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An Operative Electrostatic Slipping Mechanism along Macrocycle Flexibility Accelerates Guest Sliding during *pseudo*-Rotaxane Formation

Aldo C. Catalán,* Axel A. Loredo, Ruy Cervantes, and Jorge Tiburcio*[a]

A *pseudo*-rotaxane is a host−guest complex composed of a linear molecule encircled by a macrocyclic ring. These complexes can be assembled by sliding the host over the guest terminal groups. If there is a close match between the molecular volume of the flanking groups on the guest and the cavity size of the macrocycle, the slipping might occur slowly or even become completely hindered. We have previously shown that it is possible to overcome the restraints imposed by steric effects on the sliding process by integrating electrostatic attractive interactions during the slipping step. In this work, we extend our *electrostatically assisted slipping approach* (*EASA*) to a new host−guest system featuring a flexible macrocyclic ring and a series of asymmetric guests containing a cyclic tertiary ammonium group. Compelling evidence for *pseudo*-rotaxane formation is presented, along with thermodynamic and kinetic data. Experimental results suggests that the higher conformational flexibility of 24-crown-8 significantly increases the sliding rate, compared with the more rigid dibenzo-24-crown-8, without affecting complex stability. Furthermore, by combining the *EASA* and macrocycle flexibility, we were capable to slip a large eight-membered cyclic group across the 24-crown-8 annulus, setting a new limit on the ring molecular size that can pass through a 24-membered crown ether.

Introduction

pseudo-Rotaxane species are supramolecular host−guest complexes minimally composed of a thread-shaped molecule (*axle*) encircled by one macrocyclic ring (*wheel*), with both ends of the guest extended away from the ring.[1] In solution, these complexes are in dynamic equilibrium with their non-associated components. As expected, association/dissociation rates can be modulated by steric contacts between the wheel and the termini groups on the axle during the slipping process.[2]

In a seminal work, Stoddart et al. reported kinetic parameters for the slipping of dibenzo-24-crown-8 [**DB24C8**] on a series of dialkylammonium guests holding differently size terminal groups.[3] These results allowed to establish a relationship between the substituents' molecular volume and the cavity size of [**DB24C8**]. The guest bearing cyclohexyl substituents displayed a slipping activation free energy barrier of $\Delta G^{\neq}_{on} = 104$ kJ·mol⁻¹, at 313 K in a mixture of CDCl₃/CD₃CN (3:1). This value is 22 kJ·mol⁻¹ higher than the corresponding for the

cyclopentyl-substituted axle, and this difference is explained by an increase on the steric hindrance due to the larger molecular volume of cyclohexyl groups compared to the cyclopentyl substituent. With the bulkier cycloheptyl group it was not possible to overcome the energy barrier for complex formation, even when the system was heated up to 323 K, proving that a seven-membered cyclic group is too bulky to slide through [**DB24C8**].

By using a different set of host−guest complexes, featuring axles containing the 1,2-bis(pyridinium)ethane motif, Loeb et al. demonstrated that a cyclohexyl end-group allows the gradual passage of [**DB24C8**] at room temperature with a $\Delta G^{\neq}_{on} = 86.5$ kJ·mol⁻¹, at 298 K in CD₃CN.[4] However, when a cycloheptyl substituent was incorporated as a terminal group on the axle, the kinetic energy barrier for [**DB24C8**] threading became insurmountable. In a related work, Schalley et al. have proven that, in a family of rotaxane complexes, the rate of the deslipping reaction is highly susceptible to slight changes of the molecular volume of the axle terminal groups. The mere replacement of deuterium atoms for hydrogen leads to a 10% increment on the dethreading rate of a tetralactam macrocyclic wheel.[5] Other contributions from Hirose,[6] Credi,[7] and Schalley[8] have also assessed the importance of the ratio between ring size and terminal groups molecular volume on the slipping kinetics of interlaced molecules.

Harada et al.[9] and our group[10, 11] envisioned a way to enhance steric effects on the threading reaction, through the co-operation of electrostatic forces. A series of repulsive Coulombic interactions, between the termini groups on the axle and the wheel, contribute to slow down, or even completely halt, the deslipping process in *pseudo*-rotaxanes, enabling their transformation into rotaxanes. More recently, we showed that it

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is also possible to diminish the restraints imposed by the molecular volume of axle end-groups during the ring sliding step by using attractive electrostatic interactions, the so-called *electrostatically assisted slipping approach* (*EASA*).[12] In that report, a set of linear molecules containing a pyridinium ring attached to a cyclic ammonium group through an ethylene bridge were investigated for [**DB24C8**] complexation (Figure 1). The positively charged recognition site (N^+–CH_2–CH_2–N^+) was suitable for complexation with [**DB24C8**] ($K_a = 1.8 \times 10^3$ M^{-1}; $\Delta G_a^\circ = -18.3$ kJ·mol^{-1}) in CD$_3$NO$_2$ at 293 K. The presence of a mesityl substituent on the pyridinium ring prevented macrocycle threading through this end and directed the sliding process across the ammonium group. For a six-membered cyclic ammonium group (piperidinium), the activation free energy ($\Delta G_{on}^{\neq}$) was 15 kJ·mol^{-1} lower compared to the neutral amine. This substantial reduction led to a 500 times increment in the sliding rate of the ring, proving the effectiveness of the *EASA*.

