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Energetically Demanding Transport in a Supramolecular Assembly

Chuyang Cheng,[†] Paul R. McGonigal,[†] Wei-Guang Liu,[‡] Hao Li,[†] Nicolaas A. Vermeulen,[†] Chenfeng Ke,[†] Marco Frasconi,[†] Charlotte L. Stern,[†] William A. Goddard III,[‡] and J. Fraser Stoddart*[,†]

[†]Department of Chemistry, Northwestern University, Evanston, Illinois 60208, United States

[‡]Materials and Process Simulation Center, California Institute of Technology, Pasadena, California 91125, United States

Supporting Information

ABSTRACT: A challenge in contemporary chemistry is the realization of artificial molecular machines that can perform work in solution on their environments. Here, we report on the design and production of a supramolecular flashing energy ratchet capable of processing chemical fuel generated by redox changes to drive a ring in one direction relative to a dumbbell toward an energetically uphill state. The kinetics of the reaction pathway juxtapose a low energy [2]pseudorotaxane that forms under equilibrium conditions with a high energy, metastable [2]-pseudorotaxane which resides away from equilibrium.

The active transport of ions and small molecules across cell membranes, driven by bespoke biochemical machinery, plays a pivotal role in the operation of cells.[1] Nature's transmembrane protein pumps create concentration gradients of ions, such as Na^+, K^+ and Ca^{2+}, in addition to protons,[2] whose stored potential may then be used as a secondary energy resource[3] in metabolic processes, e.g., ATP synthesis.[4] During billions of years of evolution, these proteins have developed finely tuned secondary and tertiary structures capable of harnessing external fuel to exert precise control over the noncovalent forces—the potential energy landscape of energy barriers and wells—experienced by their cargos in order to drive them energetically uphill, temporarily away from thermodynamic equilibrium.[5]

Over the past 30 years, chemists have taken advantage of the restricted degrees of freedom available to the components of rotaxanes[6] and pseudorotaxanes[7] to construct and control increasingly sophisticated artificial molecular switches that exhibit large amplitude relative motions between their constituent parts.[8] In the majority of cases, however, the application of a stimulus to these artificial systems induces molecular motions toward a low-energy equilibrium state. The development of artificial molecular assemblies[9] that can drive a cargo away from its equilibrium position by manipulating kinetic pathways—thereby mimicking the function of their biochemical counterparts—is still very much in its infancy.[10] Here, we report a family of synthetic supramolecular pumps that exploit chemical energy to drive a ring away from its initial state in solution to form metastable, energetically demanding products that can then gradually decay back toward equilibrium. Control of this supramolecular transport is exercised by influencing the kinetics of the reaction pathway using only reversible noncovalent bonding interactions and without the need to make or break covalent bonds. The end result is that the ring is ensnared on an oligomethylene chain[11] for which it has little to no binding affinity at any stage of the pumping process.

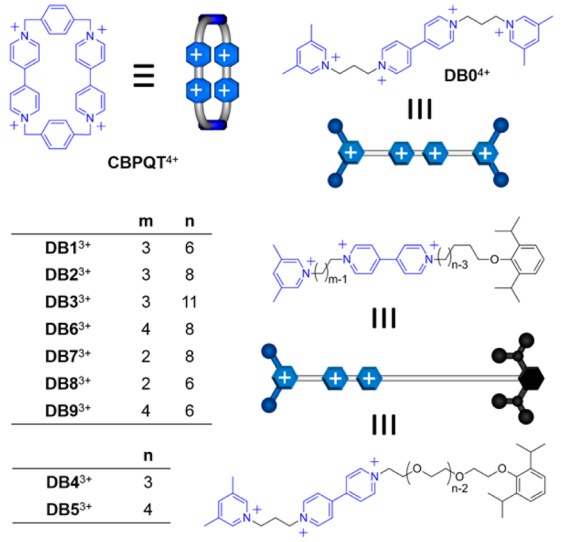

Figure 1. Structural formulas and simplified graphical representations of the **CBPQT**$^{4+}$ ring, the symmetrical dumbbell **DB0**$^{4+}$ and the nine 'one-stroke supramolecular pumps' **DB1**$-$**9**$^{3+}$ employed in this structure–function investigation. Charges are balanced by PF_6^- counterions which are omitted for the sake of clarity.

