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Bilability is Defined when One Electron is Used to Switch between Concerted and Stepwise Pathways in Cu(I)-Based Bistable [2/3]Pseudorotaxanes

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Abstract: Supramolecular switches operate as simple machines by using a stimulus to turn stations off and on, generating thermodynamic differences that define bistability and enable motion. What has not been previously investigated, yet is required to gain further control over molecular movements for complex operations, is an understanding of how the same stimulus can also switch pathways off and on, thus, defining the kinetic property of bilability. To address this challenge, the mechanisms of the forward and return reactions of redox-switchable Cu(I)-based [2/3]pseudorotaxanes have been quantitatively characterized utilizing mechanistic cyclic voltammetry and employing a series of isosteric bis-bidentate ligands. First, the bistability of the switch is retained across the series of ligands: Reduction of the ligand drives the reaction forward where a [2]pseudorotaxane switches into a reduced [3]pseudorotaxane and reoxidation drives the switching cycle back to the beginning. Second, the switch is bilabile with the forward reaction following an association-activated interchange pathway (concerted), whereas the reverse reaction follows a different dissociation-based dethreading pathway (stepwise). The forward reaction is more sensitive to denticity (bidentate tetrazinyl ligand, $k_2 = 12\,000\ M^{-1}\ s^{-1}$, versus the monodentate pyrazinyl ligand, $k_2 = 1500\ M^{-1}\ s^{-1}$) than to electronics ($k_2 = 12\,000\ M^{-1}\ s^{-1}$ for methyl and trifluoromethyl substituents). The rate of return with the pyrazinyl ligand is $k_1 = 50\ s^{-1}$. Consequently, both the mechanism and the thermodynamics of switching are stimuli dependent; they change with the oxidation state of the ligand. These findings have implications for the future design of molecular motors, which can be built from systems displaying allosterically coupled bistability and bilability.

Introduction

Stimuli-responsive changes in the relative locations of molecular subunits, that is motion, is an important topic of study in supramolecular chemistry,[1] molecular machines,[2,3] and nanoscience.[4] Proof-of-principle demonstrations have led to molecular memory[5] and walkers[6] as well as artificial muscles[7] and rotary motors.[8,9] Natural systems highlight what is ultimately possible: Kinesin biomotors[10] literally walk down microtubule tracks and the rotary flagella of bacteria propel them up and down chemical gradients.[11] Theory suggests that unidirectional motion can be generated using a flashing ratchet design.[3] Here, an external stimulus flashes the system between two differently shaped and periodic double-well potentials (Scheme 1). The stimulus acts on the thermodynamics of the energy wells by turning states off and on, a property known as bistability. At the same time, different pathways are switched off and on by moving the kinetic barriers up and down, a property defined as bilability.[3] Thus, unidirectional motion can be attained (Scheme 1) following (i) stimulation, (ii) move right, (iii) remove stimulation, (iv) move right, and continue cycling periodically. Such motions have been demonstrated in part[12] or in a *stepwise* manner.[9b] To achieve *simultaneous* types of unidirectional designs[3] requires a fundamental knowledge of kinetics in addition to synthetic control[13] and bistability.[14−17] Only a few

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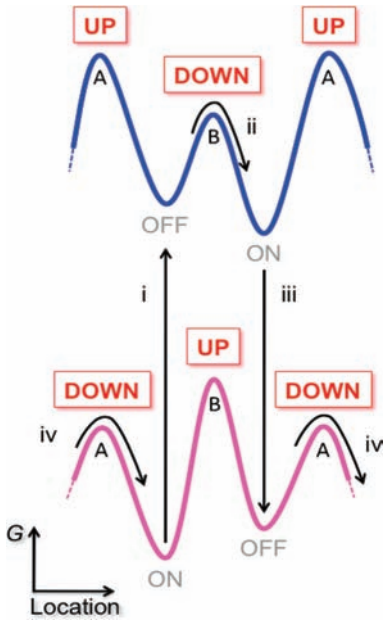
Scheme 1. Schematic Representation of a Flashing Ratchet after Ref 3 in which a Stimulus Changes Both the Kinetic and Thermodynamic Parameters to Achieve Unidirectional Motion[a]



[a] (i) Add stimuli, (ii) move, (iii) remove stimuli, (iv) move and continue periodically (dashed lines). The stimuli-driven switching of energy barriers up and down to distinguish between different pathways A and B thereby defines bilability.

studies have deliberately examined the mechanism of switching[9a,12,18−21] and few,[8] if any,[22] have investigated how the stimuli that drive molecular motions affect the pathways followed, that is, bilability. Consequently, the study of the mechanism of supramolecular switching reactions is a logical

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first step toward the understanding and eventual control over the direction of molecular motion. To this end, we report one of the first confirmed examples where the change in state responsible for driving the switching also alters the pathway of the switching reactions.

The underlying question about how the reactivity of noncovalently linked supramolecular systems changes with an input stimulus has been addressed[22] but not answered. Many investigations report the rates of various molecular motions.[23−30] Some synthetically creative studies aim to manipulate the pathway by introducing road blocks,[16d,17a,b,31] or speed bumps[32,33] along the pathway to predetermine the path of molecular motion, perhaps altering the rate-limiting step by doing so. Other studies modify the molecular structures to tune the heights of kinetic barriers[34−36] and have begun to identify structure−function relationships on the switching rates. A complementary approach, and the one taken here, is to conduct mechanistic investigations into the effect of the stimuli (e.g., electrons, protons, photons) on the native system, which can lead to the optimization of *inherent* barriers to motion.

To the best of our knowledge, there is only one related experimental study[37] of a pseudorotaxane that investigates the intrinsic mechanism of the redox-driven switching in a viologen-calix[6]arene. It was found to dethread and rethread along a dissociative pathway. Dissociative pathways might be thought of as exemplary of pseudorotaxanes:[38] (1) Weak bonds facilitate rapid in−out dynamics of the rod inside the ring, and (2) steric constraints placed upon the rod, when it is encapsulated inside the ring, can hinder an associative attack. These ideas, however, should serve as a guide rather than the rule.[39−43] The specific character of the noncovalent bonds and any associated conformational dynamics[44] also need to be considered. In the present case, reactivity around tetrahedral Cu(I)[45,46] and analogous Ag(I)[47] cations are known to proceed along bimolecular, association-activated pathways (association or associative interchange).[48,49] Considering the flexible 2,2′-bipyridine[45,47] as a model, the rate-limiting step is inferred to be the initial association of one pyridyl moiety followed by rapid closure of the chelate ring. When using rigid chelating phenanthroline ligands,[46] an associative-interchange mechanism[50] is operative.

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Theoretical studies of the redox-induced pirouetting of Cu-based rotaxanes,[19f] where the oxidation state of the $Cu^{II/I}$ ion drives movements (bistability), found that an association-activated mechanism operates for both switching forward and back with large differences in the transition-state energies. Whereas the kinetic barriers were raised and lowered, the pathway remained the same thus the property of bilability was not attained.