We also proved that there is no complex formation with [**DB24C8**] and the neutral seven-membered azepane cyclic amine-containing guest, in agreement with Stoddart's[3] and Loeb's[4] results for isosteric cycloheptyl substituents. However, a protonated azepanium-containing guest could slip through [**DB24C8**]'s cavity with an energy barrier of $\Delta G_{on}^{\neq} = 92.8$ kJ·mol^{-1}, which implies an 18.0 kJ·mol^{-1} increment with respect to the one observed for piperidinium. We could not obtain evidence of the slippage of [**DB24C8**] through a cationic eight-membered ring (azocanium), even at elevated temperature (333 K).[12]

Herein, we are taking the *EASA* a step further by utilizing a more basic and flexible crown ether version, 24-crown-8, [**24C8**], keeping the macrocycle size constant.[13] We hypothesize that lower energy barriers and faster threading rates during *pseudo*-rotaxane formation would be observed by using a macrocycle with enhanced conformational flexibility, [**24C8**] versus [**DB24C8**], allowing to adopt a more relaxed configuration during the slipping process over the protonated cyclic ammonium group, stabilizing the transition state, but without perturbing the *pseudo*-rotaxane complex structure and stability (Figure 1).

Results and Discussion

Host–guest complexes with a series of thread-shaped cationic guests and 24-crown-8 ether host [**24C8**] were investigated; thermodynamic and kinetic parameters were measured and compared with those reported for analogous complexes featuring dibenzo-24-crown-8 [**DB24C8**] as a macrocyclic ring (Figure 1).

All guests are asymmetric linear species featuring a positively charged recognition motif, (N^+–CH_2–CH_2–N^+), composed of a cyclic tertiary ammonium group and a pyridinium moiety connected by an ethylene spacer. The cyclic ammonium group also performs as a terminal unit, since the macrocycle must slip across this fragment to reach the recognition site. On the other edge, guests hold a large mesityl group acting as a stopper, preventing the macrocycle from sliding through this side. The cyclic ammonium groups incorporated into the guest structure are piperidinium, [**Pi·H**]$^{2+}$, azepanium, [**Aze·H**]$^{2+}$, and azocanium, [**Azo·H**]$^{2+}$. All guests were synthesized following our reported procedure,[12] and have been fully characterized by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry (HR-MS). All of them displayed similar proton resonances for the pyridinium and ethylene fragments, with only slight differences for the protons on the cyclic ammonium groups.

A size comparison of the different cyclic ammonium groups used in this work and their cycloalkyl analogues is shown in Figure 2. Distance values were averaged from different X-ray structures, all of them having one hydrogen and one carbon-based substituent, deposited in the Cambridge Structural Database.[14] As expected, six-, seven- and eight-membered ring pairs are isoelectronic and practically isosteric. Addition of one or two methylene units to the six-membered ring increases the width by ≈ 0.5 and ≈ 1.0 Å, and ≈ 0.3 and ≈ 0.4 Å in length, for the seven- and eight-membered rings, respectively. Regarding the macrocycles under study, it is known that C=C sp^2 bonds are ≈ 0.2 Å shorter than C–C sp^3 bonds,[15] and the presence of two catechol rings in the structure of [**DB24C8**] entails the reduction of the macrocycle circumference and increases host rigidity in comparison with [**24C8**]. Moreover, [**24C8**], with a greater conformational freedom, would be flexible enough to adapt to the structure of the cyclic ammonium group, maximizing electrostatic attractive interactions between host and guest, during ring sliding.

We started by studying the intermolecular interactions in solution between the six-membered piperidinium-based guest [**Pi·H**]$^{2+}$ and the [**24C8**] macrocycle. The ^{1}H NMR spectrum of an equimolar nitromethane-d$_3$ solution showed the presence of
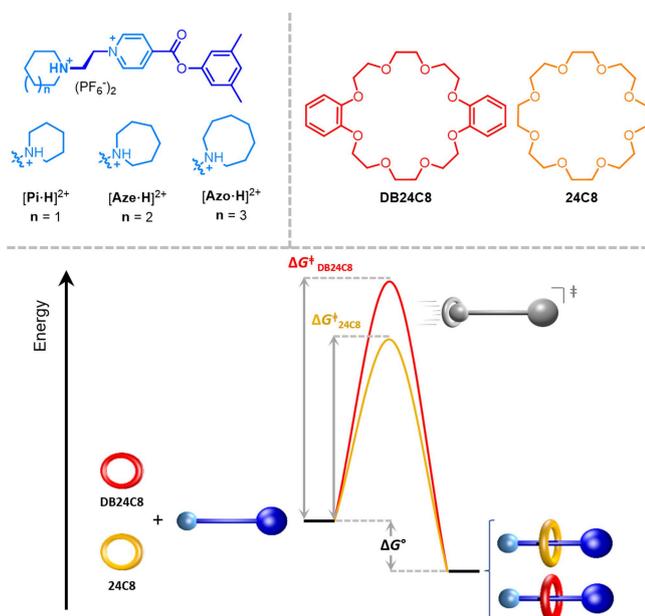