We designed (Figure 1) a homologous series of dumbbells **DB1**$-$**9**$^{3+}$ bearing 4,4′-bipyridinium (**BIPY**$^{2+}$) units as radical recognition sites[12] for cyclobis(paraquat-*p*-phenylene)[13] (**CBPQT**$^{4+}$). A 3,5-dimethylpyridinium (**PY**$^+$) unit is attached to one side of the **BIPY**$^{2+}$ unit by a short oligomethylene chain, while a bulky stopper is attached to the other side by a longer chain. Before testing the dumbbells, a symmetrical derivative **DB0**$^{4+}$ (Figure 1) was prepared as a model compound to confirm that **CBPQT**$^{2(+\bullet)}$ can thread across the **PY**$^+$ barrier in order to form the trisradical complex **DB0**$^{3+\bullet}\subset$**CBPQT**$^{2(+\bullet)}$ under the reducing conditions that can bring about radical–radical interactions. The absorption spectra of the radical cation **DB0**$^{3+\bullet}$ and diradical dication **CBPQT**$^{2(+\bullet)}$ were first of all recorded separately in MeCN at concentrations of 10^{-4} M. No absorption indicative of **BIPY**$^{+\bullet}$ dimerization was observed in the near-IR (NIR) region under these conditions. By contrast, when

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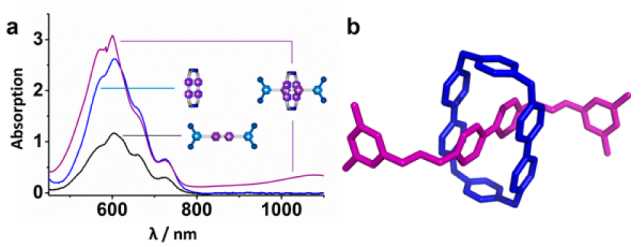

Figure 2. UV−vis−NIR absorption spectroscopic and single crystal XRD evidence that $\mathbf{CBPQT}^{2(+\bullet)}$ threads across the Coulombic $\mathbf{PY}^{+}$ barrier. (a) Spectra of $\mathbf{DB0}^{3+\bullet}$ (black trace), $\mathbf{CBPQT}^{2(+\bullet)}$ (blue trace), and a 1:1 mixture of $\mathbf{DB0}^{3+\bullet}$ and $\mathbf{CBPQT}^{2(+\bullet)}$ (purple trace). The broad peak around 1100 nm indicates formation of the trisradical inclusion complex $\mathbf{DB0}^{3+\bullet}\subset\mathbf{CBPQT}^{2(+\bullet)}$. $[\mathbf{DB}^{4+}] = 1.0 \times 10^{-4}$ M, $[\mathbf{CBPQT}^{4+}] = 1.0 \times 10^{-4}$ M. Solvent, MeCN; $T = 298$ K. (b) A tubular representation of the solid-state superstructure of $(\mathbf{DB0}\subset\mathbf{CBPQT})\cdot 6PF_6$.[14,15] Solvent molecules, hydrogen atoms, and counterions are omitted for the sake of clarity.

$\mathbf{DB0}^{4+}$ and $\mathbf{CBPQT}^{4+}$ were reduced together, a distinctive purple solution was obtained within seconds and UV−vis−NIR spectroscopy revealed (Figure 2a) features characteristic of $\mathbf{BIPY}^{+\bullet}$ radical−radical interactions, including a broad NIR band around 1100 nm that is indicative[12] of the formation of the trisradical inclusion complex $\mathbf{DB0}^{3+\bullet}\subset\mathbf{CBPQT}^{2(+\bullet)}$. Single crystals of $(\mathbf{DB0}\subset\mathbf{CBPQT})\cdot 6PF_6$ suitable for X-ray diffraction (XRD)[14] were grown in a glovebox.[15] The solid-state superstructure confirmed (Figure 2b) that the ring encircles the dumbbell.

