIP/PIP**-H⊂P24C8][PF_6]. The two naphthalene ring systems are mutually inclined by about 83° with one unit lying almost in the

plane of the linking backbone (9°) and the other oriented orthogonally (90°). The "lower" naphthalene ring in Figure 7 is involved in a parallel π–π stacking interaction with its centrosymmetrically related counterpart (mean interplanar separation 3.55 Å), whilst the "upper" ring enters into a C–H···π interaction with one of the polyether methylene groups of a symmetry related pseudorotaxane (H···π 2.89 Å, C–H···π 134°). These interactions combine to produce a loosely linked chain of pseudorotaxanes in the crystal. There are no intermolecular interactions involving either the PF_6^- ion (which is disordered) or the included CH_2Cl_2 of solvation.

And then finally, the superstructure and strength of the pseudorotaxane [**1NP**/**2NP**-H⊂DP24C8]$^+$ was investigated in CD_3CN at 298 K. The ^{1}H NMR spectrum, shown in Figure 5c, reveals the diastereotopicity[10f,15b] of the α-OCH_2 protons in the 1:1 complex involving the constitutionally asymmetric cationic guest. It was also subjected to the single-point stability constant determination,[25] yielding a K_a value of $890 \pm 50\,M^{-1}$ for the strength of the 1:1 complex; in this regard, it is little different from all the others examined (Table 1) in the DP24C8 series.

Pseudorotaxane formation with DB24C8: Figure 8 illustrates the outcome when ^{1}H NMR spectra were recorded at 298 K on solutions of DB24C8 in CD_3CN to which had been added equimolar amounts of [**PIP**/**PIP**-H][PF_6], [**2NP**/**2NP**-H][PF_6], and [**1NP**/**1NP**-H][PF_6] (a–c, respectively). Although the first two spectra (Figure 8a and b) reveal peaks for both complexed and uncomplexed species 5 min after the mixing of the components, and remain unchanged over long periods of time, the third spectrum (Figure 8c) comes as something of a surprise. The only peaks that are present are for the starting materials, the free components [**1NP**/**1NP**-H][PF_6] and DB24C8. This situation clearly represents an anomalous one and merits further investigation. We will return to a discussion of it later on. For the present, suffice it to say that the other two pseudorotaxanes, namely [**PIP**/**PIP**-H⊂DB24C8]$^+$ and [**2NP**/**2NP**-H⊂DB24C8]$^+$ behave just like their P24C8 and DP24C8 counterparts. They are formed rapidly on the laboratory timescale and exchange slowly, the latter more so than the former, on the ^{1}H NMR timescale. The net result is such that we could determine stability constants for the two pseudorotaxanes in CD_3CN at 298 K, coming up with K_a values of $520 \pm 30\,M^{-1}$ and $900 \pm 50\,M^{-1}$ for [**PIP**/**PIP**-H⊂DB24C8]$^+$ and [**2NP**/**2NP**-H⊂DB24C8]$^+$, respectively. In terms of complex strengths, the two pseudorotaxanes are more comparable with those involving DP24C8 as the host than when P24C8 is the host. Again, the take home message would seem to be that rigidity is not a virtue when it comes to forming the strongest of 1:1 complexes. This trend is one that can be bucked, however, by changing solvents. For example, in CD_2Cl_2, the stability constant for the formation of the 1:1 complex between [**PIP**/**PIP**-H][PF_6] and DB24C8 at 298 K rises to $2900 \pm 70\,M^{-1}$. This observation is one that has been noted previously[13c] for the complexation of dibenzylammonium ions with macrocyclic polyethers containing the [24]crown-8 constitution. Moreover, good quality single crystals, suitable for X-ray analysis, were grown from a solution of [**PIP**/**PIP**-H][PF_6] and DB24C8 in MeCN layered with iPr_2O. The X-ray superstructure (Figure 9) shows that the DB24C8 macrocycle adopts an extended conformation with approximate C_i symmetry. The threaded [**PIP**/**PIP**-H]$^+$ ion is bound by a combination of N^+–H···O (**a**,**b**) and C–H···O (**c**) hydrogen bonds supplemented by π–π stacking (**d**) and C–H···π (**e**) interactions. The piperonyl ring system involved in the intramolecular stacking interaction is disordered, adopting two alternate coplanar orientations (85:15), produced by an approximate 180° flip about its CH_2–C linkage (the major occupancy orientation is that illustrated in Figure 9). As was observed in the superstructure of [**PIP**/**PIP**-H⊂P24C8][PF_6], the two terminal ring systems of the cation are again oriented essentially orthogonally with respect to each other (ca. 89°). Here, however, both benzyl rings are steeply inclined to the plane of the C-CH_2-NH_2^+-CH_2-C linking backbone (by ca. 51 and 66° for the "left-" and "right-hand" ring systems, respectively, in Figure 9). The only intermolecular packing interaction of note is a π–π stacking of the benzyl rings of the "right-hand" piperonyl units in centrosymmetrically related pairs of pseudorotaxanes (mean interplanar separation 3.50 Å).

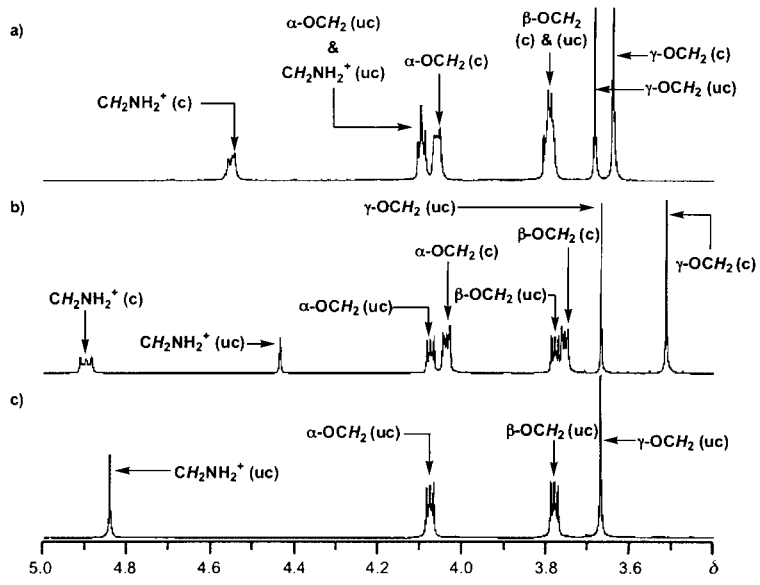

Figure 8. Partial ^{1}H NMR spectra recorded at 500 MHz showing the free species and the mixtures of DB24C8 with a) [**PIP**/**PIP**-H][PF_6], b) [**2NP**/**2NP**-H][PF_6], and c) **1NP**/**1NP**-H][PF_6] after 5 min of mixing in CD_3CN at 25 °C. Peaks associated with the uncomplexed crown ether and dialkylammonium ion are denoted by the descriptor **uc**, while those associated with the complex are denoted by the descriptor **c**. The initial concentrations of the crown ether and the salt were both 3 mM.

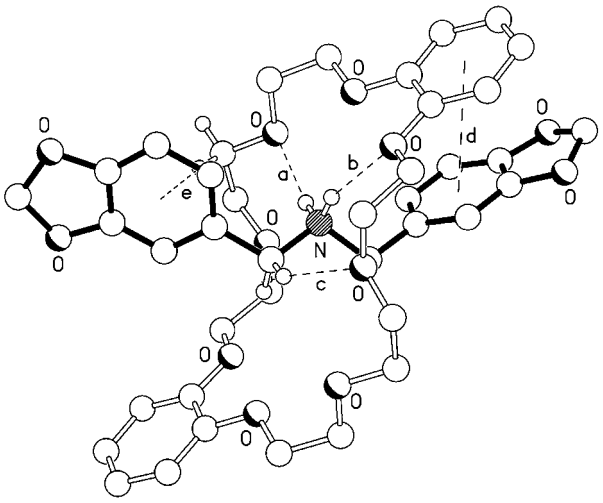

Figure 9. The solid-state superstructure of [**PIP**/**PIP**-H⊂DB24C8]$^+$. The geometries of the X–H···Y hydrogen bonds are X···Y, H···Y [Å], X–H···Y [°]: **a**) 3.03, 2.16, 161; **b**) 3.22, 2.36, 161; **c**) 3.21, 2.41, 140. The centroid–centroid and mean interplanar separations **d**) are 3.95, 3.55 Å, the rings are inclined by ca. 12°. The C–H···π interaction **e**) has H···π = 2.90 Å, C–H···π = 160°.