Considering the different possible patterns of reactivity for a Cu(I)-based pseudorotaxane, two principle questions emerge: Does the switching in bistable [2/3]pseudorotaxanes[51,52] proceed according to (a) the reactivity of the Cu(I) ion (associative) or (b) the encapsulated character of a host−guest complex (dissociative)? Second, does the reaction pathway change with redox stimulation?[22] Here, we address the two questions and find that both pathways are possible because the change in redox state changes the inherent reactivity[53] as in Scheme 1, thus achieving bilability.[3]

Systems of Study

Bistable [2/3]pseudorotaxanes have been created[51] as switching prototypes (Scheme 2) by applying the concept of a supramolecular dismutation[54,55] reaction and utilizing rod and ring precursors[56] of molecular machines. These switches are formed from a redox-active, bis-bidentate rod that is threaded through a macrocyclic ring and held in place by a Cu(I) ion. Here, the rod is 3,6-bis(5-methyl-2-pyridine)-1,2,4,5-tetrazine[57] (**TZ**) and the macrocycle is based on 1,10-phenanthroline.[58] The rod component in the [2]pseudorotaxane (**[2]PR**$^+$) retains a vacant bidentate site, which can accommodate a second Cu-macrocycle. Upon reduction (eq 1), this rod gains a negative charge to form **[2]PR**^{0} and initiates a bimolecular switching reaction ($k_2 = 1.2 \times 10^4$ M^{-1} s^{-1}) with an unreduced [2]pseudorotaxane to form (eq 2) a reduced [3]pseudorotaxane (**[3]PR**$^+$) and the free ligand **TZ**. A proposed rate-limiting step based on the known associative reactivity of Cu(I) complexes[45,46] is shown in Scheme 3. From the supramolecular perspective, a Cu-macrocycle moiety moves between the neutral and reduced rods. Reoxidation (eq 3) of the system regenerates (eq 4) the starting state.

$$2[2]PR^+ + e^- = [2]PR^+ + [2]PR^0 \quad \text{Reduction} \quad (1)$$

$$[2]PR^+ + [2]PR^0 = [3]PR^+ + TZ \quad \text{Switching forwards} \quad (2)$$

$$[3]PR^+ + TZ = [3]PR^{2+} + TZ + e^- \quad \text{Oxidation} \quad (3)$$

$$[3]PR^{2+} + TZ = 2[2]PR^+ \quad \text{Switching backwards} \quad (4)$$

Two sets of ligands (Scheme 4) have been selected to investigate the factors that impact the mechanism of switching.[59] (1) To test for electronic effects, the reactivity of dimethyl **TZ** will be compared to the isosteric and electron-withdrawing trifluoromethyl version: 3,6-bis-(5-trifluoromethyl)-2-pyridine)-1,2,4,5-tetrazine (**CF_3TZ**).[60] (2) Conformation and denticity effects will be characterized using 2,5-bis-(5-methyl-2-pyridine)-1,4-pyrazine (**PZ**) and 3,6-bis-(5-methyl-2-pyridine)-1,2-pyridazine (**PD**). These ligands

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(50) (a) Langford, C. H.; Gray, H. B. *Ligand Substitution Processes*; Benjamin: New York, 1965. (b) Richens, D. T. *Chem. Rev.* **2005**, *105*, 1961–2002.

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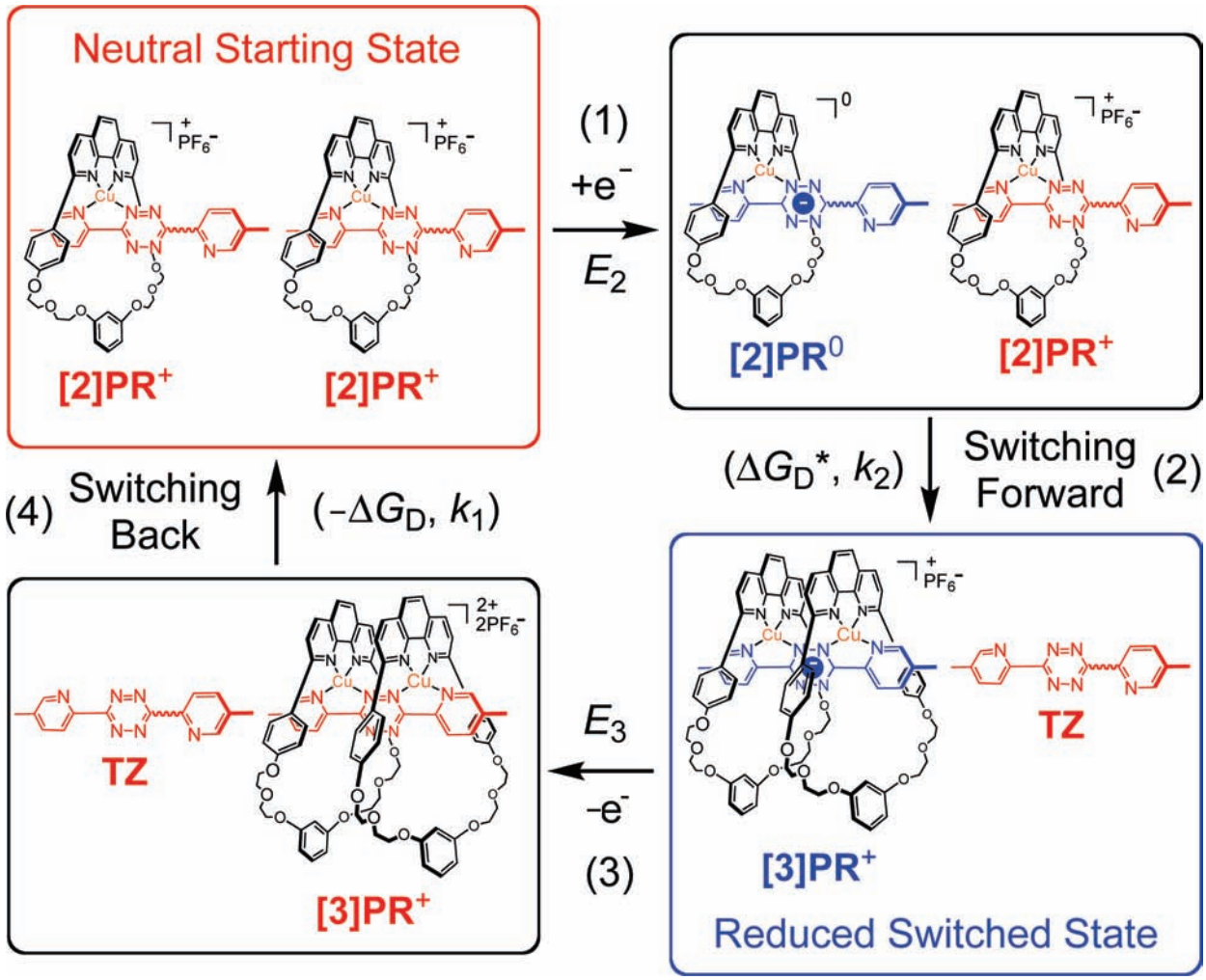
(58) Jimenez-Molero, M. C.; Dietrich-Buchecker, C.; Sauvage, J.-P. *Chem.—Eur. J.* **2002**, *8*, 1456–1466.

