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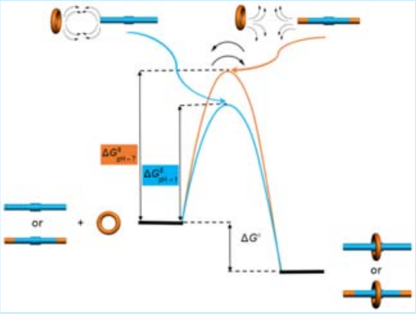
Electrostatic Kinetic Barriers in the Threading/Dethreading Motion of a Rotaxane-like Complex

Anayeli Carrasco-Ruiz and Jorge Tiburcio*

Departamento de Química, Centro de Investigación y de Estudios Avanzados (Cinvestav), México D. F., México

S *Supporting Information*

ABSTRACT: A new rigid cationic thread, based on the 1,2-bis(bipyridinium)ethane motif, and a 24-crown-8 anionic macrocycle self-assemble into a *pseudo*-rotaxane complex in aqueous solution. The presence of pH-responsive end groups on the thread, remote from the recognition motif, allows controlling the threading/dethreading rate without perturbing the complex structure or stability. The difference in the rate is attributed to the activation or deactivation of electrostatic barriers on the thread during the sliding process at different pH values.



A fundamental step toward the development of molecular machines is the precise control of the relative motions between its diverse components. This control can be achieved by regulating the different energy barriers involved in the working cycle; furthermore, because molecular machines are expected to perform during many cycles, these barriers must be fully reversible under operational conditions.[1] In addition, preserving the integrity of the molecular assembly while performing assures a more efficient machine operation by minimizing any energy losses due to molecular rearrangements.[2]

Interlocked and interpenetrated supramolecular systems, such as rotaxanes and *pseudo*-rotaxanes, are considered prototypes of molecular machines due to their ability to perform a variety of motions in response to external stimuli.[3] In the case of *pseudo*-rotaxane complexes, several efforts have been devoted toward controlling the rate of the threading/dethreading motion.

Masson[4] reported that, in the presence of alkaline metals, the dethreading rate of a cucurbit[7]uril (CB7) ring from a polyamine thread with crown ethers as end groups can be 500 times increased. In a different approach, Stoddart[5] increased the energy barrier during the threading of a positively charged ring in 58 kJ/mol (and reduced the rate by 10 orders of magnitude) by adding viologen units as end groups on the thread. In both examples, nonreversible electrostatic barriers are involved during the sliding process.

To overcome this issue, the addition of chemically reversible groups on the thread has been proposed. Nau[6] found that the rate of inclusion of cyclohexylmethylamine in CB6 is pH-dependent; a 20 times decrease is observed by protonating the neutral amine. Using aliphatic carboxylic acid groups joined to a viologen-based thread, Kaifer[7] could increase the CB7 sliding rate up to 10^6 times by varying the medium pH, from 11 to 1; however, this change induces a modification in the complex structure and stability: at low pH the CB7 ring resides on the aliphatic chains, and at high pH the ring shifts to the central viologen unit, simultaneously reducing the association constant by 1 order of magnitude. More recently, Credi[8] reported on the use of photoactive groups on the thread that can be isomerized between *Z* and *E* states in a reversible manner by the use of UV-light. In the *E*-form, threading proceeds at a rate ≥80 M^{-1} s^{-1} (K_a = 820 M^{-1}), and in the *Z*-form, the rate is reduced to 3 × 10^{-3} M^{-1} s^{-1} (K_a = 400 M^{-1}).

In these last examples, although the rate can be reversibly changed, the stability and structure of the complexes are simultaneously modified with the stimulus (pH or light), basically, because the recognition motif and the rate-controlling groups are in close proximity and electronically connected. Therefore, a new approach is needed in order to fulfill both requirements: reversibility and structure/stability conservation.

Herein, we present our design, preparation, structure, stability, and kinetics of a [2]*pseudo*-rotaxane system with a threading/dethreading motion rate that is pH-controlled, reversible behavior, and invariant stability and structure in aqueous solution (Figure 1).

Our complex has been designed to include the following: (i) a rigid linear cationic thread to prevent any conformational change, and with a pH-independent recognition motif, allowing the binding strength between the thread and wheel to remain constant; (ii) two identical end groups on the thread, isolated from the recognition site and displaying pH responsiveness, that could modify the rate of the threading/dethreading process without affecting binding with the wheel; and (iii) a water-soluble macrocycle, chemically not sensitive to the pH.