Figure 1. Chemical structures of a series of dumbbell-shaped guests ([**Pi·H**]$^{2+}$; [**Aze·H**]$^{2+}$; [**Azo·H**]$^{2+}$) and hosts [**DB24C8**] [12]; [**24C8**]. Cartoon representation of the energy profile for the threading process of an asymmetric dumbbell-shaped guest and rings having different conformational flexibility (red ring: rigid; orange ring: flexible).
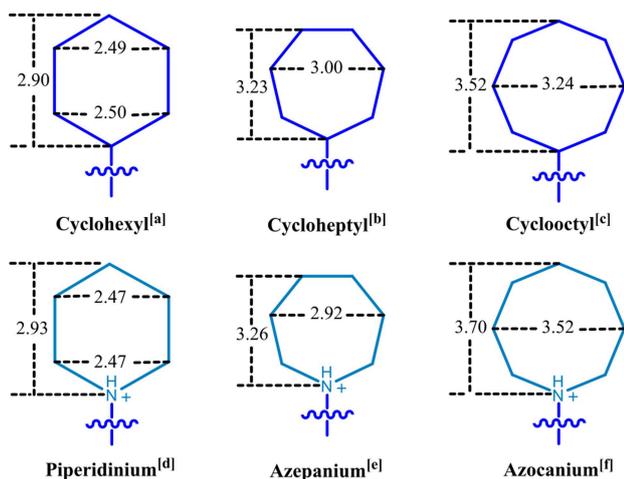
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Figure 2. Averaged values of the distances (Å) for six-, seven- and eight-membered rings. Averaged values from CCDC X-ray structures: [a] COKYAD, SERWIV; [b] DITYEK, DITYEK10; [c] GERFUE; [d] ANIHUC, APIYAA, IQIPUV ([**Pi·H**][BF$_4$]$_2$ X-ray structure reported in Ref. [12]); [e] ZUKGIX; [f] CATBOP. Standard deviation for all values is 0.01. Data taken from X-ray structures deposited in the Cambridge Structural Database.[14]

a new set of resonances, in addition to those from unbound species, suggesting a slow dynamic exchange process on the NMR time scale (Figure 3a).

The chemical shifts for the new resonances are consistent with the formation of a host−guest complex with an interpenetrated geometry [**Pi·H⊂24C8**]$^{2+}$, in which the crown ether engulfs the linear guest molecule around the cationic recognition site through a series of electrostatic and hydrogen

bonding interactions, as previously observed for [**DB24C8**].[16] A shift to higher frequency for the ethylene protons (H$_a$: +0.26; H$_b$: +0.11 ppm) and for the *ortho*-N$^+$ protons (H$_c$: +0.33 ppm) agrees with a series of C H···O hydrogen bonding interactions with the oxygen atoms of the crown ether cavity. The fact that the *meta*-N$^+$ protons signal remains practically unaffected (H$_d$: −0.04 ppm) by the presence of the [**24C8**] ether, with respect to a lower frequency shift (H$_d$: −0.62 ppm) observed in the complex with [**DB24C8**], is indicative of the absence of π-stacking interactions.[12] Moreover, methylene protons on opposite faces of the symmetric [**24C8**] crown ether become magnetically non-equivalent when its cavity is threaded by an asymmetric guest,[17] resulting in a AA'BB' four-spin system, as it is clearly observed in the resonance centered at 3.6 ppm in the ^{1}H NMR spectrum (Figure 3a, middle).

Additionally, relative integrals in the ^{1}H NMR spectrum support the formation of a host−guest complex with a 1:1 stoichiometry. This was further confirmed by experimental HR-MS. The mass spectrum shows a peak which corresponds to the expected molecular ion [**Pi+24C8**]$^+$ (m/z = 691.4166 amu, relative error = 0.3 ppm) displaying an isotopic pattern consistent with the proposed formula (Figure 3b).