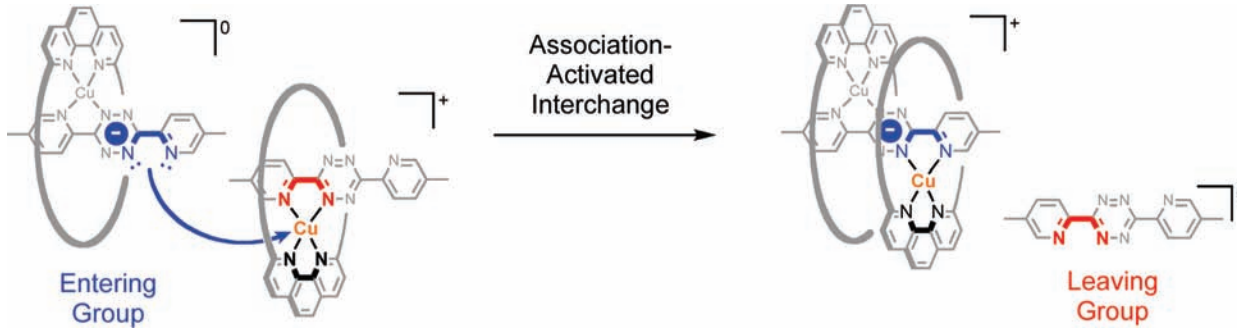
(59) The macrocycle used in the studies reported here has R = H. The **TZ**-based results are reported for R = CH_2OH. Prior studies confirm these difference do not affect the thermodynamics or kinetics.[52]

(60) (a) The effect of differences in ligand basicity on reaction rates will be considered as and when appropriate. The known basicity (pK_{BH^+}) in the neutral state has been reported; (b) Ernst, S. D.; Kaim, W. *Inorg. Chem.* **1989**, *28*, 1520–1528: pK_{BH^+} = +5.2 (pyridine) > +2.3 (pyridazine) > +0.5 (pyrazine) > ∼−5.0 (tetrazine). (c) The degree to which reduction enhances basicity is proportional to the ease of reduction and follows the order: *E*(red): −0.8 V (tetrazine) <−2.1 V (pyrazine) =−2.1 V (pyridazine) <−2.7 V (pyridine).

Scheme 2. General Square-Scheme Cycle of the Cu(I)-Based Bistable [2]Pseudorotaxanes Switching Reversibly into a [3]Pseudorotaxane Shown Here for the Redox-Active **TZ**



Scheme 3. Representation of the Entering Group (Blue) as the Reduced [2]Pseudorotaxane and the Leaving Group (Red) of the Neutral [2]Pseudorotaxane for the Rate-Limiting Step in the Association-Activated Interchange of the Forward Switching Reaction



have traditional bipy-like conformations[61−67] thus displaying monodentate sites (parts c and d of Scheme 4) as the entering groups whereas the tetrazines (**TZ** and **CF$_3$TZ**) display bidentate sites (parts a and b of Scheme 4).[68] (3) Steric interactions involving the rigid phenanthroline moieties of the Cu-macrocycle are expected to influence the relative orientation of the entering and leaving groups as either a syn or anti relationship of the two Cu-macrocycles. These two orientations will be investigated by using simple molecular models. (4) The impact of bond rotations will also be considered[69] to determine if torsional rotations or the exchange reactions are rate limiting.

(61) Neutral 2,2′-bipyridine: (a) Howard, S. T. *J. Am. Chem. Soc.* **1996**, *118*, 10269–10274. (b) Goller, A.; Grummt, U. W. *Chem. Phys. Lett.* **2000**, *321*, 399–405.

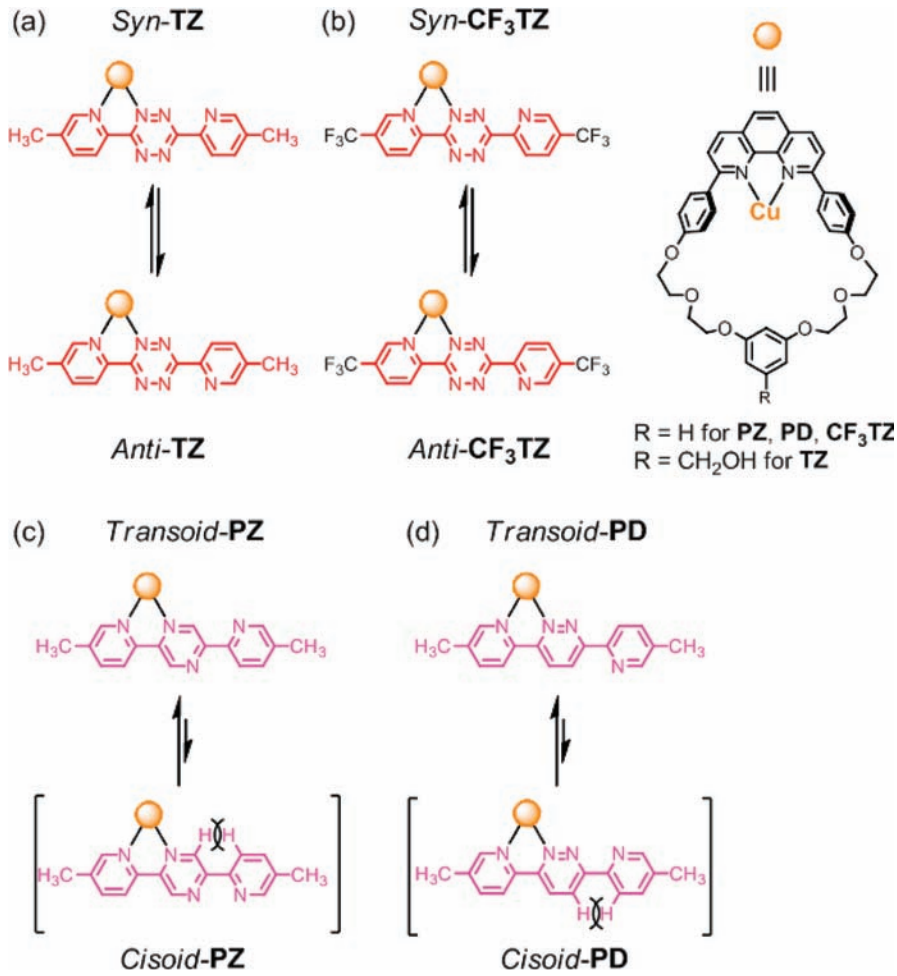
(62) Reduced 2,2′-bipyridine: (a) Lapouge, C.; Poizat, O.; Buntinx, G. *J. Mol. Struct.* **2008**, *872*, 123–128. (b) Chung, G.; Lee, D. *Bull. Korean Chem. Soc.* **2008**, *29*, 2419–2422.

(63) Coordinated 2,2′-bipyridine: Grummt, U. W.; Erhardt, S. *J. Mol. Struc. Theochem.* **2004**, *685*, 133–137.

(64) Transoid conformations of 2,2′-bipyridine are preferred in the neutral (calcd^{gas}: ∼9 k calmol^{-1}) and reduced states (calcd^{gas}: ∼5 kcal mol^{-1}), wheras cisoid is favored (calcd^{gas}: ∼50 kcal mol^{-1}) upon coordination by $\{Zn(H_2O)_2\}^{2+}$.

(65) Barboiu, M.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5201–5206. (b) *Foldamers*; Hecht, S., Huc, I., Eds.; Wiley-VCH, 2007.

Scheme 4. Conformational Preferences of the [2]Pseudorotaxanes Based on the Redox-Active (a) **TZ**, (b) **CF_3TZ**, (c) **PZ**, and (d) **PD** ligands[a]



[a] The labels (a) syn and (b) anti refer to the conformation of the uncoordinated pyridyl in **TZ** and **CF_3TZ**. Cisoid and transoid labels in (c) and (d) refer to the relative conformation of the uncoordinated pyridyl in **PZ** and **PD**.

