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Communication

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Chemical On/Off Switching of Mechanically Planar Chirality and Chiral Anion Recognition in a [2]Rotaxane Molecular Shuttle

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Supporting Information Placeholder

ABSTRACT: We exploit a reversible acid-base triggered molecular shuttling process to switch an appropriately designed rotaxane between prochiral and mechanically planar chiral forms. The mechanically planar enantiomers and their interconversion, arising from ring shuttling, have been characterized by NMR spectroscopy. We also show that the supramolecular interaction of the positively charged rotaxane with optically active anions causes an imbalance in the population of the two enantiomeric co-conformations. This result represents an unprecedented example of chiral molecular recognition and can disclose innovative approaches to enantioselective sensing and catalysis.

Mechanically interlocked molecules (MIMs)[1,2] such as catenanes and rotaxanes may exhibit large amplitude motion of their interlocked components that renders them ideal candidates for the construction of molecular machines.[2,3,4] While the absence of covalent bonds between the components enables facile relative movements, the mechanical constriction limits the possibilities for their mutual arrangement, with interesting outcomes from a stereochemical viewpoint.

In fact chiral MIMs can be obtained by interlocking molecular components which are themselves achiral.[5,6] This happens, for example, when an axle with $C_{\infty v}$ symmetry – i.e., having a principal axis and mirror planes aligned along the axle length – is surrounded by a macrocycle with a C_s symmetry[7] – i.e. having only one mirror plane coinciding with the plane of the ring (Figure 1a).[8] When the ring and axle are interlocked, the improper symmetry operations of the separated components are not symmetry operations of the rotaxane, which therefore becomes chiral (Figure 1b).[6] The synthesis of mechanically planar (MP) chiral rotaxanes was pioneered by Vögtle and coworkers,[9] and further investigated in more recent times,[10,11,12,13] when efficient and stereoselective methodologies have enabled the synthesis of highly enantiopure samples.[14,15] The exploitation of MP stereogenic elements of MIMs for the development of novel chiroptical materials, enantioselective sensors and asymmetric catalysis, is a fascinating research topic with development opportunities.[6,16]