An association constant (K_a) for complex [**Pi·H⊂24C8**]$^{2+}$ was estimated by ^{1}H NMR spectroscopy, using the single point method, providing a value of 1.9×10^3 M^{-1} ($\Delta G_a^\circ = -18.4$ kJ·mol^{-1}) from three independent measurements. This value is not so different from the one previously determined for the complex with [**DB24C8**] under similar experimental conditions (Table 1).[12] These values prove that, in CD$_3$NO$_2$ at 293 K, regardless of the macrocyclic ring used, both systems possess similar stability.
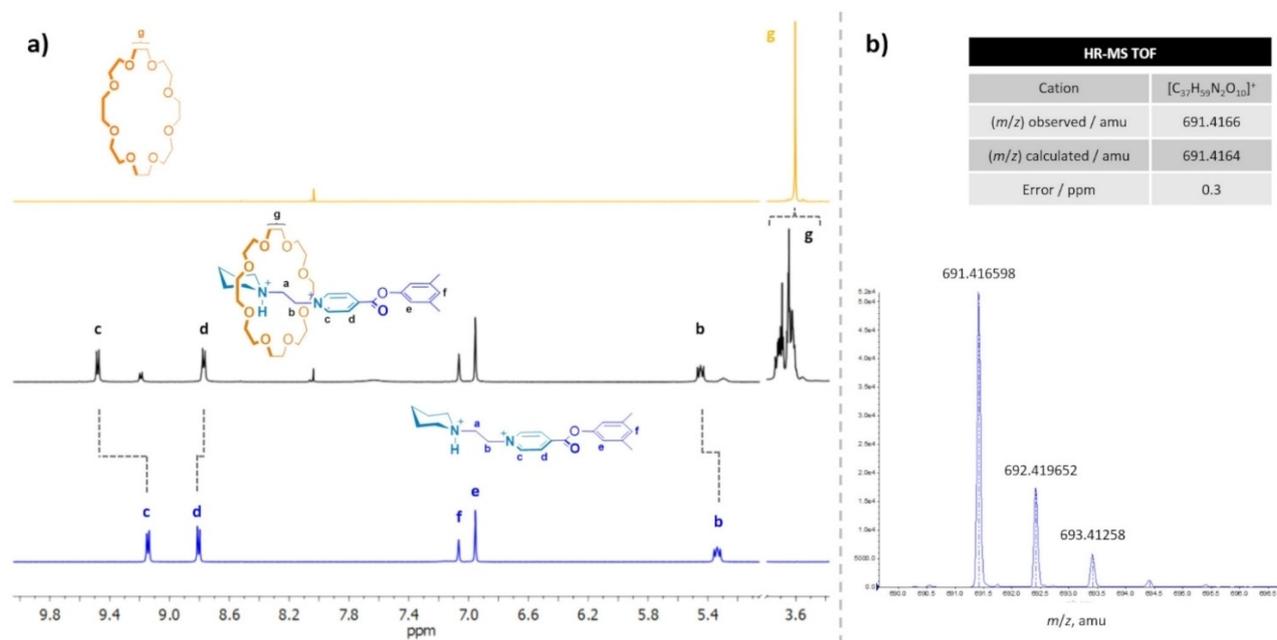

Figure 3. (a) Proposed geometry for *pseudo*-rotaxane complex [**Pi·H⊂24C8**]$^{2+}$ with partial ^{1}H NMR spectra (400 MHz, CD$_3$NO$_2$, 293 K) of: free [**24C8**] crown ether (top); an equimolar solution of host [**24C8**] and guest [**Pi·H**]$^{2+}$ ([host] = [guest] = 1 × 10^{-2} M) (middle); and free guest [**Pi·H**]$^{2+}$ (bottom). (b) High-resolution mass spectrum (ESI-TOF) of an equimolar solution of [**Pi·H**]$^{2+}$ and [**24C8**]. Experimental molecular ion (continuous line) and calculated isotopic profile (broken line).

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Table 1. Thermodynamic and kinetic parameters (CD$_3$NO$_2$, 293 K).[a]

Complex	$K_a \times 10^{-3}$ [M^{-1}]	ΔG_a° [kJ·mol^{-1}]	k_{on} [M^{-1} s^{-1}]	$\Delta G^{\ddagger}_{on}$ [kJ·mol^{-1}]
[Pi·H⊂24C8]2+	1.9(0.1)	−18.4(0.2)	>5×10$^{1[b]}$	<60[c]
[Pi·H⊂DB24C8]2+[d]	1.8(0.1)	−18.3(0.3)	3.1(0.1)×10^{-1}	74.6(0.3)
[Aze·H⊂24C8]2+	1.8(0.1)	−18.2(0.1)	1.0(0.1)×10^{0}	71.7(0.3)
[Aze·H⊂DB24C8]2+[d]	1.6(0.2)	−18.0(0.3)	1.8(0.1)×10^{-4}	92.8(0.4)

[a] Average (± SD) from three independent experiments. [b] Estimated k_{on} value. [c] Calculated from estimated k_{on} value. [d] Reported values.[12]

Interestingly, both complexes display quite different enthalpy (ΔH_a°) and entropy (ΔS_a°) values for the association process. These parameters were derived from van't Hoff plots in the 293–363 K temperature range, showing acceptable linear coefficients (Supporting Information). The association enthalpy (ΔH_a°) for complex [**Pi·H⊂DB24C8**]$^{2+}$ is exothermic and 2.5 times larger than the one for complex [**Pi·H⊂24C8**]$^{2+}$, probably because of the additional aromatic interactions between the catechol rings on [**DB24C8**] and the pyridinium ring on the axle, absent from the [**24C8**] complex. However, the same aromatic interactions might have an entropic toll (ΔS_a°); the entropic term for complex [**Pi·H⊂DB24C8**]$^{2+}$ is also negative and 15 times larger than the corresponding one for complex [**Pi·H⊂24C8**]$^{2+}$. Overall, enthalpic and entropic terms compensate each other to maintain a practically identical association free energy (ΔG_a°) for both complexes.