The mechanism of redox-driven switching forward (eq 2) in Cu(I)-based, bistable [2/3]pseudorotaxanes are investigated herein using the series of the isosteric and bis-bidentate ligands (Scheme 4). Retention of bistability across the series is confirmed from quantitative UV−vis and cyclic voltammetry (CV) studies. Variable-scan-rate and variable-concentration CV studies[70] together with simulations[71] of the CV responses are used to distinguish a concerted associative interchange from different mechanistic models.[48−50] Taking advantage of the clean CV response of the

(66) For calculations of the LUMO for bis-bidentate ligands see: (a) Kaim, W.; Kohlmann, S. *Inorg. Chem.* **1987**, *26*, 68–77. (b) Schwach, M.; Hausen, H. D.; Kaim, W. *Inorg. Chem.* **1999**, *38*, 2242–2243. (bb) Gordon, K. C.; Burrell, A. K.; Simpson, T. J.; Page, S. E.; Kelso, G.; Polson, M. I. J.; Flood, A. *Eur. J. Inorg. Chem.* **2002**, 554–563. (c) Remenyi, C.; Reviakine, R.; Kaupp, M. *J. Phys. Chem. A* **2006**, *110*, 4021–4033. (d) Li, G.; Parimal, K.; Vyas, S.; Hadad, C. M.; Flood, A. H.; Glusac, K. D. *J. Am. Chem. Soc.* **2009**, *131*, 11656–11657.

(67) (a) The behavior of 2,2′-bipyridine in its neutral,[61] reduced,[62] and coordination[63] states[64] provides a model for the conformational preferences of both **PZ** and **PD**. These ligands are, therefore, more typical of other heterocycles[65] and prefer transoid conformations. (b) The *transoid*-**PZ** and *transoid*-**PD** ligands are expected to have well-defined conformations. As with 2,2′-bipyridine, reduction of **PZ** populates a quinoidal LUMO[66a] that is predicted to enhance the stability of the transoid conformations of **PZ** and **PD** and to increase dramatically the transoid-to-cisoid barrier (for 2,2′-bipyridine the barrier increases from 7 to 24 kcal mol^{-1}).[62] Coordination of the $\{Zn(H_2O)_2\}^{2+}$ moiety to 2,2′-bipyridine sterically destabilizes the transoid conformation[63] and completely removes the barrier to reach the stabilized cisoid conformation by engaging in cation−π(Zn^{2+}···pyridine) interactions. The observation of cation−π interactions involving Cu(I) suggests this pathway will also be available in the [2]pseudorotaxanes, see: (c) Ruan, C.; Yang, Z.; Rodgers, M. *Phys. Chem. Chem. Phys.* **2007**, *9*, 5902–5918. (d) Kühl, O.; Hinrichs, W. *ChemBioChem* **2008**, *9*, 1697–1699.

(68) The central tetrazine heterocycle of **TZ** and **CF_3TZ** affords the pseudorotaxane with unique conformational behavior: Both syn and anti conformations are equally populated[52,66d] with a small barrier between them in the neutral[52,66d] and reduced states.[66] The torsional profile of the reduced form can be deduced from the nodal structure of the LUMO. The LUMO is localized on the central tetrazine heterocycle and nonbonding across the inter-ring C-C bonds.[66] Therefore, reduction should retain the flexibility of the neutral species.

(69) The products of the initial ligand exchange reactions may need to undergo bond rotations to access the stable forms of the reduced [3]pseudorotaxanes. These stable forms are expected to be syn for **TZ** and **CF_3TZ**, where stacking between phenanthrolines can occur.[52,56] For **PZ** and **PD**, their respective anti and syn orientations are predetermined by their central pyrazine and pyridazine heterocycles. For the initially formed [3]pseudorotaxane with a monodentate *transoid*-**PZ**, only the pyridyl heterocycle has to rotate. On the basis of the four-coordinate $[Zn(H_2O)_2(2,2\text{-bipyridine}]^{2+}$ model[63] and the impact of reduction, a small-to-absent barrier can be expected. For the monodentate *transoid*-**PD** and bidentate *anti*-**TZ**, rotation of the larger $\{$macrocycle-Cu-pyridyl$\}^+$ moiety is required, with possible benefits from a cation−π interaction.[63,67c,d] Lastly, for the possible monodentate *syn*-**TZ** product, multiple rotational pathways are possible.

(70) (a) Geiger, W. E. *Prog. Inorg. Chem.* **1985**, *33*, 275–352. (b) Evans, D. H. *Chem. Rev.* **1990**, *90*, 739–751.

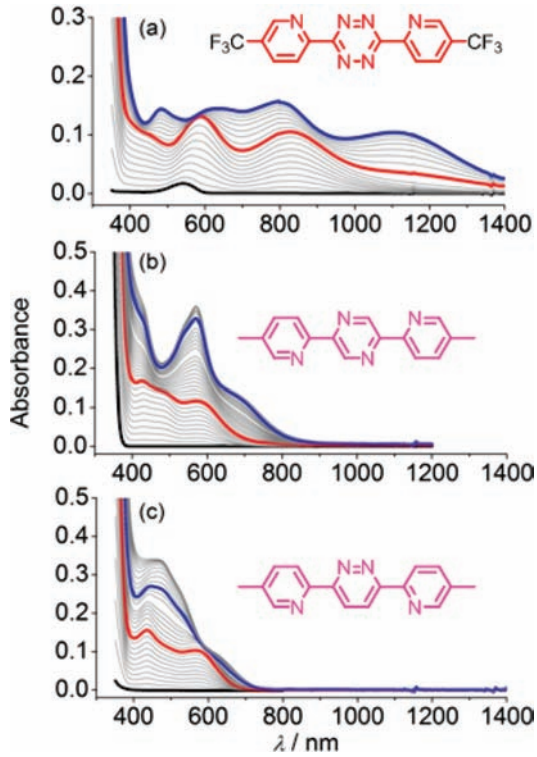


Figure 1. UV-vis-NIR titration of Cu-macrocycle (0.1 equiv per addition) into (a) **CF_3TZ** (~37 μM), (b) **PZ** (~50 μM), and (c) **PD** ligands (~50 μM) in CH_2Cl_2. The spectra of the solutions for the free ligand (black) and after 1.0 (red) and 2.0 (blue) equiv are colored. Moderate binding conditions lead to continued spectroscopic changes beyond 2.0 equiv.

pseudorotaxane formed with the **PZ** ligand, the return cycle is characterized to be a stepwise, dissociation-activated process, thus verifying the property of bilability.[3]

Results and Discussion

Thermodynamic Studies Using UV-vis-NIR and Cyclic Voltammetry Titrations. At the outset it is critical to verify the thermodynamic feasibility for redox-driven switching, that is bistability, when using the new ligands. A **PD**-based [3]pseudorotaxanes has been prepared previously,[56] indicating the feasibility of forming such species. UV-vis-NIR titrations (Figure 1) of the preformed Cu-macrocycle with each of the ligands were conducted. Metal-to-ligand charge-transfer (MLCT) transitions (Table 1) grow into the visible region (~600 nm) and then shift to longer wavelengths (~650 nm) during the stepwise formation of the [2]- and then [3]pseudorotaxanes, respectively. The red-shift of the MLCT band is consistent with stabilization of the ligand-based LUMO upon coordination of the second Cu-macrocycle moiety.