With the viability of complex formation between $\mathbf{CBPQT}^{2(+\bullet)}$ and $\mathbf{DB0}^{3+\bullet}$ verified, we hypothesized that subjecting a mixture of $\mathbf{CBPQT}^{4+}$ and a dumbbell $\mathbf{DB1{-}9}^{3+}$ (Figure 1) to a cycle of reduction and oxidation would result in the formation of a high-energy [2]pseudorotaxane. To test our hypothesis, activated zinc dust was added to a 1:1 mixture of $\mathbf{DB1}^{3+}$ and $\mathbf{CBPQT}^{4+}$ in CD_3CN, giving a purple solution indicative of trisradical complex formation within a few seconds. After filtration to remove the excess of zinc, tris(4-bromophenyl)aminium hexachloridoantimonate (magic blue) was added at 0 °C to reoxidize the radical species to their fully charged states, and a ^{1}H NMR spectrum was recorded. Comparison of the ^{1}H NMR spectra of the dumbbell, the reaction mixture, and the ring revealed (Figure 3a,b,d) formation of a product species in ∼80% yield that exhibited broadening ($H_{\alpha/\beta}$) and splitting (H_{CH_2}) of resonances associated with the ring as well as significant upfield shifts of the methylene proton resonances H_{1-4} of the dumbbell component, indicating the formation of $\mathbf{DB1}^{3+}\subset\mathbf{CBPQT}^{4+}$ in which the ring encircles the hexamethylene chain.[12b,d] This [2]pseudorotaxane was found to be metastable and to dissociate entirely within half an hour at room temperature or within 4 h at 279 K (Figure 3c). Changes in the relative proportions of $\mathbf{DB1}^{3+}\subset\mathbf{CBPQT}^{4+}$ and its separated components were monitored (Figure S4)[15] by ^{1}H NMR spectroscopy at a constant temperature (279 K) which revealed (Figure 3e) that the dethreading displays first-order kinetics with a rate constant $k = (8.4 \pm 0.6) \times 10^{-5}$ s^{-1}. Based upon these data, the transition-state energy barrier ($\Delta G^{\ddagger}$) for the $\mathbf{CBPQT}^{4+}$ ring to dissociate from $\mathbf{DB1}^{3+}$ by slipping over its positively charged $\mathbf{BIPY}^{2+}$ and $\mathbf{PY}^{+}$ units was found to be 21.5 kcal mol^{-1}.

It appears, therefore, that the design of dumbbell $\mathbf{DB1}^{4+}$ allows it to "pump" a ring actively onto its hexamethylene chain following potential energy surfaces resembling those represented as curves in Scheme 1. Initially, the tetracationic $\mathbf{CBPQT}^{4+}$ ring is repelled (Scheme 1a) by both the $\mathbf{PY}^{+}$ and $\mathbf{BIPY}^{2+}$ units. Reduction, however, simultaneously lowers the kinetic barrier to threading[7d] that comes from Coulombic repulsion between the $\mathbf{PY}^{+}$ unit and the ring, while also bringing radical−radical interactions into play to create (Scheme 1b) a new global minimum in which the dumbbell is encircled by the ring. As a result, the ring slips over the $\mathbf{PY}^{+}$ unit to form (Scheme 1c) a thermodynamically stable trisradical inclusion complex[12] $\mathbf{BIPY}^{+\bullet}\subset\mathbf{CBPQT}^{2(+\bullet)}$. A subsequent oxidation step to restore the repulsion between the highly charged ring and dumbbell components[12d] then imparts a driving force for the $\mathbf{CBPQT}^{4+}$ ring to undergo translational motion. In thermodynamic terms, the global energy minimum would be reached if the ring were to