With respect to the slipping kinetics, a substantial difference in the formation rates of *pseudo*-rotaxanes [**Pi·H⊂DB24C8**]$^{2+}$ and [**Pi·H⊂24C8**]$^{2+}$ was observed. We have reported that the slippage process for complex with [**DB24C8**] takes about 20 min to reach chemical equilibrium at 298 K,[12] with a second-order rate constant of 3.1×10^{-1} M^{-1} s^{-1}, whereas for the complex with [**24C8**], this equilibrium was attained during sample preparation, making it impossible to follow the kinetics by ^{1}H NMR experiments. Considering a literature claim that the time required for mixing and recording a meaningful NMR spectrum is around 10 s,[18] it is possible to estimate a lower-limiting value for the threading rate constant with our experimental data, $k_{on} > 5 \times 10^1$ M^{-1} s^{-1}. This value denotes, at least, a two-orders of magnitude increase in the slipping rate for the complex [**Pi·H⊂24C8**]$^{2+}$ compared to [**Pi·H⊂DB24C8**]$^{2+}$ (Table 1). We attribute this difference to the greater conformational flexibility of host [**24C8**], compared with [**DB24C8**], leading to a reduction of the kinetic energy barrier during *pseudo*-rotaxane formation ($\Delta G^{\ddagger}_{on}$) by at least 15 kJ·mol^{-1}.

The estimated low activation free energy for complex [**Pi·H⊂24C8**]$^{2+}$ ($\Delta G^{\ddagger}_{on} < 60$ kJ·mol^{-1}), must be a consequence of the co-operative action of the *EASA* and macrocycle flexibility, and clearly contrasts with other *pseudo*-rotaxanes complexes with [**DB24C8**] and guests featuring neutral cyclohexyl end-groups, with values varying between 86.5 to 104.2 kJ·mol^{-1}.[3, 4]

Furthermore, host-exchange experiments were designed in which one equivalent of crown ether [**24C8**] was added to a solution containing *pseudo*-rotaxane [**Pi·H⊂DB24C8**]$^{2+}$, in chemical equilibrium, and the opposite, addition of one equivalent of [**DB24C8**] to a solution containing [**Pi·H⊂24C8**]$^{2+}$.

Regardless of the experiment, the system reached equilibrium in about 50 min. At equilibrium, a 1:1 molar ratio between both *pseudo*-rotaxanes complexes [**Pi·H⊂DB24C8**]$^{2+}$ and [**Pi·H⊂24C8**]$^{2+}$ was observed (Figure 4). These results confirm that (*i*) both complexes possess similar stability, and (*ii*) the rate-controlling process during macrocycle swapping is the threading/dethreading process of the less flexible [**DB24C8**] macrocycle.

A more accurate picture was obtained by analyzing the slipping process of the macrocycle [**24C8**] on a seven-membered azepanium-containing guest, [**Aze·H**]$^{2+}$. The ^{1}H NMR spectrum of an equimolar solution of guest and host in nitromethane-d$_3$ provides evidence for the formation of a supramolecular complex in slow exchange with its unbound components. Analysis of the chemical shifts and relative integrals on the spectrum supports the formation of a 1:1 host−guest complex featuring a *pseudo*-rotaxane geometry, [**Aze·H⊂24C8**]$^{2+}$. We propose that the macrocycle encircles the cationic recognition site ($N^+-CH_2-CH_2-N^+$) on the guest, resembling the analogous complex containing a piperidinium fragment (Figure 5a). The complex was also characterized by HR-MS. The peak corresponding to the molecular ion [**Aze+24C8**]$^{1+}$ was observed at m/z = 705.4321 amu, displaying an isotopic pattern consistent with the proposed formula and a relative error in the molecular weight of less than 0.1 ppm (Supporting Information).

An association constant for complex [**Aze·H⊂24C8**]$^{2+}$ was estimated from integral values obtained from the ^{1}H NMR spectra, recorded in three independent experiments. The calculated $K_a = 1.8 \times 10^3$ M^{-1}, is practically identical to the one determined for its piperidinium equivalent complex (Table 1), indicating that both complexes maintain similar structural features in solution.

Remarkably, after guest [**Aze·H**]$^{2+}$ and host [**24C8**] are mixed, chemical equilibrium is attained in less than 16 min at 298 K. This result is in sharp contrast with the 14 days required for the same guest and [**DB24C8**] under identical conditions.[12, 19] It is even more impressive since a neutral cycloheptyl terminal group, on two different axles, impedes the slipping throughout the annulus of a 24-membered crown ether.[3, 4] These new observations highlight the potential of the *EASA* for the synthesis of seemingly impossible mechanically interlocked molecules.
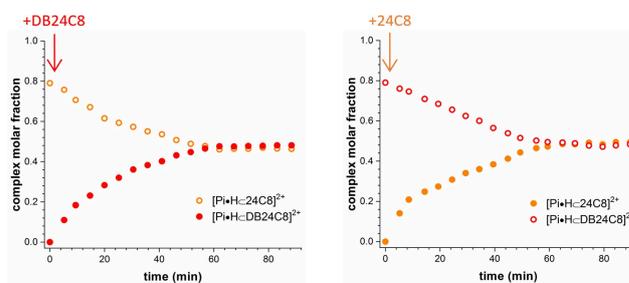

Figure 4. ^{1}H NMR host-exchange experiment starting with solutions at equilibrium of [**Pi·H⊂24C8**]$^{2+}$ (left) and [**Pi·H⊂DB24C8**]$^{2+}$ (right) (400 MHz, CD$_3$NO$_2$, [**DB24C8**] = [**24C8**] = [**Pi·H**]$^{2+}$ = 1×10^{-2} M).