Let us return to the anomaly raised by the partial ^{1}H NMR spectrum illustrated in Figure 8c. Figure 10a shows the entire ^{1}H NMR spectrum recorded at 298 K, 5 min after 3 mM solutions of [**1NP**/**1NP**-H][PF_6] and DB24C8 in CD_3CN had been mixed together. In contrast with all the other experiments reported in this paper in which pseudorotaxanes are formed in solution under apparently thermodynamic control by strict self-assembly, the formation of the pseudorotaxane [**1NP**/**1NP**-H⊂DB24C8][PF_6] is a very much more difficult supramolecular assembly process to perform. Even after standing at room temperature for two days, the ^{1}H NMR spectrum (Figure 10b) revealed only very weak signals that can be attributed to the pseudorotaxane, for example, the characteristic multiplet centered on $\delta =$ 5.6 ppm for the methylene protons adjacent to an NH_2^+ center encircled by a DB24C8 ring. This signal, together with those representative of DB24C8 are the [**1NP**/**1NP**-H]$^+$ ion in their complexed forms, continued to become more prominent with a concomitant decrease in the relative intensities of the peaks for the free species until, after 22 days, equilibrium was reached: see the ^{1}H NMR spectrum reproduced in Figure 10c. A similar trend, indicating the operation of kinetic control in the formation of [**1NP**/**1NP**-H⊂DB24C8][PF_6], was also observed in CD_2Cl_2 at 298 K, except that equilibration occurs much more quickly in this solvent to form a stronger 1:1 complex in the fullness of time. Thus, in CD_3CN, while only 8% of the free components are present as the pseudorotaxane after two days, in CD_2Cl_2 the percentage is 28. In CD_2Cl_2 equilibration is complete after six days, affording 83% of the starting materials as the 1:1 complex, compared with 63% at equilibrium after 22 days in CD_3CN. The ^{1}H NMR spectra for these two equilibrium situations are illustrated in Figure 11a and b, respectively. At equilibrium, single-point determinations of the stability constants yielded K_a values of $760 \pm 40\,M^{-1}$ and $3570 \pm 70\,M^{-1}$, respectively, for 1:1 complex formation in CD_3CN and CD_2Cl_2.

Because the passage of the DB24C8 ring over the 1-naphthyl substituents of the [**1NP**/**1NP**-H]$^+$ ion is not rapid on the laboratory timescale relative to the other $[R_2NH_2]^+$ ions, we decided to investigate the kinetics of the complexation/decomplexation process by ^{1}H NMR spectroscopy. First of all, however, we determined stability constants for the 1:1 complex formed between DB24C8 and [**2NP**/**2NP**-H][PF_6] in CD_3CN and CD_2Cl_2 and in a mixed solvent system (MSS) composed of $CDCl_3$:CD_3CN (3:1) at 25°C and 40°C using the single-point method[25] on equilibrated systems. The K_a values are summarized in full in Table 2, along with the derived free energies of complexation ($\Delta G°$). Two points are worthy of note. First, for a particular solvent, the K_a value decreases with increasing temperature, for example, $3300\,M^{-1}$ at 25°C versus $1700\,M^{-1}$ at 40°C in the MSS. Second, these K_a values are considerably higher than those ($900\,M^{-1}$ and $480\,M^{-1}$, respectively) obtained in CD_3CN, but not all that far short, at least at 25°C, of the K_a value of $3570\,M^{-1}$ obtained in CD_2Cl_2.

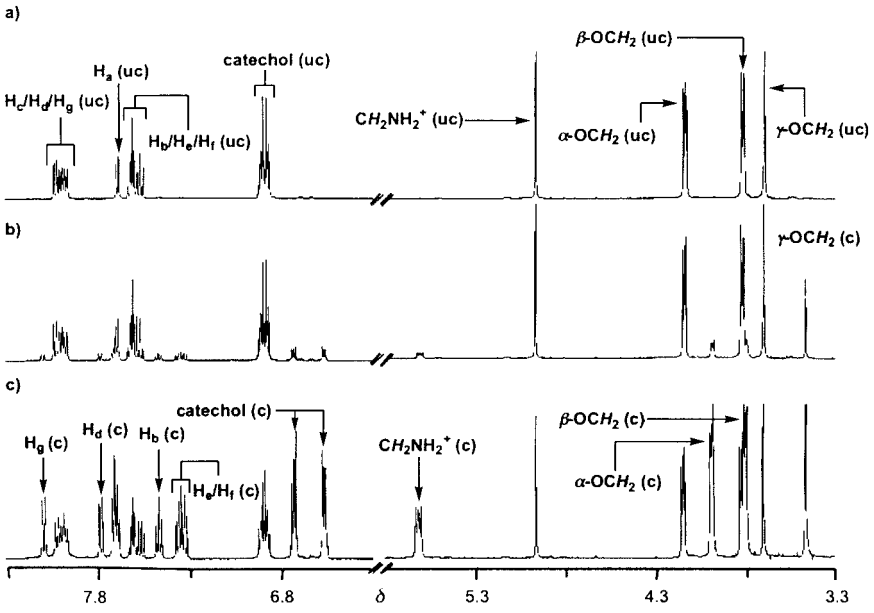

Figure 10. Partial ^{1}H NMR spectra (CD_3CN, 500 MHz, 25°C) of a 1:1 mixture of DB24C8 and [**1NP**/**1NP**-H][PF_6], illustrating the slow formation of the [**1NP**/**1NP**-H⊂DB24C8][PF_6] complex. The spectra portrayed were recorded after a) 5 min, b) 2 days, and c) 22 days. Peaks associated with the uncomplexed crown ether and dialkylammonium ion are denoted by the descriptor **uc**, while those associated with the complex are denoted by the descriptor **c**. The initial concentrations of the crown ether and the salt were both 3 mM.

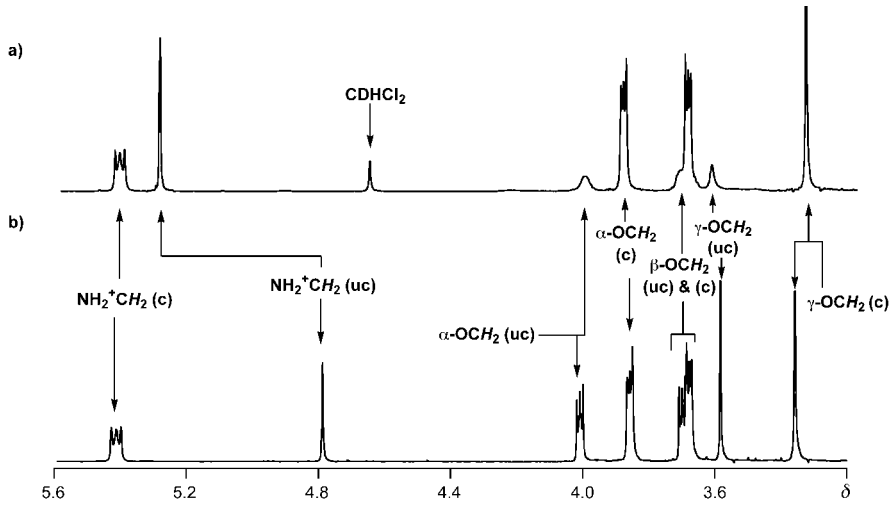

Figure 11. Partial ^{1}H NMR spectra (500 MHz, 298 K) of a 1:1 mixture of [**1NP/1NP**-H][PF_6] and DB24C8 (both 3 mM) in a) CD_2Cl_2 and b) CD_3CN after 6 and 22 days, respectively. Peaks associated with the uncomplexed crown ether and dialkylammonium ion are denoted by the descriptor **uc**, while those associated with the complex are denoted by the descriptor **c**.