Quantitative analysis of the titration data using equilibrium-restricted factor analysis[72] was used to determine the free energy for the supramolecular dismutation reaction (ΔG_D, Scheme 2), which corresponds to the driving force for switching back at the end of the switching cycle. This energy also represents the minimum amount that needs to be overcome for switching to occur in the forward direction, viz. for the population ratio of ending:starting states to exceed 50:50. The extra energy (ΔG_E) required to achieve this outcome is provided by the electrostatic stabilization of the reduced ligand when the second electropositive Cu-macrocycle moiety is present relative to the first. The difference between the reduction potentials measured by CV at fast scan rates (Table 1) for the [2]- and [3]pseudorotaxanes, E_2 and E_3 (defined in Scheme 2) respectively, provides an estimate of this energy, $\Delta G_E = -nF(E_3 - E_2)$. The reduction of ligands and pseudorotaxanes formed from **PZ** and **PD** are noted to have significant cathodic shifts of ~1 V compared to **TZ**, which is consistent with the weaker π acceptor ability of the central pyrazine and pyridazine rings, respectively.[60b] Nevertheless, the stabilization of the reduced ligand upon formation of the [3]pseudorotaxane is about the same $\sim 0.3V = 8$ kcal mol^{-1} (Table 2) irrespective of the nature of the ligand. Therefore, switching forward (ΔG_D*) and back again ($-\Delta G_D$) is favorable: If low-energy pathways are available, switching should occur for each ligand.

Table 1. UV-Vis-NIR Absorption (~50 μM, for **TZ**, **PZ**, and **PD**. ~37 μM for **CF_3TZ** in CH_2Cl_2) and Electrochemistry Data (~1 mM, 0.1 M $TBAPF_6$, CH_2Cl_2) for Ligands **TZ**, **CF_3TZ** (~37 μM, CH_2Cl_2), **PZ** and **PD**, and Their Pseudorotaxanes

compound	λ_{max}/nm (ϵ_{max}/M^{-1} cm^{-1})	assignment[a]	E(reduction)/V[b](vs Ag/AgCl)
TZ	520 (500)	LC	−1.00
[2]PR$^+_{TZ}$	796 (3500)	MLCT	−0.65
[3]PR$^{2+}_{TZ}$	1096 (3000)	MLCT	−0.285
CF_3TZ	541 (500)	LC	−0.90
[2]PR$^+_{CF3TZ}$	830 (3000)	MLCT	−0.55
[3]PR$^{2+}_{CF3TZ}$	1102 (3000)	MLCT	−0.185
PZ	340 (10 000)	LC	−1.9[c]
[2]PR$^+_{PZ}$	580 (2200)	MLCT	−1.65
[3]PR$^{2+}_{PZ}$	694 (2300)[d]	MLCT	−1.35
PD	350 (10 000)	LC	−2.0[c]
[2]PR$^+_{PD}$	570 (2000)	MLCT	−1.73
[3]PR$^{2+}_{PD}$	648 (1500)[d]	MLCT	−1.43

[a] LC = Ligand-centered, MLCT = metal-to-ligand charge-transfer. [b] Fast scan rates (~10 V s^{-1}) were used to establish the reduction potentials for the pseudorotaxanes. [c] Cathodic peak position reported for the irreversible process. [d] Shoulder.

Table 2. Switching Parameters for [2]Pseudorotaxanes with Different Central Ligands that Relate to Switching Back (ΔG_D)[a], Electrostatic Stabilization (ΔG_E)[b], and Switching Forward (ΔG_D*, k_2)[c]

central ligand	ΔG_D kcal mol^{-1}	ΔG_E kcal mol^{-1}	ΔG_D* kcal mol^{-1}	k_2 M^{-1} s^{-1}
TZ	+3 ± 1	−8.4 ± 0.1	−5.4 ± 1	1.2 ± 0.2 × 10^4
CF_3TZ	+2.8 ± 1	−8.4 ± 0.1	−5.6 ± 1	1.1 ± 0.2 × 10^4
PZ	+3.5 ± 0.5	−6.9 ± 0.1	−3.4 ± 1	1.5 ± 0.3 × 10^3
PD[d]	+3.0 ± 0.5	−6.9 ± 0.1	−3.9 ± 1	1.5 ± 0.3 × 10^3

[a] Obtained from analysis of UV-vis-NIR titration data (~50 μM, CH_2Cl_2, 293 K). [b] Obtained from CV (~1 mM, CH_2Cl_2, 0.1 M $TBAPF_6$, 291 K). [c] ΔG_D* = ΔG_D + ΔG_E. [d] For **PD**, switching was only observed at high concentrations (>8 mM). The rate constant was based on simulations of the anodic peak height corresponding to the rate of generation of the reduced **[3]PR$^+$**. See text for details.

Kinetics Studies of Forward Switching Using Cyclic Voltammetry. To test the kinetics hypotheses, CVs of the [2]pseudorotaxanes were recorded as a function of scan rate (10 − 0.2 V s^{-1}, Supporting Information). Systematic variations in relative peak heights with scan rate are characteristic of EC (electrochemistry−chemistry)[70] processes and are signatures of switching.[73] All of the ligands facilitate switching. When using **PD**, however, the conversion into reduced **[3]PR$^+$** occurs with a lower yield presumably through the formation of another species[74] (vide infra). Representative CVs that were recorded under conditions that promote switching are shown in Figure 2 for **PZ** and Figure 3 for **PD** and **CF_3TZ**. Variable concentration studies (Supporting Information) demonstrated that the forward reactions involving **CF_3TZ**, **PZ**, and **PD** are bimolecular, which

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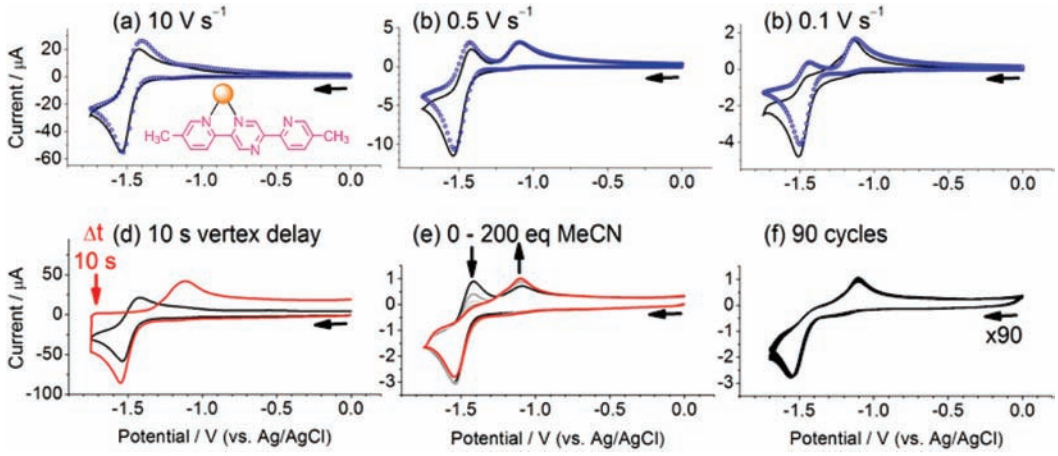

Figure 2. CVs of the **PZ**-based [2]pseudorotaxane (4 mM) at (a) 10, (b) 0.5, and (c) 0.1 V s^{-1} corresponding to reaction times of ~60 ms, 0.6 and 6 s, respectively; simulations are represented as blue circles. (d) Overlay of CVs recorded at 10 V s^{-1} with delays of 0 s (black) and 10 s (red) at the vertex potential of −1.75 V. (e) CVs of the **PZ**-based [2]pseudorotaxane (1 mM) at 0.5 V s^{-1} upon the addition of 0, 40, 80, 120, 160, and 200 equiv of MeCN. (f) CV at (1 mM) 0.5 V s^{-1} for 90 cycles with 2% MeCN (400 equiv). Conditions: 1:1:1 mixture of Cu:macrocycle:**PZ**, 0.1 M $TBAPF_6$, Ar degassed, CH_2Cl_2, glassy carbon electrode (0.785 mm^2), Pt counter electrode, *iR* compensation applied.