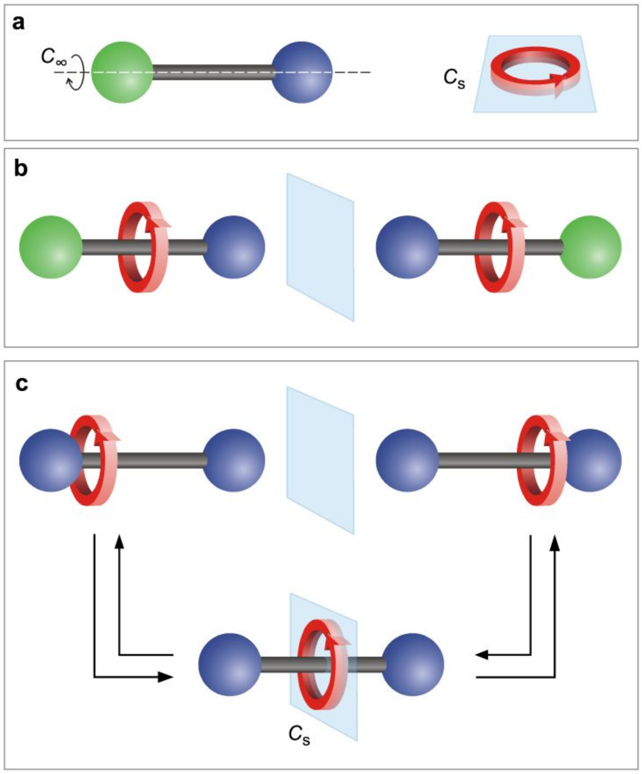
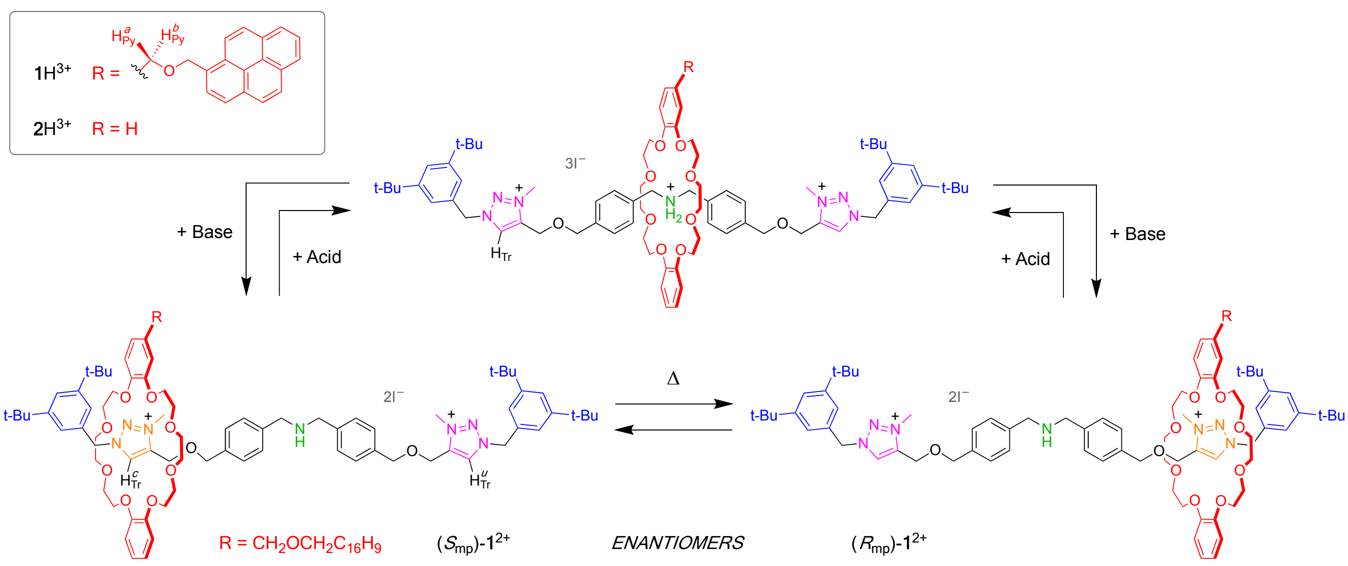


Figure 1. Schematic representation of: a $C_{\infty v}$ symmetric axle and a C_s symmetric ring (a); the two enantiomers of a mechanically planar (MP) chiral rotaxane (b); the two enantiomers of a co-conformationally MP chiral rotaxane and their interconversion by ring shuttling through an achiral co-conformation that features a mirror plane (c).

MP Chiral rotaxanes can also be obtained by interlocking a C_s symmetric macrocycle with an axle that has identical extremities, provided that the ring is located on either side of the mirror plane at the center of the axle (Figure 1c).[6,17] In other words, it is the position of the oriented macrocycle that desymmetrizes the axle component, yielding a MP chiral [2]rotaxane. In systems of this kind, ring shuttling along the axle leads to interconversion of the two enantiomers by passing through an achiral co-conformation in which the ring is located in the center of the axle (Figure 1c). Only one co-conformationally mechanically planar chiral rotaxane has been reported to date, whose enantiomers were separated and their racemization rate was determined.[17] However, in this case the position of the ring along the axle could not be controlled because of the absence of any recognition site.

The relation between co-conformational dynamics and chirality[13] in systems such as those shown in Figure 1c prompted us to investigate the possibility to exploit the stimuli-controlled switching of a molecular shuttle to enable MP chirality. Here we describe a [2]rotaxane that can be reversibly switched between prochiral and chiral states upon chemical stimulation. The presence of two enantiomers in the chiral state was probed experimentally, and the inversion of the MP stereogenic element *via* thermally activated ring shuttling was investigated. Finally, we report on the effect of optically active counteranions on the co-conformational behavior and stereochemical properties of the positively charged rotaxane.