The rate constants (k_{on}) for the passage of the DB24C8 ring over one of the 1-naphthyl substituents in the [**1NP/1NP**-H]$^+$ ion were calculated by using Equation (1):

$$P_t = [D_0^2 P_e e^{(k_{on}t(D_0^2-P_e^2)/P_e} - D_0^2 P_e]/[D_0^2 e^{(k_{on}t(D_0^2-P_e^2)P_e)} - P_e^2] \quad (1)$$

in which D_0 is the initial concentration of the uncomplexed [**1NP/1NP**-H][PF_6] or DB24C8, and P_e and P_t correspond to the concentration of the pseudorotaxane [**1NP/1NP**-H⊂DB24C8][PF_6] at equilibrium and at time t, respectively. Nonlinear curve fitting of the plot of P_t against t affords values of k_{on}, from which estimates of the respective free energies of activation for ingression ($\Delta G^{\neq}_{on}$) and egression ($\Delta G^{\neq}_{off}$) can be calculated (Table 2). The values of $\Delta G^{\neq}_{on}$ and $\Delta G^{\neq}_{off}$ are in the range that we would normally associate with the process we refer to as slippage.[24] When compared (Table 2) with slippage studies carried out previously[24m] on pseudorotaxanes formed between DB24C8 and the dibenzylammonium ion carrying isopropyl substituents on the *para*-positions of the two phenyl rings, that is, [**4IPP/4IPP**-H]$^+$, it is evident that the thermodynamic data associated with the formation of [**1NP/1NP**-H⊂DB24C8][PF_6] and [**4IPP/4IPP**-H⊂DB24C8][PF_6] are very similar indeed. They even share an apparent anomaly that was not commented upon previously, that is, that in all cases, the $\Delta G^{\neq}_{on}$ and $\Delta G^{\neq}_{off}$ values increase ever so slightly with increasing temperature. It is tempting to speculate that this trend is a consequence of the entropic penalty paid at the transition state by a negative entropy of activation. It is a phenomenon that is worthy of further investigation.

Single crystals of the pseudorotaxane [**1NP/1NP**-H⊂DB24C8][PF_6], suitable for X-ray analysis, could be grown from a solution of [**1NP/1NP**-H][PF_6] and DB24C8 in CH_2Cl_2 layered with iPr$_2$O. The X-ray superstructure reveals that the DB24C8 macrocycle once again adopts an extended conformation with approximate C_i symmetry (Figure 12). The [**1NP/1NP**-H]$^+$ ion is bound to the macrocycle by a combination of N^+–H···O (**a**,**b**) and C–H···O (**c**) hydrogen bonds supplemented by a π–π stacking interaction (**d**) between one of the naphthalene rings of the cation and one of the catechol rings of the DB24C8 host. The planes of two naphthalene rings of the cation are mutually orthogonal (90°). The "upper" and "lower" naphthalene rings are inclined by approximately 30 and 76°, respectively, to the plane of their C-CH_2-NH_2^+-CH_2-C linking backbone. The

Table 2. Kinetic and thermodynamic data for the formation[a] of the [2]pseudorotaxane [**1NP/1NP**-H⊂DB24C8][PF_6] in CD_3CN, CD_2Cl_2, and MSS[b] at 25 and 40 °C; in each case the concentrations of the components were 3 mM. A comparison is made with data taken from the literature (see ref. [24m]) relating to the formation of [**4IPP/4IPP**-H⊂DB24C8][PF_6] in MSS[b] at 25 and 40 °C; in each case the concentrations of the components are 3 mM.

	Solvent	T [°C]	K_a [M^{-1}][c]	$-\Delta G°$ [kcal mol^{-1}][d]	k_{on} [$M^{-1}s^{-1}$][e]	$\Delta G^{\neq}_{on}$ [kcal mol^{-1}][g]	k_{off} [s^{-1}][f]	$\Delta G^{\neq}_{off}$ [kcal mol^{-1}][g]
[**1NP/1NP**-H⊂DB24C8][PF_6]	CD_3CN	25[h]	900	4.0	3.0×10^{-4}	22.4	4.0×10^{-7}	26.4
[**1NP/1NP**-H⊂DB24C8][PF_6]	CD_3CN	40[h]	480	3.7	1.6×10^{-4}	23.8	3.3×10^{-7}	27.5
[**1NP/1NP**-H⊂DB24C8][PF_6]	CD_2Cl_2	25[h]	3570	4.9	2.1×10^{-3}	21.3	5.8×10^{-7}	26.1
[**1NP/1NP**-H⊂DB24C8][PF_6]	MSS	25[h]	3300	4.8	2.9×10^{-3}	21.1	8.7×10^{-7}	25.9
[**1NP/1NP**-H⊂DB24C8][PF_6]	MSS	40[h]	1700	4.4	1.3×10^{-3}	21.5	7.4×10^{-7}	26.0
[**4IPP/4IPP**-H⊂DB24C8][PF_6]	MSS	20[i]	2870	4.6	1.1×10^{-3}	21.5	3.9×10^{-7}	25.7
[**4IPP/4IPP**-H⊂DB24C8][PF_6]	MSS	40[i]	2470	4.9	3.2×10^{-3}	21.9	1.3×10^{-7}	26.8

[a] The reactions were followed with ^{1}H NMR spectroscopy by monitoring the changes in the relative intensities of the signals associated with the probe protons in the complexed and uncomplexed ammonium cations. [b] MSS = mixed solvent system (3:1, $CDCl_3/CD_3CN$). [c] The K_a values were obtained from single-point measurements of the concentrations of the complexed and uncomplexed cations in the relevant ^{1}H NMR spectrum. [d] The free energies of complexation ($\Delta G°$) were calculated from the K_a values by using the expression $\Delta G° = -RT\ln K_a$. [e] The second-order rate constants (k_{on}) were calculated by employing Equation (1). [f] The first-order rate constants for the egression (k_{off}) were calculated from k_{on} and K_a values by using the expression $k_{off} = k_{on}/K_a$. [g] The free energies of activation for the ingression ($\Delta G^{\neq}_{on}$) of the macrocycle over the R substituents of the $[R_2NH_2]^+$ ion and the egression ($\Delta G^{\neq}_{off}$) process were calculated using the relationships $\Delta G^{\neq}_{on} = -RT\ln(k_{on}h/kT)$ and $\Delta G^{\neq}_{off} = -RT\ln(k_{off}h/kT)$, in which R, h, and k correspond separately to the gas, Planck and Boltzmann constants, respectively. [h] The probe protons were the methylene ones adjacent to the NH_2^+ center. [i] The probe protons were the isopropyl methine ones situated *para* on the phenyl rings.

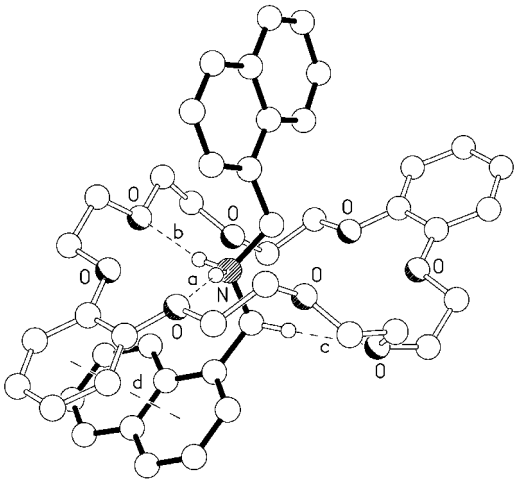

Figure 12. The solid-state superstructure of [**1NP/1NP**-H⊂DB24C8]$^+$. The geometries of the X–H···Y hydrogen bonds are X···Y, H···Y [Å], X–H···Y [°]: **a**) 3.05, 2.17, 166; **b**) 3.00, 2.11, 168; **c**) 3.31, 2.33, 178. The centroid–centroid and mean interplanar separations **d**) are 3.79, 3.60 Å, the rings are inclined by approximately 10°.

only inter-pseudorotaxane interaction of note is a π–π stacking of the "upper" naphthalene rings of centrosymmetrically related pairs of molecules (the mean interplanar separation is 3.39 Å). The PF_6^- ion and the included CH_2Cl_2 solvent are both disordered.