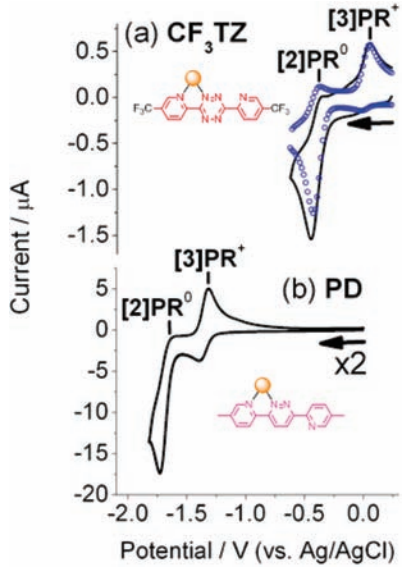

Figure 3. CVs of the [2]pseudorotaxanes formed from (a) **CF_3TZ** (0.9 mM, 0.2 V s^{-1}, 293 K; simulation: blue circles) and (b) **PD** (8 mM, 0.2 V s^{-1}, 293 K), recorded using conditions known to promote switching. (0.1 M $TBAPF_6$, Ar degassed, CH_2Cl_2, glassy carbon electrode (0.785 mm^2), Pt counter electrode).

suggests an association-activated mechanism centered on the Cu(I) ion.[46] To verify the Cu(I)-based reactivity, MeCN was added to ascertain if a faster solvent-assisted pathway could become operative.[20,46] A systematic change in the relative intensities of peak heights (part e of Figure 2) during addition of MeCN shows that ~200 equiv of MeCN saturate this pathway at a scan rate of 0.5 V s^{-1}. Addition of MeCN also prevented any degradation in the fidelity of the switching CVs recorded during 90 cycles (part f of Figure 2).

Simulations of the Forward Switching Mechanism. A range of possible mechanisms[45−47,49,50] were employed as models to simulate the variable-scan-rate and variable-concentration CVs of the exemplary **PZ**-based [2]pseudorotaxane (Figure 2, blue circles). Some of the possible mechanisms (dissociation, Eigen−Wilkins interchange and dissociatively activated interchange) were excluded because no combination of rate and equilibrium constants could reproduce the data. Other mechanisms (Eigen−Wilkins association and Eigen−Wilkins dissociation) were only able to generate a correspondence to the experimental CVs by utilizing unrealistic rates and/or equilibrium constants. Included among these unsuccessful models was one that could be formulated on the basis of the pseudorotaxane's supramolecular character: Fast dethreading (dissociation) of the unreduced [2]pseudorotaxane, **[2]PR**$^+$, followed by a slow threading of Cu-macrocycle onto the reduced [2]pseudorotaxane, **[2]PR**^{0}. Only the association or associative-interchange mechanisms reproduced the data and generated reasonable combinations of rate and equilibrium constants. Van Koten[47] and Vincent[45d] proposed the former mechanism while Geier suggested the latter.[46] For the former, molecular modeling (vide infra) for either a four- or five-coordinate intermediate, which would be formed in an association mechanism, appears too sterically congested to be viable. Therefore, the forward switching is proposed to proceed along an association-activated interchange process akin to a concerted S_N2-like mechanism.

The other ligands behave in a similar way as **PZ** and are consequently simulated (Figure 3, blue circles) and analyzed according to the same mechanism. The **CF_3TZ**-based pseudorotaxane switches at the same rate ($1.1 \pm 0.2 \times 10^4$ M^{-1} s^{-1}) as its parent **TZ**. With **PZ**, the rate constant is found to be 10-times smaller ($1.5 \pm 0.3 \times 10^3$ s^{-1} M^{-1}) than **TZ** and **CF_3TZ**.

Simulations of the Forward Switching Mechanism with PD. In contrast to the other ligands, switching with **PD** shows a smaller yield of conversion into **[3]PR**$^+$, a result that is attributed to the formation of another species. The [3]pseudorotaxane formed from **PD** shows two redox processes at −1.35 and −1.89 V (Supporting Information) where the latter initiates

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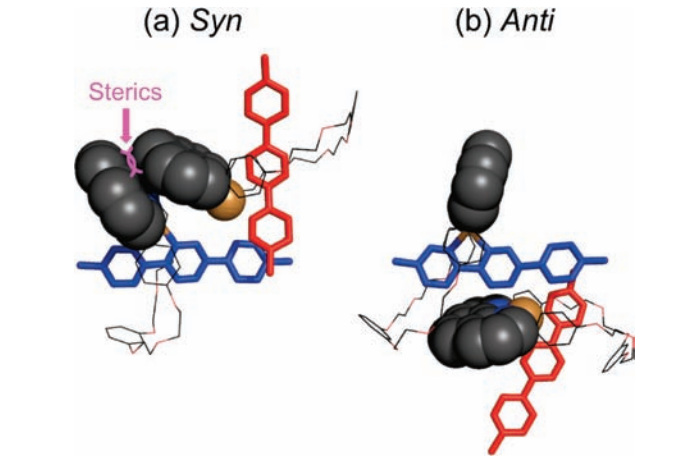


Figure 4. MM2 models of the possible encounter complexes for the (a) syn and (b) anti attacks of **[2]PR**^{0} on **[2]PR**$^+$. The entering ligand (blue) exchanges with the leaving ligand (red) in a reaction around the Cu(I) ion (orange, space fill), whereas the phenanthroline (dark-gray, space-fill) units on the macrocycles are retained; hydrogen atoms omitted.

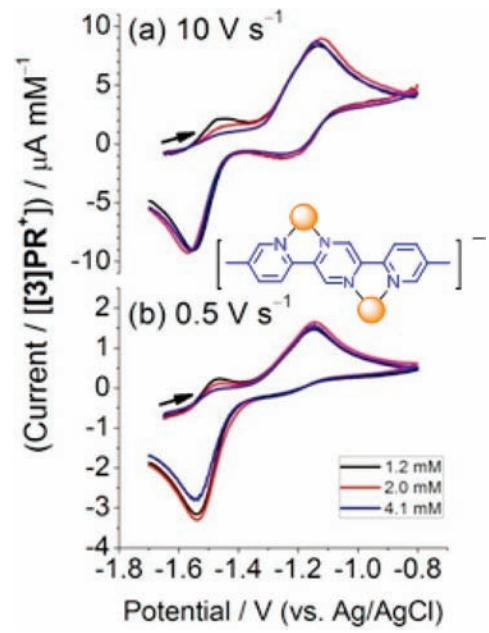


Figure 5. CVs of the [3]pseudorotaxane formed from the reduction of the **PZ**-based [2]pseudorotaxane at 4.1 (blue), 2.0 (red), and 1.2 mM (black) at (a) 10 V and (b) 0.5 V s^{-1}. The CVs were scaled to the concentration. Conditions: 1:1 mixture of (Cu-macrocycle):**PZ**, 0.1 M $TBAPF_6$, Ar degassed, CH_2Cl_2, glassy carbon electrode (0.785 mm^2), Pt counter electrode, *iR* compensation applied.

an irreversible chemical reaction. The [2]pseudorotaxane has only one redox process at −1.71 V and upon the reduction, switching generates **[3]PR**$^+$ + **PD**. At the reducing potentials used, the second reduction of **[3]PR**$^+$ becomes thermally accessible leading to the formation of the unstable **[3]PR**^{0} species. Given this situation, switching was only observed convincingly at high concentrations (8 mM, part b of Figure 3) of the [2]pseudorotaxane where the bimolecular switching rate can generate observable quantities of the **[3]PR**$^+$ in competition with any irreversible EC processes. No single model was able to successfully simulate all the features in the CVs recorded at different scan rates. Consequently, a simplified association-activated dismutation reaction ($k = 1.5 \pm 0.3 \times 10^3$ s^{-1} M^{-1}) was used to simulate just one of the observed features: the increase in the anodic peak intensity corresponding to the production of the reduced [3]pseudorotaxane, **[3]PR**$^+$, during the switching reaction.