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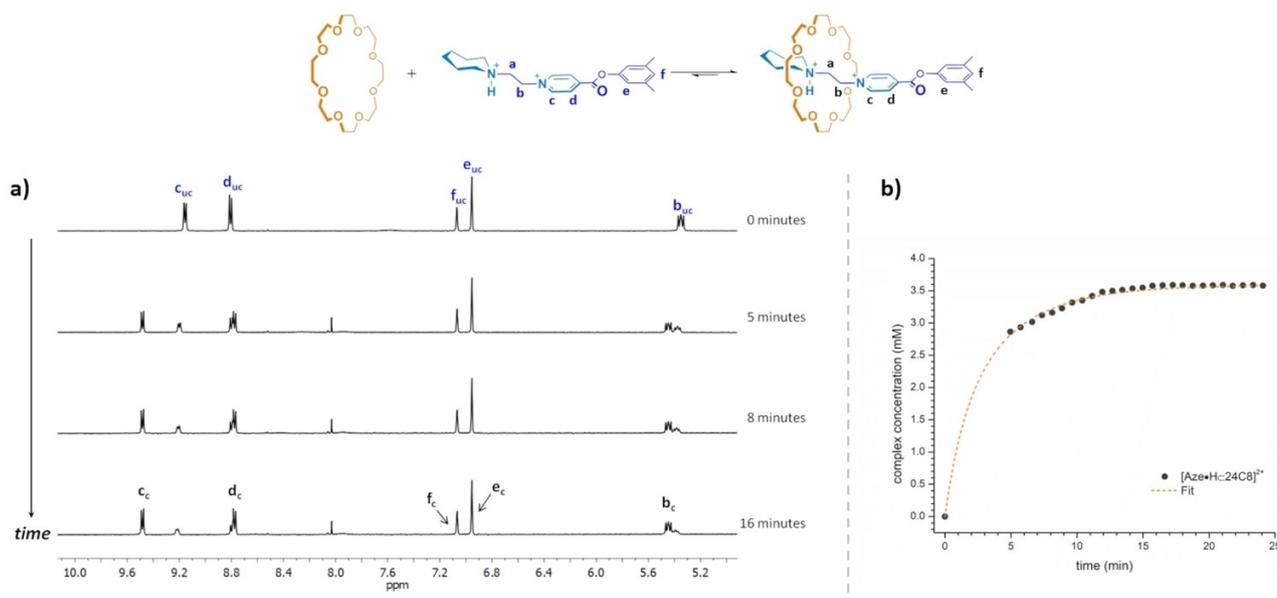
Figure 5. (a) Partial ^{1}H NMR spectra of time-evolution of an equimolar solution of [**Aze·H**]$^{2+}$ and [**24C8**] (400 MHz, CD$_3$NO$_2$, 293 K, 1×10^{-2} M). The proposed geometry for [**Aze·H⊂24C8**]$^{2+}$ complex is also shown (uc = uncomplexed, c = complexed). (b) ^{1}H NMR analysis of complex [**Aze·H⊂24C8**]$^{2+}$ formation (400 MHz, CD$_3$NO$_2$, [host] = [guest] = 5×10^{-3} M). The second-order rate constant was derived from the non-linear fitting analysis (orange line).

This period is long enough to obtain a second-order rate constant by non-linear fitting analysis of complex concentration as a function of time, derived from ^{1}H NMR data (Figure 5b). Notably, the determined rate constant for the formation of the azepanium-based complex with [**24C8**] ($k_{on} = 1.0 \times 10^0$ M^{-1} s^{-1}) is four orders of magnitude higher than the k_{on} reported for the more rigid [**DB24C8**] macrocycle (1.8×10^{-4} M^{-1} s^{-1}),[12] proving that a rise on the conformational flexibility of the macrocyclic host, from [**DB24C8**] to [**24C8**], significantly reduces the energy barrier about 21 kJ·mol^{-1}, accelerating the rate of the ring slipping process. Finally, the k_{on} rate for complex [**Aze·H⊂24C8**]$^{2+}$ is at least 50 times smaller than the estimated value for the formation of the piperidinium complex, [**Pi·H⊂24C8**]$^{2+}$, proving that augmenting the steric hindrance in the axle cyclic ammonium end-group (≈ 0.5 Å width) slows the association process ($\varDelta\varDelta G_{on}^{\neq} = 12$ kJ·mol^{-1}).

Additional efforts to assess the limit of the combined operation of the *EASA* and the usage of a flexible macrocyclic ring were undertaken by investigating a guest featuring a positively charged eight-membered ring (azocanium) as an end-group, [**Azo·H**]$^{2+}$. For this guest, no complex was observed with [**DB24C8**] even at 333 K and despite the operation of *EASA*.[12]

After mixing [**Azo·H**]$^{2+}$ and [**24C8**] in nitromethane-d$_3$ at 293 K, no complex could be detected in the ^{1}H NMR spectrum after 10 days. This result would imply that, at room temperature, it is not possible to overcome the kinetic energy barrier associated with the macrocycle slippage through the azocanium end-group. However, the same experiment at 323 K showed the appearance of a new set of signals, clearly visible after 48 h, compatible with an interpenetrated *pseudo*-rotaxane complex [**Azo·H⊂24C8**]$^{2+}$ (Supporting Information). The mole fraction of complex attained a maximum value of 0.33 after 18 days. At this point, guest decomposition was observed, and the experiment was not further followed. Presence of a complex [**Azo·H⊂24C8**]$^{2+}$ was also evidenced by HR-MS; the spectrum exhibited the species [**Azo + 24C8**]$^{1+}$, with the expected isotopic profile and a m/z = 719.4483 amu, which deviates 0.7 ppm from the calculated value (Supporting Information).