Whereas the [**2NP/2NP**-H]$^+$ ion threads its way through DB24C8 with relative ease, it is a considerable struggle for the [**1NP/1NP**-H]$^+$ ion to accomplish a similar feat. Thus, it was intriguing to learn how the mixed [**1NP/2NP**-H]$^+$ ion would fare. In the event, what one might predict happens: when [**1NP/2NP**-H][PF_6] and DB24C8 are mixed together in CD_3CN in equimolar proportions at 298 K, their equilibration to form the pseudorotaxane [**1NP/2NP**-H⊂DB24C8][PF_6] is certainly all over inside 5 min. The ^{1}H NMR spectrum illustrated in Figure 5d reveals not only signals for both complexed and uncomplexed species, but also the diastereotopicities[10f,15b] imposed upon the different OCH_2 groups in the DB24C8 host. The K_a value of 370 ± 30 M^{-1} for the 1:1 complex, which was determined using the single-point method,[25] was less than for those involving the constitutionally isomeric ions for whatever reason. These differences in ground-state free energies are almost insignificant relative to the transition-state free energy differences, when the DB24C8 ring passes over a 1-naphthyl substituent rather than over a 2-naphthyl one to form a pseudorotaxane. Consequently, it was decided to investigate computationally the very different barriers to threading and dethreading of DB24C8 in relation to the two constitutionally isomeric cationic dumbbells, [**1NP/1NP**-H]$^+$ and [**2NP/2NP**-H]$^+$.

The two isomeric pseudorotaxanes [**1NP/1NP**-H⊂DB24C8]$^+$ and [**2NP/2NP**-H⊂DB24C8]$^+$ were studied with the AMBER* force field[26] and GB/SA solvent model[27] for $CHCl_3$. In order to model the dethreading process (Figure 13a), a "dummy" atom was placed at a distance of 55.0 Å from the nitrogen atom in each dumbbell with the positions of both the dummy and the nitrogen atoms fixed. The distance between the dummy atom and the carbon at position **t** on one of DB24C8's two catechol rings was then reduced incrementally and energy minimization was performed at each step. A 30 ps molecular dynamics simulation (1.5 fs time step) at a simulation temperature of 500 K, followed by energy minimization of 150 randomly selected co-conformations gave a local energy minimum for each fixed distance. The energies were then normalized relative to the fully separated DB24C8 ring and dumbbell components.

The resulting energy differences (ΔE) were plotted against distance in order to construct the energy profiles shown in Figure 13d. It is clear from the results that the energies associated with the threading/dethreading processes involving the [**2NP/2NP**-H]$^+$ ion (co-conformations **E**→**F**→**G**→**H**) are much lower than those for the isomeric [**1NP/1NP**-H]$^+$ dumbbell (co-conformations **A**→**B**→**C**→**D**). This observation is in agreement with the results of experiments (Table 2). A comparison of the two computed transition states (the highest energy co-conformations on their respective computed energy profiles) of the [**1NP/1NP**-H⊂DB24C8]$^+$ and [**2NP/2NP**-H⊂DB24C8]$^+$ pseudo-

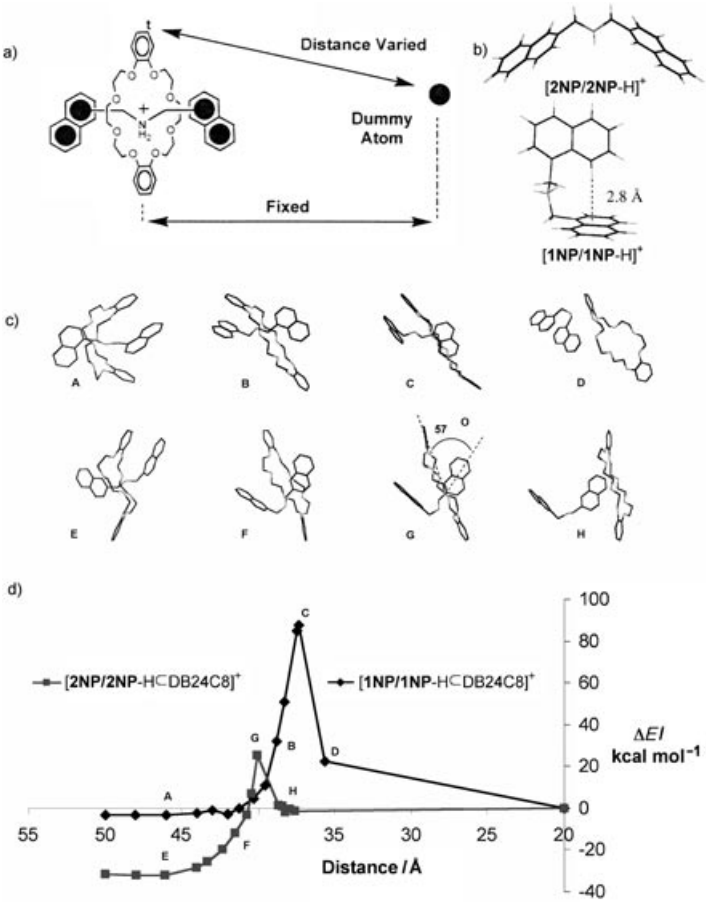

Figure 13. a) Schematic diagram illustrating the protocol utilized for the computational simulations delineated in this article. b) The computationally generated energy-minimized conformations of the ground state of [**2NP/2NP**-H]$^+$ and [**1NP/1NP**-H]$^+$ ions showing the intramolecular [C–H···π] interaction in the latter ion. c) The snapshots depicting the journey of the naphthyl groups of the [**1NP/1NP**-H]$^+$ and [**2NP/2NP**-H]$^+$ ions through the cavity of DB24C8. d) The energy profiles associated with the passage of the macrocyclic polyether DB24C8 over the terminal groups of the cationic isomers [**2NP/2NP**-H]$^+$ and [**1NP/1NP**-H]$^+$.

rotaxanes (Figure 13c **C** and **G**, respectively) shows the steric interactions that contribute to the energy barriers observed in Figure 13d. When viewed from similar perspectives, it is apparent that one of the main differences between the two transition states is the relative orientations of the naphthyl groups as they are being enticed to pass through the cavity of the DB24C8 macrocycle. In the [**1NP**/**1NP**-H⊂DB24C8]$^+$ ion, the 1-naphthyl group is positioned such that its longest axis is parallel with that of DB24C8 (Figure 13c **C**). This relative arrangement results in the 1-naphthyl group occupying the majority of the space within the cavity of the macrocycle. Consequently, the conformation of the macrocycle becomes highly constrained, thus lowering the entropy activation for egression. By contrast, in the [**2NP**/**2NP**-H⊂DB24C8]$^+$ ion, the long axis of the 2-naphthyl group is angled at approximately 57° to that of the DB24C8 ring (Figure 13c **G**), allowing it to adopt a more favorable conformation for the passage of the 2-naphthyl group through its cavity.

The experimental barriers for $\Delta G^{\ddagger}_{on}$ and $\Delta G^{\ddagger}_{off}$ for [**1NP**/**1NP**-H⊂DB24C8] in CD_2Cl_2 are 21.3 and 26.1 kcal mol^{-1}, respectively (Table 2), while the calculated barriers for these two processes are 79.6 kcal mol^{-1} for $\Delta G^{\ddagger}_{on}$ and 90.8 kcal mol^{-1} for $\Delta G^{\ddagger}_{off}$. The calculated values are notably higher than the experimental ones, an outcome which is most likely a consequence of the force field being less able to calculate the energy of a system accurately under high steric strain. Although experimental values for $\Delta G^{\ddagger}_{on}$ and $\Delta G^{\ddagger}_{off}$ could not be obtained for [**2NP**/**2NP**-H⊂DB24C8] on account of fast threading/dethreading, they are anticipated to be on the order of 14–18 kcal mol^{-1}. The calculated values for the same processes are 25.0 kcal mol^{-1} for $\Delta G^{\ddagger}_{on}$ and 56.5 kcal mol^{-1} for $\Delta G^{\ddagger}_{off}$. In these cases, the calculated values are clearly in closer agreement with the experimental values.