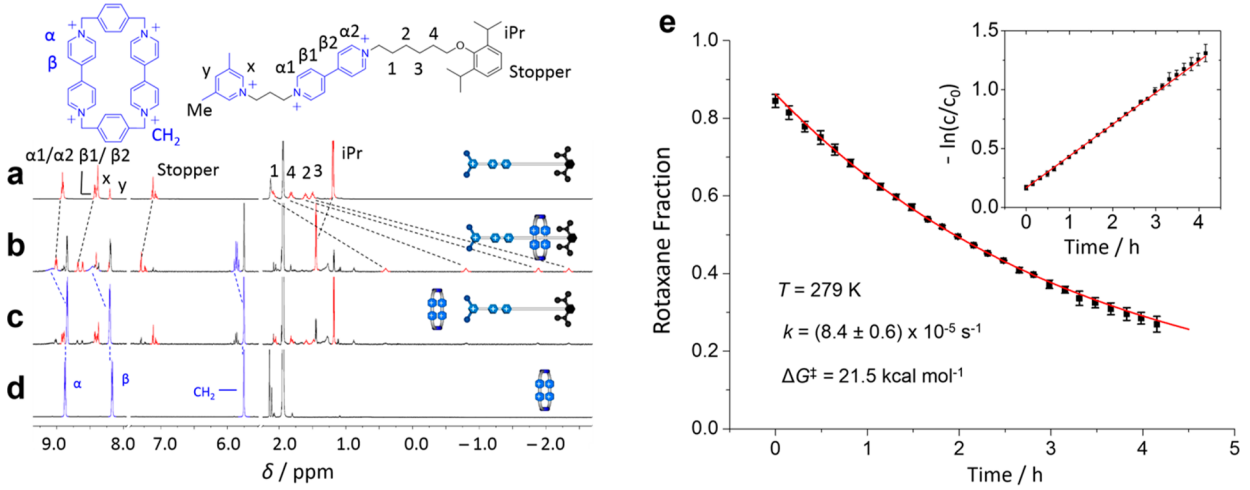

Figure 3. ^{1}H NMR spectroscopic analysis of [2]pseudorotaxane formation and the kinetic barrier to disocciation. Partial ^{1}H NMR spectra (600 MHz, CD_3CN, 279 K) of (a) the dumbbell $\mathbf{DB1}^{3+}$, (b) a reaction mixture containing $\mathbf{DB1}^{3+}\subset\mathbf{CBPQT}^{4+}$ after performing a cycle of reduction and oxidation, (c) after standing at 279 K for 4 h, and (d) $\mathbf{CBPQT}^{4+}$. Peaks are highlighted in red and blue for $\mathbf{DB1}^{3+}$ and $\mathbf{CBPQT}^{4+}$, respectively. The changes in chemical shifts (blue and black dashed lines) are indicative of [2]pseudorotaxane formation. (e) Plot of the change in molar fraction over time at 279 K based on integration of the ^{1}H NMR spectra. Inset: linear relationship between $-\ln(c/c_0)$ and time, indicating that the dethreading process obeys first-order kinetics. The activation barrier $\Delta G^{\ddagger}$ was calculated using the Eyring equation.

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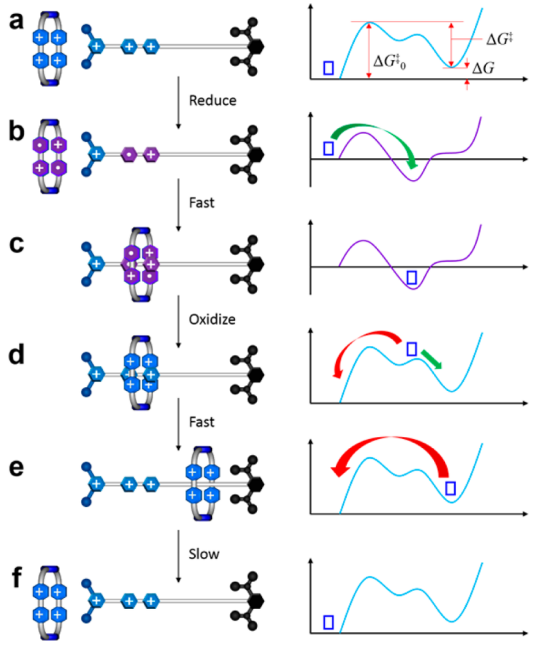
Scheme 1. Graphical Representation of the Pumping Mechanism and Corresponding Energy Profiles



retrace its path and dissociate from the dumbbell. The electrostatic barrier to translation originating from the PY^+ group, however, is restored upon oxidation, kinetically disfavoring the backward pathway and forcing the ring to shuttle away (Scheme 1d) in the opposite direction. Consequently, the $CBPQT^{4+}$ ring is ensnared (Scheme 1e) as part of a metastable [2]pseudorotaxane that does not benefit from stabilizing noncovalent bonding interactions. Indeed, the enforced proximity of the three charged viologen units dictates that the [2]pseudorotaxane resides in an energetically demanding state compared to its separated components.