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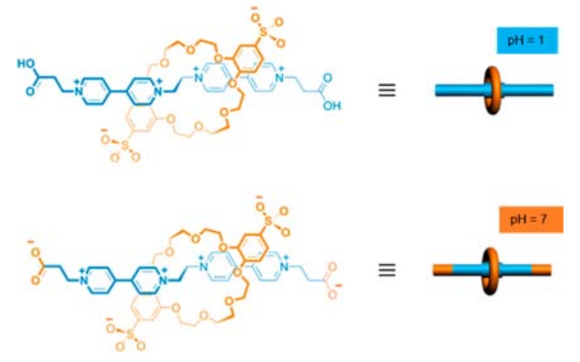

Figure 1. Schematic representation of the [2]*pseudo*-rotaxane complex at pH = 1, [**1**·H_2⊂**DSDB24C8**]$^{2+}$, and pH = 7, [**1**⊂**DSDB24C8**].

As a recognition motif on the thread, we chose a bis(bipyridinium)ethane cationic moiety because it is capable of generating stable interpenetrated complexes with 24-crown-8 macrocycles[9] and is rigid enough to prevent any molecular rearrangement. As end units on the thread, we select propionic acid groups; these can be reversibly switched between neutral and anionic states, depending on the pH of the media and, because of its aliphatic chain, would be remote and electronically disconnected from the recognition site. As a macrocyclic wheel, we opt for *anti*-disulfo-dibenzo-24-crown-8 ether [**DSDB24C8**]$^{2-}$, because of its highly acidic sulfonate groups,[10] which remains fully dissociated and negatively charged in aqueous solution; in addition, its selectivity and ability to generate stable interpenetrated complexes with bis(bipyridinium)ethane derivatives in aqueous media is well established.[11] Based on these components, we expect a host−guest complex with a *pseudo*-rotaxane geometry and steady stability in solution but markedly different rates of threading/dethreading at different pH values. Any observed difference in the rate must be a consequence of electrostatic interactions between the thread terminal groups (neutral or anionic) and the macrocycle electron-rich cavity during the sliding process.

A symmetrical thread based on a propionic-*N*-substituted bis(bipyridinium)ethane bromide salt, compound [**1**·H_2][Br]$_4$, was prepared in quantitative yield from the reaction between 1,2-bis(bipyridinium)ethane,[9] and an excess of 3-bromopropionic acid in water and was fully characterized by ^{1}H (Figure 2A) and ^{13}C NMR spectroscopy, elemental analysis, and high resolution mass spectrometry. An experimental estimation of its pK_a provided an average value of 3.7 for both propionic groups (see Figure S16), reflecting its weak acid character; for an initial concentration of 1×10^{-3} M, the percentage of the protonated thread at pH = 1 is 99.83%, while at pH = 7 it is only 0.05% (see Table S1). It is important to note that the appearance of the ^{1}H NMR spectra is not significantly modified with the pH (see Figure S15). On the other hand, the macrocycle [NMe_4]$_2$[**DSDB24C8**] was prepared following a reported procedure,[11] and its ^{1}H NMR is shown in Figure 2D. Based on an estimated pK_a value of −0.7 and an initial concentration of 1×10^{-3} M, 98% and 99% of the crown ether would be fully dissociated at pH = 1 and pH = 7, respectively (see Figure S17 and Table S2).