A calculated $-\Delta H°$ value of 11.2 kcal mol^{-1} was obtained for the [**1NP**/**1NP**-H⊂DB24C8]$^+$ ion, a value which is considerably higher than the experimental values (Table 2) of 4.0 kcal mol^{-1} in CD_3CN and 4.9 kcal mol^{-1} in CD_2Cl_2 at 298 K. While the threading/dethreading of the [**2NP**/**2NP**-H]$^+$ ion with DB24C8 is too fast to allow for the accurate determination of an experimental value, the computationally estimated $-\Delta H°$ value of 31.5 kcal mol^{-1} is certainly much larger than the "real" number. GB/SA calculations of cations in solution typically have errors of ±5 kcal mol^{-1}.[28] The calculated $-\Delta H°$ values for each complex, however, both overestimate the stability of the complexed species by greater than 5 kcal mol^{-1}. In addition, the [**2NP**/**2NP**-H⊂DB24C8]$^+$ ion is predicted to be 20.3 kcal mol^{-1} more stable relative to its isolated components than the [**1NP**/**1NP**-H⊂DB24C8]$^+$ ion. A major contributing factor to this overestimation may arise from the fact that the global minimum of the [**1NP**/**1NP**-H]$^+$ ion is more stable (11.7 kcal mol^{-1}) than that of the [**2NP**/**2NP**-H]$^+$ ion. This difference in energy could be attributed to the stabilizing C–H···π interaction (Figure 13b) that is present in the isomeric [**1NP**/**1NP**-H]$^+$ ion.

In order to help determine the magnitude of error in these force field calculations, the complexation energy of a dimethylammonium ion with diethylene glycol dimethyl ether (diglyme) was calculated both with the AMBER* force field and with a quantum mechanical calculation that should give a relatively accurate interaction energy. The interactions governing complexation in the dimethylammonium/diglyme system should be the same as those governing the complexation in the [**1NP**/**1NP**-H⊂DB24C8]$^+$ and [**2NP**/**2NP**-H⊂DB24C8]$^+$ ions, and their energies should therefore be comparable. A MCMM conformational search by using the AMBER* force field and GB/SA solvent model for $CHCl_3$ of dimethylammonium, diglyme, and their complex resulted in a $-\Delta H°$ value of 19.4 kcal mol^{-1}. Density functional theory, B3LYP6-31G*[29] calculations using the cpcm solvent model[30] for $CHCl_3$ indicated a free energy of complexation $-\Delta G°$ of 8.1 kcal mol^{-1}. This value is within reasonable expectation for such a system. It is apparent that calculations with the AMBER* force field and GB/SA solvent model for $CHCl_3$ overestimate complexation energies for systems like [**1NP**/**1NP**-H⊂DB24C8]$^+$ and [**2NP**/**2NP**-H⊂DB24C8]$^+$ by around 11 kcal mol^{-1}. Investigations into further parameterization of the force field to reflect more accurately the experimental values for this type of dialkylammonium binding are underway.

While computations were unable to reproduce quantitatively the experimental values for $\Delta G^{\ddagger}_{off}$, the magnitudes of the calculated energy barriers are relatively comparable for two supramolecular systems that are not too dissimilar. Previous studies have shown that small changes in the size of the terminal groups in similar dialkylammonium dumbbells result in large differences in the ease of threading/dethreading with respect to DB24C8 as the crown ether host. In this case, however, it has been demonstrated that constitutional isomerism in the guest dialkylammonium ions can also exercise a large influence on the dynamics of threading/dethreading.

Competition experiments: When thermodynamic control is operative in a system involving a complex set of interconnected equilibria, competition experiments can provide a rapid and precise way of comparing the relative stabilities of the different entities that are in equilibrium with each other. Consequently, competition experiments were devised in which *one* guest PF_6^- salt—where the cation is either [**1NP**/**1NP**-H]$^+$, [**1NP**/**2NP**-H]$^+$, [**2NP**/**2NP**-H]$^+$, or [**PIP**/**PIP**-H]$^+$—was mixed with the *three* crown ether hosts, namely, P24C8, DP24C8 and DB24C8, in equimolar proportions (3 mM) in CD_3CN at 298 K.

In the first experiment with [**PIP**/**PIP**-H][PF_6] as the single guest salt, the ^{1}H NMR spectrum recorded after 5 min revealed that the most stable pseudorotaxane was that formed with P24C8, followed by DP24C8, with DB24C8 a close third; this is in line totally with the K_a values reported in Table 1. However, the sheer complexity of the spectrum made the assignment of percentages a dubious activity and so it was resisted. This problem did not haunt the analogous competition experiment in which [**2NP**/**2NP**-H][PF_6] was the single guest salt in search of the three crown ether hosts. The ratio of the pseudorotaxanes were easily deduced from the appropriate signals in the ^{1}H NMR spectrum and were, once again, in agreement with the K_a values listed in

Table 1. The crown ether host P24C8 accounted for 49% of the pseudorotaxanes present at equilibrium with 31% and 20% being claimed by DP24C8 and DB24C8, respectively. When [**1NP/1NP**-H][PF_6] was the single guest salt present, the ratio of pseudorotaxanes containing the crown ether hosts P24C8, DP24C8, and DB24C8 was 50:30:20 on the percentage scale but only after waiting for 22 days for the system to reach equilibrium. An unexpected additional observation, however, came to light during this competition experiment, whereby kinetic control dominates the early stages of the experiment. The ^{1}H NMR spectrum (Figure 14a) recorded after 5 min not only confirmed the absence of [**1NP/1NP**-H⊂DB24C8][PF_6], but it also revealed that the [2]pseudorotaxane involving the [**1NP/1NP**-H]$^+$ ion forms faster with DP24C8 than it does with P24C8. The relative ratios are 86:14. It was only after 7 days that the ratio changes to 46:54 in favor of [**1NP/1NP**-H⊂P24C8][PF_6]. These observations tell us that the more rigid DP24C8 forms a [2]pseudorotaxane faster than the more flexible P24C8. Ultimately, however, this latter [2]pseudorotaxane predominates (Figure 14c) at equilibrium after 22 days over the former one, that is, [**1NP/1NP**-H⊂DP24C8][PF_6], presumably because the cooperative strength of the intracomplex noncovalent bonds are stronger in [**1NP/1NP**-H⊂P24C8][PF_6] than in its DP24C8 counterpart. This kind of interplay between kinetic and thermodynamic products has been observed previously[31] during template-assisted clipping reactions that occur under equilibrium control to afford rotaxanes between dumbbell components containing NH_2^+ centers (the templates) and the macrocycles containing two imine bonds whose formation is reversible under the conditions of the reaction. Thus, an intellectually satisfying link has been established between two thermodynamically controlled phenomena, namely, slippage[24] and dynamic covalent chemistry;[32] these depend upon the reversible formation of noncovalent bonds, that is, strict self-assembly[2] within the context of supramolecular chemistry,[33] and the dynamic nature of certain covalent bonds, respectively.

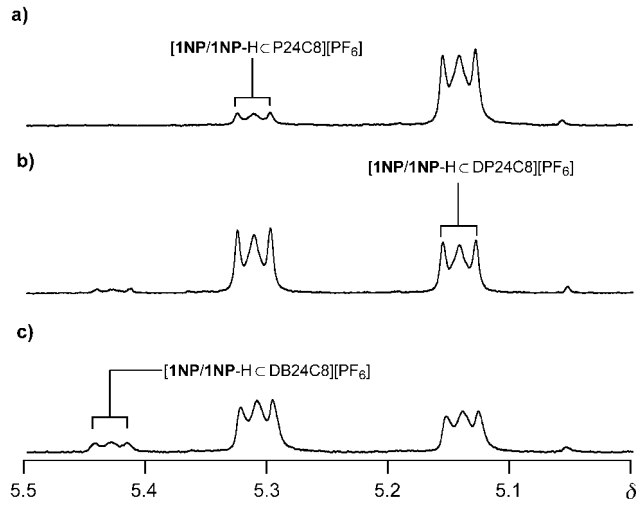

Figure 14. Partial ^{1}H NMR (500 MHz) spectra detailing the changes in the relative abundances of the [**1NP/1NP**-H⊂P24C8]$^+$, [**1NP/1NP**-H⊂DP24C8]$^+$, and [**1NP/1NP**-H⊂DB24C8]$^+$ ions after a) 5 min, b) 7 days, and c) 22 days in CD_3CN at 25°C. The spectra were obtained as part of a competition experiment wherein [**1NP/1NP**-H][PF_6] was equilibrated at 3 mM concentration with P24C8, DP24C8, and DB24C8.