Molecular Modeling of the Orientations of Ligand Exchange. Molecular modeling (Supporting Information) of possible encounter complexes involving **TZ** shows that the rigid phenanthroline portion of the Cu-macrocycle moiety on the entering ligand (Scheme 3) interacts unfavorably (part a of Figure 4) with the phenanthroline moiety of the macrocycle on the Cu(I) substrate during a syn approach to distort the tetrahedral geometry around the Cu(I) ion in the reduced **[2]PR**^{0} (blue colored ligand). This situation indicates that successful reactions are likely to occur more readily when the phenanthroline components of the two Cu-macrocycle moieties are on opposite sides of the entering group, that is an association-based transition state is anti in character (part b of Figure 4).

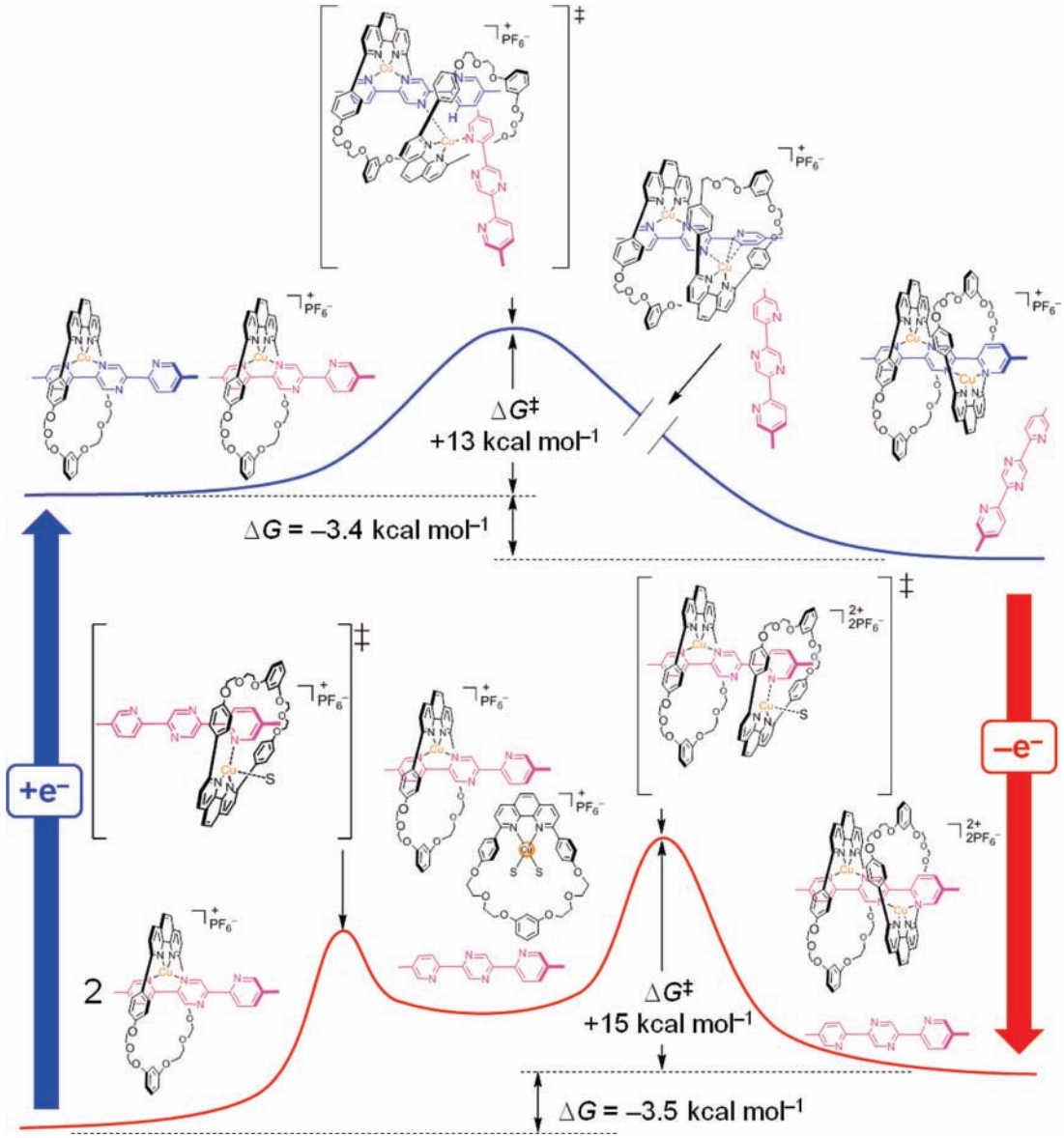
Analysis of the Forward Switching Mechanism. The results of the kinetics experiments provide a series of mechanistic findings associated with the forward switching reaction (eq 1). The use of electron withdrawing CF_3 groups on **CF_3TZ** stabilize the reduction of the ligand by ∼100 mV[75] when compared to **TZ**; however, the rates of ligand exchange for **TZ** and **CF_3TZ** are unchanged. This finding indicates that steric, rather than electronic properties, dominate the reactivity of this step. (2) Successful switching with *transoid*-**PZ** indicates that a monodentate entering group is capable of activating ligand exchange. (3) The 10-fold slower rate of switching with *transoid*-**PZ** compared to **TZ** is attributed to an intrinsically lower reactivity of a monodentate site compared to bidentate ones. The rate difference cannot be rationalized from differences in nucleophilicity between *reduced* **PZ** and **TZ**: When the **PZ** of the [2]pseudorotaxane is reduced, it is expected[60] to be more nucleophilic and thus, more reactive than **TZ**, and not the reverse. (4) Molecular modeling indicates that the anti approach, with respect to the relative location of the two Cu-macrocycle moieties, is more favorable than the syn. (5) These interpretations and the low rotational barrier for **TZ**[68] imply that, although switching via the monodentate *syn*-**TZ** conformation (Scheme 4) of the reduced [2]pseudorotaxane is feasible, the reaction is believed to proceed exclusively via the bidentate *anti*-**TZ** conformation. The syn and anti forms rapidly equilibrate allowing the reaction to access the lower energy pathway.

Lastly, the rotations that are necessary to achieve the stable forms of the reduced [3]pseudorotaxanes appear to be slightly different between the two sets of ligands, for example **PZ** versus **TZ**. The reactive *transoid*-**PZ** ligand of **[2]PR**^{0} is initially monodentate with a three-coordinate Cu(I) ion. Following an anti approach, therefore, pyridyl ring rotation is required to achieve bidentate coordination to the Cu(I) center to generate **[3]PR**$^+$. For 2,2′-bipyridine, reduction[62] raises the transoid-to-cisoid barrier while binding of a Zn(II) ion removes it.[63] It is not clear a priori which of these two factors will dominate. Attempts to model the former by fitting the CV data using a model with an initial associative pre-equilibrium step to form a metastable state followed by a slow rotation failed to account for the concentration dependence in the data. Therefore, ring rotation is believed to be faster than ligand exchange for **PZ**.