By performing the same reduction and oxidation protocol with the entire homologous series of dumbbells $DB2{-}8^{3+}$, we were able to gain some insight into the relationship between the structure and energetics of the supramolecular pumps. Extension of the oligomethylene chain between the $BIPY^{2+}$ and stopper units resulted in two pseudorotaxanes, namely $DB2^{3+}{\subset}CBPQT^{4+}$ and $DB3^{3+}{\subset}CBPQT^{4+}$, that exhibited prolonged half-lives compared to $DB1^{3+}{\subset}CBPQT^{4+}$. The dissociations of $DB2^{3+}{\subset}CBPQT^{4+}$ and $DB3^{3+}{\subset}CBPQT^{4+}$ were monitored by ^{1}H NMR spectroscopy at 331 and 365 K, respectively, which allowed the kinetic barriers to dethreading to be determined (Figures S5 and S6)[15] as 25.3 and 29.0 kcal mol^{-1}. Although the intrinsic barrier to association $\Delta G^{\ddagger}_0$ (Scheme 1a), which stems mainly from Coulombic repulsion between positively charged $BIPY^{2+}/PY^+$ units and the $CBPQT^{4+}$ ring, is similar for dumbbells $DB1{-}3^{3+}$, the large variation in the kinetic barriers to dethreading can be rationalized by considering the difference in the Gibbs free energy ΔG of the metastable [2]pseudorotaxanes. A shorter oligomethylene chain confines the like-charged $CBPQT^{4+}$ ring and $BIPY^{2+}$ unit in closer proximity to one another, destabilizing the pseudorotaxane and resulting in a higher ΔG.[12d] Density functional theory (DFT) calculations support this reasoning. We calculated (Table S3)[15] increases in enthalpy (ΔH) of 14.9, 8.8, and 7.0 kcal mol^{-1} for the [2]pseudorotaxanes based on $DB1^{3+}$, $DB2^{3+}$, and $DB3^{3+}$, respectively, compared to their separated components.

The oligomethylene portion of the dumbbell can be replaced by an oligoethylene glycol chain without diminishing the efficiency of the pumping process. Dumbbells $DB4^{3+}$ and $DB5^{3+}$, bearing triethylene glycol and tetraethylene glycol tails, respectively, gave rise to [2]pseudorotaxanes in ~85% yield, as estimated by ^{1}H NMR spectrocopy.[15] While the dissociation of $DB4^{3+}{\subset}CBPQT^{4+}$ follows (Figure S7)[15] first-order kinetics in a manner consistent with the oligomethylene derivatives, our observations indicate that the dissociation (Figure S8)[15] of $DB5^{3+}{\subset}CBPQT^{4+}$ is autocatalytic. The most probable explanation for this phenomenon is that hydrogen bonding between the tetraethylene glycol chain and $CBPQT^{4+}$ ring, which is a well-established interaction,[16] stabilizes the transition state to dethreading.[7d,17] Indeed, the addition of 1.0 equiv of dumbbell $DB5^{3+}$ to a solution of $DB5^{3+}{\subset}CBPQT^{4+}$ accelerated the dissociation of the [2]pseudorotaxane.[15] In order to avoid this complication in subsequent investigations, we decided to limit dumbbell design to those containing oligomethylene chains.