Conclusion

The research reported in this full paper emphasizes the importance of kinetics as well as thermodynamics during the expression of the phenomena we refer to as slippage[24] for the preparation of pseudorotaxanes and rotaxanes. The concept is not unrelated to our recent observation that multivalency[34]—which is ultimately a thermodynamic phenomenon—can also be expressed kinetically, at least in unnatural host–guest systems,[35] in the initial stages of its happening!

Experimental Section

General methods: All chemicals were purchased from Aldrich and used as received. Pyrido[24]crown-8[19–23] and dipyrido[24]crown-8[18] were prepared according to literature procedures. Solvents were dried according to literature procedures. All reactions were performed under an anhydrous argon atmosphere unless otherwise stated. Melting points were determined using an Electrothermal AI9000 series melting point apparatus and are uncorrected. All ^{1}H and ^{13}C NMR spectra were recorded on either 1) a Bruker Avance500 (500 MHz and 125 MHz, respectively) or 2) a Bruker ARX500 (500 MHz and 125 MHz, respectively) spectrometer with the deuterated solvent as the lock and the residual solvent as the internal standard. Samples were prepared in CD_3CN purchased from Cambridge Isotope Labs. All chemical shifts are quoted using the δ scale, and all coupling constants (J) are expressed in Hertz (Hz). Electrospray mass spectra (ESMS) were measured on a VG ProSpec triple focusing mass spectrometer with MeCN as the mobile phase. Fast atomic bombardment (FAB) mass spectra were obtained 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) were employed as reference compounds.

Bis(1-naphthylmethyl)ammonium hexafluorophosphate [1NP/1NP-H][PF_6]: A solution of 1-naphthaldehyde (2.00 g, 12.8 mmol) and 1-naphthylmethylamine (2.01 g, 12.8 mmol) was dissolved in PhMe (100 mL), and the solution heated under reflux with stirring for 15 h. The H_2O generated during the reaction was collected in a Dean–Stark trap. The solvent was removed under vacuum, and the pale yellow solid obtained was dissolved in anhydrous MeOH to which $NaBH_4$ (2.9 g, 76.6 mmol) was added. The resulting solution was stirred at 25°C overnight. Next, the reaction mixture was treated with HCl (2 M, 20 mL), and the solvents were removed under reduced pressure. The solid residue was suspended in NaOH (8 M, 50 mL) and extracted with $CHCl_3$ (3×100 mL). The combined organic fractions were dried ($MgSO_4$), filtered and the solvents were evaporated off to give the bis(1-naphthylmethyl)amine (3.43 g, 90%) as a pale yellow oil, which crystallized on standing. This solid was dissolved in CH_2Cl_2, to which HCl (12 M, 0.5 mL) was added with stirring over a period of 1 h. After filtration, the white precipitate was dissolved in boiling H_2O to which a saturated aqueous solution of NH_4PF_6 was added. The white, crystalline precipitate was subsequently filtered, washed with copious amounts of H_2O and dried, affording [**1NP/1NP**-H][PF_6] (3.91 g, 69%). M.p. 193°C; ^{1}H NMR (CD_3CN, 500 MHz): δ = 4.84 (s, 4H), 7.55–7.62 (m, 6H), 7.69 (d, J = 10 Hz, 2H), 7.96–7.99 (m, 4H), 8.03 ppm (d, J = 10 Hz, 2H); ^{13}C NMR (CD_3CN, 125 MHz): δ = 48.5, 122.7, 125.3, 126.2, 126.5, 127.1, 128.9, 129.7, 130.6, 131.1, 133.7 ppm; MS (ESI): m/z (%): calcd 298.1596; found 298.1597 (100) $[M-PF_6]^+$.

1-Naphthylmethyl-2-naphthylmethylammonium hexafluorophosphate [1NP/2NP-H][PF_6]: A solution of 2-naphthaldehyde (1.00 g, 6.4 mmol) and 1-naphthylmethylamine (1.03 g, 6.5 mmol) in PhMe (50 mL) was heated under reflux with stirring in a Dean–Stark apparatus for 14 h.

After the reaction mixture had been cooled down to room temperature, the solvent was removed under pressure to give the imine as an off-white solid. This solid was dissolved in a MeOH/THF (3:1, 60 mL) mixture, followed by the portionwise addition of $NaBH_4$ (1.45 g, 38.2 mmol) and stirring at room temperature after which HCl (2 M, 10 mL) was added to the mixture. After evaporation of the solvent, the residue was suspended in NaOH (8 M, 10 mL) and extracted with CH_2Cl_2 (2×50 mL). The combined extracts were washed with H_2O (20 mL) and brine (20 mL), and dried ($MgSO_4$). Removal of the solvents under pressure afforded the amine (1.5 g, 80%) as a yellow oil. The amine was dissolved in CH_2Cl_2 and 10 drops of concentrated HCl were then added. The reaction mixture was stirred for a further 2 h. The solvent was evaporated off under pressure and the hydrochloride salt was dissolved in hot MeOH (25 mL). A saturated aqueous solution of NH_4PF_6 (5 mL) was added to this solution until a white precipitate appeared. The mixture was allowed to cool down to room temperature before being filtered. The precipitate was washed with copious amounts of H_2O and air dried, affording [**1NP/2NP**-H][PF_6] (1.36 g, 61%). M.p. 193 °C; ^{1}H NMR (CD_3CN, 500 MHz): δ = 4.52 (s, 2H), 4.75 (s, 2H), 7.54–7.64 (m, 6H), 7.67 (d, J = 10 Hz, 1H), 7.91–8.02 ppm (m, 7H); ^{13}C NMR (CD_3CN, 125 MHz): δ = 48.1, 51.8, 116.7, 122.9, 125.3, 126.3, 126.5, 126.8, 126.9, 127.1, 127.2, 127.6, 127.9, 128.8, 128.9, 129.6, 130.3, 130.5, 131.0, 132.9, 133.4, 133.7 ppm; (ESI): m/z (%): calcd 298.1596; found 298.1595 (100) [$M-PF_6$]$^+$.

Bis(2-naphthylmethyl)ammonium hexafluorophosphate [2NP/2NP-H][PF$_6$]: A solution of 2-naphthaldehyde (0.61 g, 3.8 mmol) and 2-naphthylmethylamine (0.60 g, 3.8 mmol) was heated under reflux for 20 h in PhMe (75 mL) using a Dean–Stark apparatus. The solvent was evaporated off under vacuum and the residue dissolved in MeOH (75 mL). $NaBH_4$ (0.87 g, 22.9 mmol) was added portionwise to the solution with stirring. The reaction mixture was quenched with HCl (2 M, 10 mL) and the solvents were removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL) and the combined organic layers were dried ($MgSO_4$). The solvents were evaporated off to give an off-white solid (1.00 g, 88%), which was subsequently dissolved in CH_2Cl_2 (25 mL) to which HCl (12 M, 10 mL) was added. The precipitate was then dissolved in boiling H_2O (35 mL) and saturated aqueous NH_4PF_6 (5 mL) added to yield a white crystalline precipitate, which was filtered off, washed with H_2O, and dried, affording [**2NP/2NP**-H][PF_6] (0.85 g, 64%). M.p. 216 °C; ^{1}H NMR (CD_3CN, 500 MHz): δ = 4.44 (s, 4H), 7.55–7.59 (m, 6H), 7.93–7.99 ppm (m, 8H); ^{13}C NMR (CD_3CN, 125 MHz): δ = 51.5, 126.7, 126.9, 127.2, 127.6, 127.7, 127.9, 128.7, 130.1, 132.9, 133.4 ppm; MS (ESI): m/z (%): calcd 298.1596; found 298.1586 (100) [$M-PF_6$]$^+$.