For the **TZ**-based [2]pseudorotaxane, the product of exchange with the reactive anti conformation is the *anti*-**[3]PR**$^+$. Assuming the syn form is more stable, there exist multiple rotation

(75) The 100 mV difference amounts to a weakened basicity of ∼13 pK_b units.

Scheme 5. Schematic Representations and Proposed Models for the Reaction Coordinate of the **PZ**-Based [2/3]Pseudorotaxane for Switching Forward after Reduction (Blue) and Switching Back after Re-oxidation (Red) (Reduced Ligand = Blue, Neutral Ligand = Magenta)[a]



[a] It is not clear if the rapid pyridyl rotations occur in a stepwise or concerted manner. The representations of the transition states are for illustrative purposes only.

pathways for the generation of **[3]PR**$^+$.[69] The CVs of the **TZ**-based **[2]PR**$^+$ show[52] a redox process whose peak intensity decays over a ~1 s time scale and which can therefore be attributed to a metastable intermediate. It is plausible that this intermediate is the *anti*-**[3]PR**$^+$ switched state. By contrast, the CV response for **CF_3TZ** does not show evidence for this intermediate, suggesting the CF_3 substituents either hasten rotations and/or alter the relative stabilities of this intermediate. Alternatively, the *anti*-**[3]PR**$^+$ conformation might be relatively stable by itself.

The rate constants for the association-activated interchange processes (1500 M^{-1} s^{-1} for **PZ** and 12 000 M^{-1} s^{-1} for **TZ**) occurring in the forward direction (eq 2) are comparable to those obtained for ligand exchange at Cu(I) centers.[46] Therein, the rigid phenanthroline ligands exchanged with bimolecular rates constants of ~2000 M^{-1} s^{-1} in the noncoordinating solvent acetone. These values also compare favorably with flexible bidentate ligands exchanging[45d] by a purported association mechanism in CD_2Cl_2 with rate constants ranging from 70 to 1100 M^{-1} s^{-1} depending upon the sterics. In all cases, the initial association-activated attack on the Cu(I) center was slower (rate limiting) than subsequent chelate ring formation.

Mechanistic Analysis of the Return Switching Process Using PZ. The variable scan-rate CVs of the **PZ**-based [2]pseudorotaxane (parts a−d of Figure 2) were sufficiently clean to allow an examination of the return switching process (Figure 5). The switched state, **[3]PR**$^+$ + **PZ**, was prepared by equilibrating the solution at a reducing potential of ca. −1.8 V and then cycling to less negative potentials, ca. −0.8 V, and back again as a function of scan rate (0.5 − 100 V s^{-1}) and concentration (1.2 − 4.1 mM). These studies verified a unimolecular process. Simulations of the CVs using a stepwise dissociation-activated dethreading pathway (Supporting Information) are consistent with a rate constant of $k_1 = 50$ s^{-1}. None of the other possible mechanisms satisfactorily simulated the experimental CVs. The intermediate state that will be produced

in the dethreading two-step mechanism most likely generates the free Cu-macrocycle moiety, which can rapidly thread onto the free **PZ** ligand to regenerate the **[2]PR**$^+$ present at the beginning of the switching cycle. By contrast, prior observations[46] on the ligand exchange of bidentate ligands around a Cu(I) center are reported to occur through an association or interchange pathway. Therefore, observing a dissociation-activated pathway suggests that the supramolecular character of the [3]pseudorotaxane dominates the reactivity. Likely causes include (a) the threading-dethreading dynamics are faster than associative ligand exchange in the unreduced state and (b) the additional steric crowding of the Cu(I) ion within the [3]pseudorotaxane may hinder any associative attacks of an entering **PZ** ligand.

Bilability of the PZ-based [2/3]Pseudorotaxane. The simplicity of the CVs corresponding to the redox-switching observed for the **PZ**-based system provided an opportunity to generate a schematic of the reaction coordinate for the cycle (Scheme 5) of switching forward and back again. The representations of the transition states are for illustrative purposes only and are not meant to convey specific knowledge of their structures. The forward reaction follows an intrinsically different pathway (association-activated) from the return (dissociation), thus verifying the bilabile character of the supramolecular switch. Note that the change in molecularity dictates that even though the barrier is lower for the bimolecular reaction, and the initial reaction rate at 4 mM and 291 K is only 6 mM s^{-1} versus 200 mM s^{-1} for the returning unimolecular process.

It is important to note that these systems satisfy the principle of microscopic reversibility.[53] The pathway is different for the forward and return switching processes because they proceed along different stimuli-dependent potential-energy surfaces, reduced and neutral, respectively: As long as the oxidation state does not change, the pathway forward and back along a single surface should be the same. Therefore, the reaction of the neutral species, 2 **[2]PR**$^+ \rightarrow$ **[3]PR**$^{2+}$ + **PZ** (reverse of eq 4), should follow a unimolecular dissociation-activated pathway. The importance of this pathway was observed in the slow scan-rate (0.25 mV s^{-1}) spectroelectrochemistry studies with the **[2]PR**$^+$ generated from the **TZ** ligand.[52] Therein, the **[3]PR**$^{2+}$ reduction peak in the forward cycle was found to be larger at the slow scan rates compared to fast ones (200 mV s^{-1}). This observation is consistent with equilibration along the potential-energy surface for the unreduced state to generate **[3]PR**$^{2+}$ + **TZ**, which is followed by the [3]pseudorotaxane's reduction to rectify the switching. This type of pathway is an elementary process of a Brownian ratchet.[3] Likewise, the reaction along the reduced surface, **[3]PR**$^+$ + **TZ** $\rightarrow$ **[2]PR**^{0} + **[2]PR**$^+$ (reverse of eq 2), would be a bimolecular reaction. In other words, the mechanism of switching, as well as the thermodynamics, is based on the oxidation state of the system: one electron defines the line between inorganic and supramolecular patterns of reactivity.

This mechanistic picture provides a basis to consider subsequent designs of molecular machines. For instance, an interlocked rotaxane based on the [2/3]pseudorotaxanes studied herein will need to take advantage of reasonably short and flexible linkers to facilitate the bimolecular pathway, which requires attack of the reduced ligand on the Cu(I) center. Alternatively, it might be possible to redesign the pseudorotaxane's structure as a means to redirect switching along unimolecular pathways while maintaining the same driving force for switching. In this case, bilability may be lost unless a different unimolecular pathway is opened up. Lastly, the profiles shown in Scheme 5 are reminiscent of a flashing ratchet.[3] However, they are not periodic and thus the hysteresis[76] exists in state rather than in location.

Conclusions

The bilability of a Cu(I)-based [2/3]pseudorotaxane, where the mechanistic pathways are switched off and on using reduction as the stimulus, has been verified. When reduced, a [3]pseudorotaxane and a free ligand are formed through a bimolecular associative interchange pathway similar to that of a ligand exchange reaction around a Cu(I) center. Upon reoxidation, the [2]pseudorotaxanes are reformed, but along a unimolecular dissociative path, which is consistent with a supramolecular dethreading−threading reaction. The same electron that affects the thermodynamics, therefore, also affects the mechanism of this supramolecular machine. With this lesson in mind, it is likely that some of the stimuli that have previously been used to effect bistability in other supramolecular and molecular systems have also affected the kinetics and the mechanism of their associated switching reactions. Lastly, by utilizing the intrinsic differences in reactivity of bilabile systems, opportunities arise for the design of molecular motors and other complex operations.

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Supporting Information Available: Experimental, syntheses, self-assembly procedures, binding constant determinations, CV titrations, digital CV simulations, and molecular modeling is available. This material is available free of charge via the Internet at http://pubs.acs.org.

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