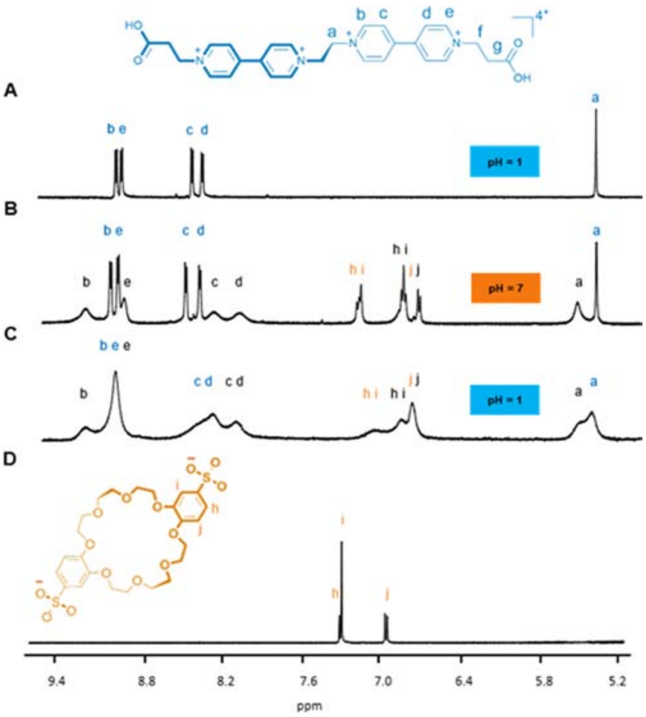

Figure 2. Partial ^{1}H NMR spectra (500 MHz, D_2O, 298 K) of thread [**1**·H_2][Br]$_4$ (A); a 1:1 mixture (5 mM) of thread and macrocycle (B–C); and macrocycle [NMe_4]$_2$[**DSDB24C8**] (D).

An aqueous solution of compound [**1**·H_2][Br]$_4$ and [NMe_4]$_2$[**DSDB24C8**] in water turns yellow immediately after mixing, indicating interaction between both components. Its UV/vis spectrum displays a charge-transfer band centered at 384 nm at pH = 7 and at 390 nm at pH = 1 (see Figure S20), associated with the electronic interaction between electron-rich catechol units in the crown ether and the electron-poor pyridinium rings on the thread.[9] The ^{1}H NMR spectrum in D_2O at pH = 7 (Figure 2B), adjusted using a C_5D_5N solution, displays two sets of signals, indicating a slow exchange rate between complexed and uncomplexed species. The observed chemical shifts for the complex are consistent with a *pseudo*-rotaxane geometry, i.e. a higher frequency shift for the *ortho*-N^+ and ethylene protons, and a lower frequency shift for *meta*-N^+ protons, with the crown ether encircling the central part of the linear molecule.[9,11] An additional feature of the resonances attributed to the *pseudo*-rotaxane is the broadness; this is probably a manifestation of the complex dynamic nature. In sharp contrast, a ^{1}H NMR spectrum of the same mixture but at pH = 1 (Figure 2C), adjusted using a solution of 48% DBr in D_2O, displays only broad signals; this was interpreted as fast threading/dethreading motion in the NMR time scale. The comparison of these spectra provides a qualitative picture of the supramolecular system kinetics, with markedly different rates in the threading/dethreading at both pH values. Remarkably, this difference is not observed in a closely related compound with pH-insensitive propyl end groups (see Figure S18). This model compound proves that the difference observed in the ^{1}H NMR spectra at different pH values for the *pseudo*-rotaxane complex must be due to the acid/base behavior of the end groups on the thread.

Interestingly, this fast/slow movement can be reversed upon addition of an acid or base, for up to three cycles, without decomposition (see Figure S19). A comparison of the chemical shifts, at both pH values, clearly indicates that the structure of the complex in solution is not disturbed by the medium acidity (see Table S3). In order to confirm the prevalence of the complex structure, single crystals were isolated at pH = 1 and pH = 7 and studied by X-ray diffraction (Figure 3).

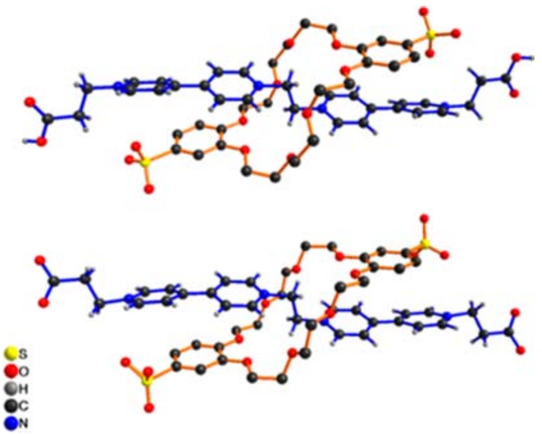

Figure 3. Ball-and-stick representations of the X-ray structure of complexes $[\mathbf{1}\cdot H_2\subset\mathbf{DSDB24C8}]^{2+}$ and $[\mathbf{1}\subset\mathbf{DSDB24C8}]$; hydrogen atoms on the crown and counterions are omitted for clarity.