These results indicate that, by combining the *EASA* and a flexible macrocycle, the early observed limiting steric hindrance of a six-membered neutral cyclohexyl group for slipping a 24-membered crown ether can be scaled up to an eight-membered ring cationic azocanium group, almost 1 Å wider.

Conclusion

A series of rigid and linear guest molecules, containing a (N^+ —CH$_2$—CH$_2$—N^+) recognition motif, with six-, seven- and eight-membered cyclic tertiary ammonium substituents as end-groups, yielded stable interpenetrated *pseudo*-rotaxane complexes with 24-crown-8 ether macrocycle, [**24C8**], using an *electrostatically assisted slippage approach* (*EASA*). The higher conformational flexibility of [**24C8**], compared to the more rigid dibenzo-24-crown-8 ether, [**DB24C8**], increased the association slipping rates with piperidinium and azepanium as end-groups on the guest, without affecting complex stability. Moreover, co-operative sliding of flexible [**24C8**] through an eight-membered cyclic ammonium end-group (azocanium) was observed at 323 K. These results set a new limit on the steric hindrance of a cyclic thread end-group which can slip through the cavity of a 24-membered crown ether macrocycle. The results described in this work suggest *EASA* as a potential application in the

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synthesis of rotaxane-based molecular motors whose operation involves variation of kinetic barriers with controlled unidirectional motions.[20] This investigation is currently in progress in our group.

Experimental Section

General

All chemicals were purchased from Aldrich and used without further purification. Compound 24-crown-8 ether was obtained from TCI Company. NMR spectra were recorded on Bruker AVANCE 400 MHz or Jeol Eclipse 400 MHz spectrometers. Mass spectra were obtained on an Agilent G1969 A electrospray-ionization time-of-flight spectrometer. Sample temperature was controlled with a PolyScience circulating bath and the NMR equipment controller.

Synthesis

Host molecules were used as they were purchased. All guests were synthesised and characterized following the reported procedure.[12]

Association Constant Estimation

Association constant was determined using three independent measurements from ^{1}H NMR data by the single-point method. Following Equation (1):

$$K_a = \frac{\left[\left(\frac{\int C}{\int C + \int F}\right) C_o\right]}{\left[\left(\frac{\int F}{\int F + \int C}\right) C_o\right]^2} \tag{1}$$

where C denotes the integral value for the complex, F the integral value for the free species and c_0 the initial concentration of free species.

Association Rate Constant Estimation

Equation (2) was used to estimate an association rate constant, k_{on}, assuming a second-order kinetic law, taking the initial concentration of the guest molecule, $[D]_0$, its concentration at equilibrium, $[D]_e$, as well as the time needed to reach equilibrium, t_e.[18]

$$k_{on} = \left(\frac{1}{[D]_e} - \frac{1}{[D]_0}\right)/t_e \tag{2}$$

Association Rate Constant Determination

An equimolar mixture (5×10^{-3} M) of macrocycle and the appropriate guest was prepared in CD_3NO_2. Sample ^{1}H NMR spectra were recorded at 298 K, at regular time intervals, until equilibrium was attained. The second-order rate constant for the association processes, k_{on}, was determined from a non-linear curve fitting analysis employing Equation (3),[21]

$$[C]_t = \frac{[D]_0^2 [C]_e \, e^{\left(\frac{k_{on} \, t([D]_0^2 - [C]_e^2)}{[C]_e}\right)} - [D]_0^2 [C]_e}{[D]_0^2 \, e^{\left(\frac{k_{on} \, t([D]_0^2 - [C]_e^2)}{[C]_e}\right)} - [C]_e^2} \tag{3}$$

where $[D]_0$ corresponds to the initial guest concentration; $[C]_t$, concentration at time t; and $[C]_e$ concentration at equilibrium. Free and complexed guest concentration were estimated, at any time t, by evaluating the integrals of the probe protons (*ortho*-N$^+$) on the pyridine moiety.

Dissociation rate constant determination

When the equilibrium between reactants and the pseudo-rotaxane complex is reached, the threading and dethreading rates become identical. Equation (4) can be used to evaluate the rate constant for the dissociation processes, k_{off}, from K_a and k_{on} values.

$$K_a = \frac{k_{on}}{k_{off}} \tag{4}$$

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

[1] J.-P. Sauvage, C. Diedrich-Buchecker, *Molecular Catenanes, Rotaxanes and Knots. A Journey Through the World of Molecular Topology*, Wiley-VCH, Weinheim, Germany **1999**, pp 143–144.