Scheme 1. Rotaxanes $1H^{3+}$ and $2H^{3+}$ (top), and their base-triggered switching to 1^{2+} and 2^{2+} (bottom). The latter species can exist in two interconverting co-conformations, that constitute an enantiomeric pair for 1^{2+} (see ref. 6 for the assignment of the absolute configurations) while they are the same molecule in the case of 2^{2+}. The starting rotaxanes are regenerated upon addition of an acid.

We based our design on a crown ether macrocycle, and on dibenzylammonium and triazolium recognition sites located along the axle (Scheme 1) to exploit acid-base stimulation of the molecular shuttle.[18,19,20] A dibenzo[24]crown-8 (DB24C8)-type ring encircles preferentially the ammonium center because of strong hydrogen bonding, and can be moved on the triazolium station upon deprotonation of the ammonium.

Rotaxanes **1**H^{3+} and **2**H^{3+}, equipped respectively with an oriented (C_s) and a non-oriented (D_{2h}) macrocycle (Scheme 1, top), were synthesized by stoppering of the corresponding pseudorotaxanes *via* CuAAC. In rotaxane **1**H^{3+} the DB24C8 skeleton is desymmetrized by placing a substituent in the 4-position of one of its 1,2-dioxybenzene moieties. A pyrenyl tether was chosen as the ring orienting substituent, with the aim of (i) enhancing the transfer of chiral information with a large aromatic moiety, and (ii) having a fluorescent reporter for the switching process. In the symmetric rotaxane **2**H^{3+} the ring is plain DB24C8.

In both **1**H^{3+} and **2**H^{3+} the ring encircles the ammonium center, in line with literature data.[18–20] We treated **2**H^{3+} with a polymer-bound phosphazene base in CD_2Cl_2 to afford rotaxane **2**$^{2+}$ (Scheme 1, bottom). The ^{1}H NMR signal of H_{Tr} in **2**H^{3+} (9.14 ppm) splits at low temperature into two, H^c_{Tr} and H^u_{Tr}, associated respectively with the complexed and uncomplexed triazolium station in slow exchange on the NMR timescale. Total line-shape analysis of H^c_{Tr} and H^u_{Tr} at various temperatures (Figure 2a) allowed us to estimate the shuttling activation parameters (see the SI). These results confirm that the crown ether encircles one of the two equivalent triazolium sites, and moves between them. Similar results were obtained upon deprotonation of **1**H^{3+} to yield **1**$^{2+}$ (Figure 2b), showing that the pyrenyl tether of the macrocycle does not affect the kinetics of the co-conformational equilibrium.

In contrast with **2**$^{2+}$, however, ring shuttling in **1**$^{2+}$ generates a 50:50 population of two mirror image co-conformations, that is, a racemic mixture of two enantiomers (R_{mp})-**1**$^{2+}$ and (S_{mp})-**1**$^{2+}$.[21] In this regard, **1**$^{2+}$ is an example of a degenerate molecular shuttle[22] whose co-conformations are energetically equivalent but not superimposable (Scheme 1, bottom). The presence of the MP enantiomers of **1**$^{2+}$ in the racemate was confirmed by analyzing the NMR signals of the two methylene protons in the pyrenyl thether of the macrocycle, adjacent to the dioxybenzene unit (H_{Py}, Scheme 1). These protons are enantiotopic – and thus isochronous – in **1**H^{3+}, while they become diastereotopic in **1**$^{2+}$. We therefore envisioned that in the deprotonated rotaxane they should resonate at different frequencies and form a coupled spin system.[23]