A close resemblance between $[\mathbf{1}\cdot H_2\subset\mathbf{DSDB24C8}][Br]_2$ and $[\mathbf{1}\subset\mathbf{DSDB24C8}]$ structures is observed in the solid state. Both compounds are interpenetrated species with a [2]*pseudo*-rotaxane geometry. In both structures, the thread and the crown ether are essentially parallel, with the thread adopting an *anti*-conformation in the central ethylene fragment and the crown ether in an S-shape conformation. This arrangement allows the aromatic rings of both components to be conveniently separated by 3.6 Å to facilitate π-stacking interactions. A series of hydrogen bonds between the central ethylene and *ortho*-N^+ hydrogen atoms on the thread with the different oxygen atoms in the crown ether are observed. The main difference between both structures is the presence of counterions for the complex isolated at low pH and the relative orientation of the propionic end groups.

Once the structure of the *pseudo*-rotaxane complex was proven to be unmodified despite the medium's acidity, we aimed to obtain a quantitative picture of association in solution by UV/vis spectrophotometry. Association constants (K_a) at two different pH values (1 and 7) were determined by using an adapted method previously reported by Ray.[12] The slope of linear plots of C_0/A_{obs} versus $(A_{obs})^{-1/2}$ yields $(1/K_a\varepsilon l)^{1/2}$, and the intercept is equivalent to $1/\varepsilon l$ (see Figure S21). Association constants and related thermodynamic parameters are summarized in Table 1. Measured association constants are in the same range as those determined for related systems.[13] van't Hoff plots in the temperature range of 278 to 328 K, at both pH values, show linear behavior and allowed derivation of the enthalpic and entropic contributions (see Figure S22).

Table 1. Thermodynamic and Kinetic Parameters for the [2] *pseudo*-Rotaxane Complex at Two Different pH Values

parameter	pH = 1[a]	pH = 7[a]
$\Delta H°$ (kJ mol^{-1})	−44.1 (±1.6)	−44.3 (±1.7)
$\Delta S°$ (J mol^{-1} K^{-1})	−88 (±6)	−89 (±6)
K_a (M^{-1}) at 298 K	1.3 (±0.1) × 10^3	1.2 (±0.1) × 10^3
$\Delta G°_{298\ K}$ (kJ mol^{-1})	−17.9 (±1.9)	−18.1 (±2.0)
$\Delta H^{\ddagger}_{on}$ (kJ mol^{-1})	19.0 (±0.3)	38.0 (±0.5)
$\Delta S^{\ddagger}_{on}$ (J mol^{-1} K^{-1})	−86.2 (±1.2)	−61.3 (±1.6)
k_{on} (M^{-1} s^{-1}) at 298 K	9.0 (±0.1) × 10^4	1.0 (±0.1) × 10^3
$\Delta G^{\ddagger}_{on}$ (kJ mol^{-1}) at 298 K	44.6 (±0.6)	56.4 (±0.9)

[a] Calculated uncertainties are shown in brackets.

Interestingly, association constants, in addition to enthalpic and entropic terms, are not significantly different at both pH values, confirming that the recognition site in the thread is chemically unchanged and the noncovalent interactions between thread and wheel are not modified by the presence or absence of a negative charge on the ends of the thread ($-COO^-$ or $-COOH$). After establishing that no difference is observed in solution and solid state structures, as well as no differences are indicated by thermodynamic parameters, we proceeded to perform quantitative kinetic measurements.

Concentration−jump kinetic experiments[14] were carried out in the pH range 1 to 7, by using stopped-flow methodology. At low pH values, when both $-COOH$ units are protonated, the time to re-establish equilibrium after perturbation is less than 0.1 s, while, under neutral conditions (pH = 7), when both propionate end groups on the thread are negatively charged, the time for reaching equilibrium is around 10 s (Figure 4).