Bis(piperonylmethyl)ammonium hexafluorophosphate [PIP/PIP-H][PF$_6$]: A solution of piperonylamine (2.00 g, 13.2 mmol) and piperonal (1.99 g, 13.2 mmol) was heated under reflux in PhMe (100 mL), and the liberated H_2O was separated by means of a Dean–Stark apparatus. The organic phase was cooled and the PhMe was evaporated off, yielding a white solid. The solid was taken up in warm MeOH (100 mL) and $NaBH_4$ (3.00 g, 79.2 mmol) was added portionwise to the solution over the following 2 h. The reaction mixture was stirred for 15 h at ambient temperature. Aqueous HCl (2 M, 50 mL) was added to the MeOH solution and then the solvents were evaporated under vacuum. The solid residue was suspended in aqueous NaOH (8 M, 50 mL) and extracted with $CHCl_3$ (3×40 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated to give the amine as a white solid (3.12 g, 83%). HCl (12 M, 0.5 mL) was added to a solution of the amine in Me_2CO (30 mL), and the reaction mixture stirred at ambient temperature for 2 h. Evaporation of the solvents produced a white solid, which was dissolved in hot MeOH (60 mL). A saturated aqueous solution of NH_4PF_6 in H_2O was added dropwise until no further precipitation was detected. The aqueous phase was extracted with CH_2Cl_2 (2×25 mL). The organic phase was dried ($MgSO_4$) and the solvent evaporated to give [**PIP/PIP**-H][PF_6] (4.26 g, 75%) as a white solid. M.p. 210 °C; ^{1}NMR (CD_3CN, 500 MHz): δ = 4.09 (s, 4H), 5.99 (s, 4H), 6.87–6.89 (m, 4H), 6.92–6.94 ppm (m, 2H); ^{13}C NMR (CD_3CN, 125 MHz): δ = 50.9, 101.9, 108.4, 109.9, 123.6, 124.4, 148.0, 148.7 ppm; MS (ESI): m/z (%); calcd 286.1079; found 286.1086 (100) [$M-PF_6$]$^+$.

{[Bis(1-naphthylmethyl)ammonium][DP24C8]}-[2]pseudorotaxane hexafluorophosphate ([1NP/1NP-H⊂DP24C8][PF$_6$]): Single crystals of the complex [**1NP/1NP**-H⊂DP24C8][PF_6] suitable for X-ray crystallographic analysis were grown by layer diffusion of iPr$_2$O into a solution of **1NP**/**1NP**-H][PF_6] and DP24C8 in CH_2Cl_2. Crystal data: [$C_{35}H_{47}N_2O_{11}$][PF_6], M_r = 816.7, monoclinic, space group $P2_1/c$ (no. 14), a = 11.0238(3), b = 12.0503(4), c = 29.1325(8) Å, β = 98.870(2), V = 3823.7(2) Å^3, Z = 4, ρ_{calcd} = 1.419 g cm^{-3}, $\mu(Mo_{K\alpha})$ = 0.16 mm^{-1}, T = 150(2) K, colorless plate; 6713 independent measured reflections, F^2 refinement, R_1 = 0.0743, wR_2 = 0.169, 3724 independent observed reflections [$I > 2\sigma(I)$, $2\theta_{max}$ = 50°], 523 parameters.

{[Bis(1-naphthylmethyl)ammonium][DB24C8]}-[2]pseudorotaxane hexafluorophosphate ([1NP/1NP-H⊂DB24C8][PF$_6$]): Single crystals, suitable for X-ray analysis, were obtained by layering a 1:1 solution of [**1NP/1NP**-H][PF_6] and DB24C8 in CH_2Cl_2 with hexane and allowing the mixture to stand undisturbed at ambient temperature for 7 d. Crystal data: [$C_{44}H_{50}N_3O_6$][PF_6]·CH_2Cl_2, M_r = 946.8, monoclinic, space group $P2_1/n$ (no. 14), a = 16.809(2), b = 15.134(3), c = 18.364(3) Å, β = 102.432(14), V = 4562.0(13) Å^3, Z = 4, ρ_{calcd} = 1.378 g cm^{-3}, $\mu(Cu_{K\alpha})$ = 2.26 mm^{-1}, T = 203(2) K, colorless platy needle; 6387 independent measured reflections, F^2 refinement, R_1 = 0.0740, wR_2 = 0.171, 4081 independent observed reflections [$I > 2\sigma(I)$, $2\theta_{max}$ = 120°], 592 parameters.

{[Bis(piperonylmethyl)ammonium][P24C8]}-[2]pseudorotaxane hexafluorophosphate ([PIP/PIP-H⊂P24C8][PF$_6$]): Single crystals suited for X-ray crystallographic analysis were obtained when a solution of [**PIP/PIP**-H][PF_6] (1 mol equiv) and P24C8 (1.5 mol equiv) in CH_2Cl_2 was layered with iPr$_2$O and left to stand at ambient temperature for 14 d. Crystal data: [$C_{40}H_{48}NO_{12}$][PF_6], M_r = 879.8, triclinic, space group $P\bar{1}$ (no. 2), a = 10.7086(4), b = 10.8555(6), c = 19.1354(10) Å, α = 100.981(5), β = 106.281(4), γ = 92.004(6)° V = 2086.9(2) Å^3, Z = 2, ρ_{calcd} = 1.400 g cm^{-3}, $\mu(Cu_{K\alpha})$ = 1.37 mm^{-1}, T = 293(2) K, colourless prism; 7085 independent measured reflections, F^2 refinement, R_1 = 0.0546, wR_2 = 0.152, 5754 independent observed reflections [$I > 2\sigma(I)$, $2\theta_{max}$ = 130°], 605 parameters.

{[Bis(piperonylmethyl)ammonium][DB24C8]}-[2]pseudorotaxane hexafluorophosphate ([PIP/PIP-H⊂DB24C8][PF$_6$]): Single crystals suitable for X-ray crystallography were grown by liquid diffusion of iPr$_2$O into an equimolar solution of [**PIP/PIP**-H][PF_6] and DB24C8 in MeCN. Crystal data: [$C_{46}H_{52}NO_8$][PF_6]·CH_2Cl_2, M_r = 976.8, triclinic, space group $P\bar{1}$ (no. 2), a = 10.5365(14), b = 11.2223(6), c = 19.6179(13) Å, α = 80.469(6), β = 86.905(8), γ = 89.464(6)° V = 2284.3(4) Å^3, Z = 2, ρ_{calcd} = 1.420 g cm^{-3}, $\mu(Cu_{K\alpha})$ = 2.30 mm^{-1}, T = 203(2) K, colorless platy prism; 6704 independent measured reflections, F^2 refinement, R_1 = 0.0601, wR_2 = 0.154, 4971 independent observed reflections [$I > 2\sigma(I)$, $2\theta_{max}$ = 120°], 650 parameters.

CCDC-218958 ([**1NP/1NP-H**⊂DP24C8][PF_6]), CCDC-218959 ([**1NP/1NP-H**⊂DB24C8][PF_6]), CCDC-218960 ([**PIP/PIP-H**⊂P24C8][PF_6]), and CCDC-218961 ([**PIP/PIP-H**⊂DB24C8][PF_6]) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033: or deposit@ccdc.cam.uk).

General procedure for the preparation of the [2]pseudorotaxanes: Equimolar amounts of the hexafluorophosphate salt of [**1NP/1NP**-H]$^+$, [**1NP/2NP**-H]$^+$, [**2NP/2NP**-H]$^+$, or [**PIP/PIP**-H]$^+$ were added to the appropriate macrocyclic polyether (P24C8 or DP24C8 or DP24C8) dissolved in CD_3CN or CD_2Cl_2 in an NMR tube and the solutions were mixed at room temperature for 1 min. The ^{1}H NMR spectra were recorded after 5 min. The δ values—for protons labeled on the structural formulas in Figure 1—obtained from spectra recorded in CD_3CN for the [2]pseudorotaxanes are compared in Table 3 with each other and with the appropriate free hexafluorophosphate salts and free crown ethers.