[2] C. J. Bruns, J. F. Stoddart, *The Nature of the Mechanical Bond. From Molecules to Machines*, John Wiley & Sons, Inc., USA **2017**, pp 3–7.

[3] P. R. Ashton, I. Baxter, M. C. T. Fyfe, F. M. Raymo, N. Spencer, J. F. Stoddart, A. J. P. White, D. J. Williams, *J. Am. Chem. Soc.* **1998**, *120*, 2297–2307.

[4] M. A. Bolla, J. Tiburcio, S. J. Loeb, *Tetrahedron* **2008**, *64*, 8423–8427.

[5] T. Felder, C. A. Schalley, *Angew. Chem. Int. Ed.* **2003**, *42*, 2258–2260; *Angew. Chem.* **2003**, *115*, 2360–2363.

[6] K. Hirose, Y. Shiba, K. Ishibashi, Y. Doi, Y. Tobe, *Chem. Eur. J.* **2008**, *14*, 981–986.

[7] J. Groppi, L. Casimiro, M. Canton, S. Corra, M. Jafari-Nasab, G. Tabacchi, L. Cavallo, M. Baroncini, S. Silvi, E. Fois, A. Credi, *Angew. Chem. Int. Ed.* **2020**, *59*, 14825–14834; *Angew. Chem.* **2020**, *132*, 14935–14944.

[8] M. Gaedke, H. Hupatz, H. V. Schröder, S. Suhr, K. F. Hoffmann, A. Valkonen, B. Sarkar, S. Riedel, K. Rissanen, C. A. Schalley, *Org. Chem. Front.* **2021**, *8*, 3659–3667.

[9] a) Y. Kawaguchi, A. Harada, *J. Am. Chem. Soc.* **2000**, *122*, 3797–3798; b) Y. Takashima, K. Otani, Y. Kobayashi, H. Aramoto, M. Nakahata, H. Yamaguchi, A. Harada, *Macromolecules* **2018**, *51*, 6318–6326.

[10] A. Carrasco-Ruiz, J. Tiburcio, *Org. Lett.* **2015**, *17*, 1858–1861.

[11] R. A. Luna-Ixmatlahua, A. Carrasco-Ruiz, R. Cervantes, A. Vela, J. Tiburcio, *Chem. Eur. J.* **2019**, *25*, 14042–14047.

[12] A. C. Catalán, J. Tiburcio, *Chem. Commun.* **2016**, *52*, 9526–9529.

[13] A. A. Loredo, Bachelor's Thesis, Universidad de las Américas Puebla (Mexico), **2016**. http://catarina.udlap.mx/u_dl_a/tales/documentos/lnm/loredo_p_aa/.

[14] a) C. R. Groom, I. J. Bruno, M. P. Lightfoot, S. C. Ward, *Acta Crystallogr.* **2016**, *B72*, 171–179; for structures, see: b) COKYAD; c) SERWIV;

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d) DITYEK; e) DITYEK10; f) GERFUE; g) ANIHUC; h) APIYAA; i) IQIPUV; j) ZUKGIX; k) CATBOP.

[15] F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry Part A. Structure and Mechanisms*, Kluwer Academic/Plenum Publishers, USA **2000**, p 13.

[16] S. J. Loeb, J. Tiburcio, S. J. Vella, J. A. Wisner, *Org. Biomol. Chem.* **2006**, *4*, 667–680.

[17] N. Georges, S. J. Loeb, J. Tiburcio, J. A. Wisner, *Org. Biomol. Chem.* **2004**, *2*, 2751–2756.

[18] M. Baroncini, S. Silvi, M. Venturi, A. Credi, *Chem. Eur. J.* **2010**, *16*, 11580–11587.

[19] M. A. Soto, J. Tiburcio, *Chem. Commun.* **2016**, *52*, 14149–14152.

[20] a) M. Baroncini, S. Silvi, M. Venturi, A. Credi, *Angew. Chem. Int. Ed.* **2012**, *51*, 4223–4226; *Angew. Chem.* **2012**, *124*, 4299–4302; b) G. Ragazzon, M. Baroncini, S. Silvi, M. Venturi, A. Credi, *Nat. Nanotechnol.* **2015**, *10*, 70–75; c) H. Li, C. Cheng, P. R. McGonigal, A. C. Fahrenbach, M. Frasconi, W.-G. Liu, Z. Zhu, Y. Zhao, C. Ke, J. Lei, R. M. Young, S. M. Dyar, D. T. Co, Y.-W. Yang, Y. Y. Botros, W. A. Goddard, III, M. R. Wasielewski, R. D. Astumian, J. F. Stoddart, *J. Am. Chem. Soc.* **2013**, *135*, 18609–18620; d) C. Cheng, P. R. McGonigal, S. T. Schneebeli, H. Li, N. A. Vermeulen, C. Ke, J. F. Stoddart, *Nat. Nanotechnol.* **2015**, *10*, 547–553; e) C. Pezzato, M. T. Nguyen, C. Cheng, D. J. Kim, M. T. Otley, J. F. Stoddart, *Tetrahedron* **2017**, *73*, 4849–4857.

[21] K. J. Laidler, *Chemical Kinetics*, McGraw-Hill, USA **1965**, pp 19–21.