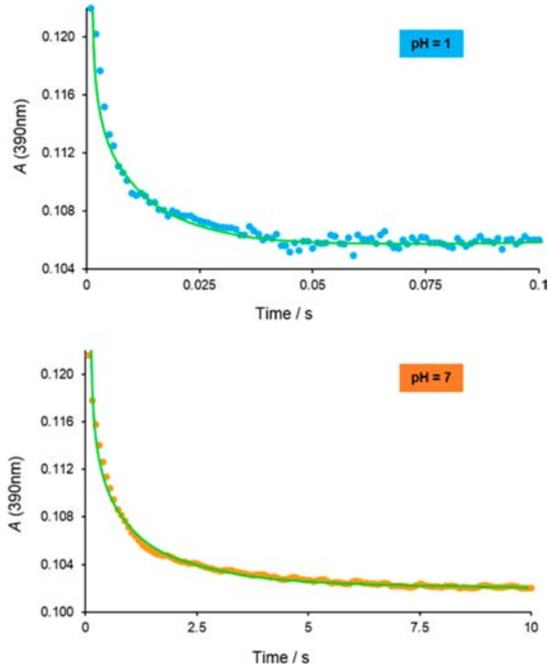

Figure 4. Kinetic traces obtained from stopped-flow concentration-jump experiments recorded at 298 K. Absorption changes are monitored at 390 nm upon diluting a 1 × 10^{-3} M solution of [2] *pseudo*-rotaxane complex in aqueous solution.

From these experiments, threading and dethreading rate constants were derived at temperatures between 278 and 328 K following a modified methodology,[15] and Eyring plots allowed determination of the enthalpy and entropy activation parameters (see Figure S23). Activation free energy was calculated from the equation $\Delta G^{\ddagger}_{298} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$. Rate constants and related kinetic parameters are summarized in Table 1.

A 2 orders of magnitude increase in the rate of threading (k_{on}) from pH = 7 to 1 is clearly observed; this pH variation also induces a reduction of the activation enthalpy to half its value, probably due to a reduction of the electrostatic repulsive interactions on the activated complex, resulting in an ~12 kJ/mol difference in $\Delta G^{\ddagger}_{298}$ between these pH values.

This difference is consistent with a stronger electrostatic repulsion during the threading process at neutral pH, between anionic end groups on the thread and the electron-rich crown ether cavity, compared to under acidic conditions, when the end groups on the thread are fully protonated, finally confirming the behavior previously observed in the NMR spectroscopy.

Further evidence that the thread end groups control the threading/dethreading rate of the *pseudo*-rotaxane complex was provided by comparing the variation of the protonated thread mole fraction and the experimentally measured rate constants at different levels of media acidity. Effectively, a graph of log k_{on} versus pH shows a similar trend to the one displayed by the variation of the protonated thread mole fraction as a function of the pH (Figure 5); this behavior indicates that electrostatic charges on the thread end groups (neutral versus anionic) are responsible of the threading/dethreading process rate.

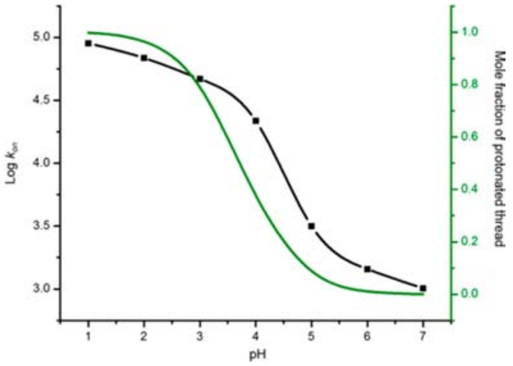

Figure 5. Protonated thread mole fraction (green line) and log k_{on} (black line) as a function of the medium acidity (pH).

In summary, we have shown that the utilization of a rigid thread, with a pH-insensitive recognition motif, jointly with an anionic macrocycle wheel, allowed the self-assembly of a *pseudo*-rotaxane complex in aqueous solution. This complex presents identical structures and binding at both, neutral, and acidic pH values. Because of the inclusion of pH-responsive groups on the thread, the threading/dethreading rate can be fine-tuned by the solution acidity, achieving an ∼100 times increase by a pH change from 7 to 1. The difference in the rate has been attributed to the activation or deactivation of electrostatic barriers on the thread during the sliding process. The rational selection and inclusion of two different end groups on the thread could lead to achieving unidirectional motion on interpenetrated supramolecular systems.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental and synthetic details; NMR and HR-MS spectra; equilibrium and rate constants measurements; van't Hoff and Eyring plots; crystallographic CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jtiburcio@cinvestav.mx.

Notes

The authors declare no competing financial interest.

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