Having explored the effect of altering the length and nature of the chain between the $BIPY^{2+}$ unit and the stopper, we turned our attention to assessing the influence of the short oligomethylene linker connecting the Coulombic barrier[18] PY^+ to the rest of the dumbbell. Taking $DB2^{3+}$ as a point of reference, two dumbbells were synthesized bearing a butylene ($DB6^{3+}$) and a bismethylene ($DB7^{3+}$) linker in place of the propylene one in $DB2^{3+}$. Surprisingly, this seemingly minor alteration in molecular structure was found to have a dramatic effect on the outcomes of redox cycling. Subjecting a mixture of $CBPQT^{4+}$ and $DB6^{3+}$ to the standard protocol gave only a physical mixture after reduction and oxidation (Figure S9),[15] suggesting that elongating the linker diminishes considerably the ability of the $BIPY^{2+}$ and PY^+ units to act together in creating a highly charged end group that retains the ring on the dumbbell on account of Coloumbic repulsion. In contrast, when $CBPQT^{4+}$ and $DB7^{3+}$ were reduced and oxidized under the same conditions, a bench stable [2]rotaxane was produced that could be isolated (Figure S1)[15] and fully characterized by NMR spectroscopy and mass spectrometry. Indeed, the stability of the mechanically interlocked product precluded measurement of any barrier to dethreading; no dissociation could be observed (Figure S10),[15] even after refluxing in MeCN for 18 h! In order to quantify the change in the energy barrier that occurs upon shortening the propylene linker, we prepared $DB8^{3+}$ with a bismethylene linker and a hexamethylene chain on which to collect the ring, rather than the octamethylene one in $DB7^{3+}$. The [2]pseudorotaxane $DB8^{3+}{\subset}CBPQT^{4+}$ dissociates at 355 K with a rate constant $k = (2.2 \pm 0.1) \times 10^{-5}$ s^{-1}, corresponding to a dethreading barrier of 28.5 kcal mol^{-1} (Figure S11).[15] It is quite remarkable that, with the removal of a single methylene group from $DB1^{3+}$ (propylene linker) to give $DB8^{3+}$ (bismethylene linker), we observe an increase of 7.0 kcal mol^{-1} in the barrier to dissociation, from 21.5 to 28.5 kcal mol^{-1}. This phenomenon can be accounted for to a certain extent by considering that the magnitude of Coloumbic forces are inversely proportional to the square of the distance between two charged species and that the longer the linker, the further the ring resides away from the PY^+ unit. DFT calculations indicate, however, that the interplay between the PY^+ and $BIPY^{2+}$ units also plays a role. The calculated potential energy profile for dissociation of $DB8^{3+}{\subset}CBPQT^{4+}$ is characterized (Figure S12)[15] by one major energy barrier of 18.7 kcal mol^{-1}. The profile of a model [2]pseudorotaxane analog that contains a butylene linker, $DB9^{3+}{\subset}CBPQT^{4+}$, exhibits (Figure S13)[15] two smaller barriers, the highest of which is only 12.4 kcal/mol. It

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appears, therefore, that the dense buildup of charge between closely tethered $\mathbf{BIPY}^{2+}$ and $\mathbf{PY}^{+}$ units (e.g., in $\mathbf{DB7{-}8}^{3+}$) acts in an additive manner in repelling the slippage of the $\mathbf{CBPQT}^{4+}$ ring, although this effect is diminished if a longer spacer is employed.[19]

In summary, we have designed, synthesized, and operated a family of artificial supramolecular pumps which couple the dissipation of redox chemical energy to the formation of a non-equilibrium state. The alternation between the asymmetric potential energy surfaces that they create shapes the kinetically favored pathway followed by a positively charged ring, leading to a metastable [2]pseudorotaxane in which the ring is trapped on a dumbbell in the absence of any stabilizing interactions. By studying a homologous series of supramolecular pumps and their respective [2]pseudorotaxanes, we have elucidated the delicate balance between molecular structure and the energetics of the pumping process. Judicious choice of molecular structure allows for both high-efficiency [2]pseudorotaxane formation and the regulation of its subsequent dissociation over a Coloumbic barrier, which can be tuned within a range >10 kcal mol^{-1}. The supramolecular pumps we have described exhibit some of the qualities of the active transport[1,2] of ions and small molecules that takes place in Nature—i.e., they harness an energy input in order to oscillate between asymmetric potential energy surfaces and, thus, transport a species to a high-energy state. In their current form, however, these synthetic supramolecular pumps are unable to act in the repetitive manner reminiscent of their natural counterparts in order to push a system incrementally further and further from equilibrium, as occurs, e.g., when carrier proteins create concentration gradients. By bringing the knowledge gained in this structure—function study to bear on the design of synthetic supramolecular pumps, it may be possible to devise more sophisticated systems capable of this kind of repetitive and progressive action.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed synthesis procedures and characterization data (NMR spectroscopy and mass spectrometry) for all compounds. UV—vis—NIR spectroscopic and single crystal XRD characterization of the [2]pseudorotaxane $(\mathbf{DB0}\subset\mathbf{CBPQT})\cdot 6PF_6$. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

stoddart@northwestern.edu

Notes

The authors declare no competing financial interest.

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(15) See the SI.

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(19) Taking all of the calculated and experimentally measured thermodynamic data together (Table S18), the fraction of the redox energy input that is stored in the high-energy pseudorotaxanes can be calculated to be between 5 and 10%.