General procedure for the preparation of the samples used in the competition experiments: One equivalent of one hexafluorophosphate salt—[**1NP/1NP**-H][PF_6], [**1NP/2NP**-H][PF_6], **2NP/2NP**-H][PF_6] or [**PIP/PIP**-H][PF_6]—was added to a solution containing P24C8, DP24C8 and DB24C8 (1 mol equiv of each) in CD_3CN in an NMR tube which was inverted to accomplish mixing. ^{1}H NMR spectra were obtained at different time intervals, for example, after 5 min. However, in the case in which [**1NP/1NP**-H][PF_6] was added to a solution containing P24C8, DP24C8 and DB24C8 in CD_3CN, the ^{1}H NMR spectra were recorded at different time intervals until equilibrium was established (22 days). Spectra recorded after 22 days showed no change in the ratios of the free and complexed components. The same procedure was followed for the preparation of the samples for FAB mass spectrometry experiments, except that MeCN was substituted for the deuterated solvent.

Table 3. ^{1}H NMR spectroscopic data[a] (δ values) for 1) the crown ethers P24C8, DP24C8, and DB24C8; 2) the [**1NP/1NP**-H][PF_6], [**1NP/2NP**-H][PF_6] and [**2NP/2NP**-H][PF_6] salts; and 3) the [2]pseudorotaxanes formed between the compounds in CD_3CN at 298 K.

	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	s	t	u	v
[**1NP/1NP**-H][PF_6]	7.69	7.57	7.97	8.00	7.60	7.62	8.03	4.84	–	–	–	–	–	–	–	–	–	–	–	–
[**1NP/1NP**-H⊂P24C8][PF_6]	7.74	7.35	7.92	7.96	7.55	7.60	8.25	5.31	–	–	–	–	–	–	–	–	–	–	6.97	7.81
[**1NP/1NP**-H⊂DP24C8][PF_6]	7.64	7.29	7.90	7.94	7.44	7.54	7.96	5.14	–	–	–	–	–	–	–	–	–	–	7.12	7.65
[**1NP/1NP**-H⊂DB24C8][PF_6]	7.71	7.32	7.78	7.68	7.35	7.46	8.09	5.43	–	–	–	–	–	–	–	–	6.57	6.73	–	–
[**1NP/2NP**-H][PF_6]	7.68	7.55	7.97	7.99	7.61	7.63	8.01	4.75	4.52	7.56	7.93	7.94	7.58	7.60	7.98	8.02	–	–	–	–
[**1NP/2NP**-H⊂P24C8][PF_6]	7.70	7.39	7.93	7.95	7.50	7.61	8.31	5.21	4.85	7.58	7.85	7.73	7.54	7.52	7.87	8.02	–	–	7.06	7.68
[**1NP/2NP**-H⊂DP24C8][PF_6]	7.63	7.30	7.92	7.90	7.47	7.51	8.06	5.06	4.71	7.45	7.78	7.62	7.46	7.51	7.85	7.87	–	–	7.15	7.66
[**1NP/2NP**-H⊂DB24C8][PF_6]	7.74	7.33	7.80	7.69	7.56	7.48	8.11	5.34	4.99	7.44	7.72	7.66	7.46	7.46	7.75	7.86	6.30	6.70	–	–
[**2NP/2NP**-H][PF_6]	–	–	–	–	–	–	–	–	4.44	7.55	7.94	7.93	7.58	7.59	7.98	8.00	–	–	–	–
[**2NP/2NP**-H⊂P24C8][PF_6]	–	–	–	–	–	–	–	–	4.73	7.56	7.84	7.75	7.51	7.52	7.88	7.95	–	–	7.14	7.65
[**2NP/2NP**-H⊂DP24C8][PF_6]	–	–	–	–	–	–	–	–	4.64	7.44	7.76	7.65	7.47	7.51	7.85	7.80	–	–	7.19	7.69
[**2NP/2NP**-H⊂DB24C8][PF_6]	–	–	–	–	–	–	–	–	4.90	7.45	7.70	7.66	7.46	7.48	7.77	7.83	6.70	6.70	–	–
P24C8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7.37	7.78
DP24C8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7.31	7.69
DB24C8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6.89	6.91	–	–

[a] The ^{1}H NMR spectra were recorded on either a Bruker Avance 500 or ARX500 spectrometer (at 500 MHz) with CD_3CN solvent as the lock and the residual solvent peak as internal reference.

Kinetic experiments: In a typical kinetic experiment, an equimolar mixture of DB24C8 and the [**1NP/1NP**-H][PF_6] salt were dissolved in either CD_3CN, CD_2Cl_2, or the MSS. The samples were placed in an NMR spectrometer (500 MHz), then ^{1}H NMR spectra of the solutions were recorded at the appropriate temperature (the kinetic and thermodynamic data are summarized in Table 1), at regular time intervals, until equilibrium was reached, that is, until no further changes in the spectra could be detected. By evaluating the relative intensities of the probe protons identified in Table 1, the concentrations of both the free and complexed species at time, *t*, could be calculated from each spectrum. Since equilibration takes about 22 days in CD_3CN, it was not practical to leave the sample in an NMR spectrometer. The equilibration had to be carried out in a sealed NMR tube which was heated in a thermostatic oil-bath at 25 °C and 40 °C in two separate experiments.

Molecular modeling: Both [**1NP/1NP**-H][PF_6] and [**2NP/2NP**-H][PF_6] were constructed within the input mode of Maestro 3.0.038[36] and then subjected to a Monte Carlo Multiple Minimization (MCMM) conformational search of 1000 randomly generated structures in order to determine the global energy minimum to be used as the starting geometry. The AMBER* force field[26] with the GB/SA solvent model[27] for $CHCl_3$ was used. In order to model the extrusion process, a "dummy" atom was placed at a distance of 55.0 Å from the nitrogen atom of each dumbbell, with the positions of both the dummy and nitrogen atoms fixed. The distance between the dummy atom and the carbon atom **t** (see Figure 1) on one of DB24C8s two catechol rings was then varied from 50.0 to 35.0 Å. This procedure forced the macrocyclic polyether to move along the axis of the dumbbell and eventually over one of the naphthyl groups. The distance from the carbon at the 4-position (**t** in Figure 1) to the dummy was varied by 0.5 Å from 50.0 to 48.0 Å and then by 0.3 Å from 47.7 Å to 35.0 Å; this corresponds to the area around the transition state. Energy minimization was performed at each step using the Polak–Ribiere conjugate (PRCG)[36] algorithm. A 30 ps molecular dynamics simulation (1.5 fs time step) at a simulation temperature of 500 K, followed by energy minimization of 150 randomly selected superstructures was carried out for each superstructure in order to find the local energy minimum at each fixed distance. The output from each calculation was then used as the input for each subsequent calculation. The energies were then normalized relative to the fully separated macrocyclic ring and dumbbell components, which were calculated by performing a 1000 step MCMM conformational search (AMBER* force field and $CHCl_3$ solvent model) on each of [**1NP/1NP**-H][PF_6], [**2NP/2NP**-H][PF_6], and DB24C8 and then adding the global minima for each dumbbell/macrocycle pair.

Quantum mechanical calculations: Dimethylammonium, diglyme, and the dimethylammonium/diglyme complex were each constructed within the input mode of Maestro 3.0.038[36] and then subjected to an MCMM conformational search of 1000 randomly generated structures in order to determine the global energy minimum of each structure in the GB/SA solvent model[27] for $CHCl_3$. These structures were then imported into the program GAUSSIAN 98[38] in order to perform density functional calculations. B3LYP6-31G*[29] gas-phase optimizations of each structure were performed and frequency calculations were used in order to obtain free energy values for each structure. Single-point B3LYP6-31G* calculations of the optimized structures in $CHCl_3$ were then performed with the keywords scrf=(solvent=chcl3, cpcm) and scf=tight in order to determine their respective solvation free energies. The free energies of solvation were then added to each structures calculated gas phase free energy and these values were then used to calculate $-\Delta G°$ of complexation for the dimethylammonium/diglyme system.

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