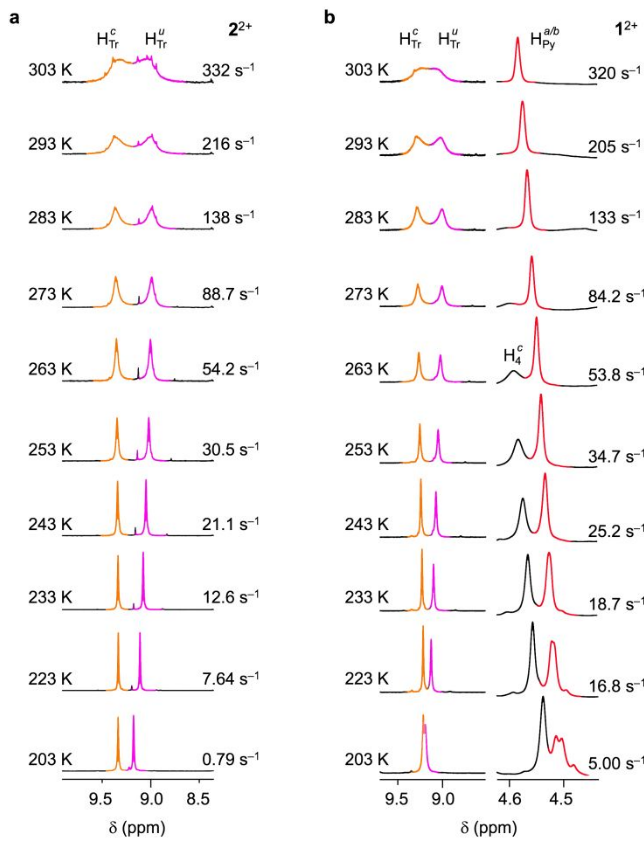


Figure 2. (a) Variable temperature (VT) ^{1}H NMR spectra (500 MHz, CD_2Cl_2) of **2**$^{2+}$ in the region of the triazolium protons (H^u_{Tr}, H^c_{Tr}). (b) VT ^{1}H NMR spectra (500 MHz, CD_2Cl_2) of **1**$^{2+}$ in the regions of the triazolium protons (H^u_{Tr}, H^c_{Tr}; left) and of the methylene protons in the pyrenyl tether of the macrocycle, adjacent to the dioxybenzene unit (H^a_{Py}, H^b_{Py}; right). See Scheme 1 and SI for proton labeling.

The ^{1}H NMR spectra of **1**$^{2+}$ recorded at 223 K and 203 K showed that the signal at 4.60 ppm, associated with H_{Py}, consistently splits into a couple of two almost overlapped doublets (Figure 2b).[24] Additionally, analysis of the signals corresponding to $H^{a/b}_{Py}$ and $H^{u/c}_{Tr}$ in CD_2Cl_2 revealed that the rate constants for shuttling (k_{sh}) and racemization (k_{rac}) are approximately the same (see the SI). This observation confirms that in **1**$^{2+}$ ring shuttling and inversion of the MP chiral configuration are two aspects of the same phenomenon (Scheme 1) which, interestingly, can be monitored separately. In fact, while the exchange of H^u_{Tr} and H^c_{Tr} (Figure 2b, left) yields information on the ring shuttling rate – an observation that can also be made for **2**$^{2+}$ (Figure 2a) – the exchange of H^a_{Py} and H^b_{Py} (Figure 2b, right) is related to the racemization rate. This set of results is consistent with the emergence of two enantiomers of $\mathbf{1}^{2+}$ upon deprotonation.

The switching of $\mathbf{1}H^{3+}/\mathbf{1}^{2+}$ can also be followed by absorption and luminescence spectroscopy (Figure 3). The spectrum of $\mathbf{1}H^{3+}$ shows an absorption tail in the 280-430 nm region assigned to a charge-transfer interaction between the pyrenyl electron donor and a triazolium electron acceptor. Such a tail disappears in $\mathbf{1}^{2+}$, presumably because the pyrenyl unit cannot undergo efficient electronic interactions with either triazolium unit (the complexed one is surrounded by the crown ether, and the free one is relatively distant). Consistently, in $\mathbf{1}H^{3+}$ the pyrenyl fluorescence is strongly quenched with respect to the free macrocycle,[19d,g] and it is 5-fold enhanced upon addition of base. Such a luminescence turn-on behavior provides a useful signal to monitor the occurrence of the chiral state, even by the naked eye (see the SI).

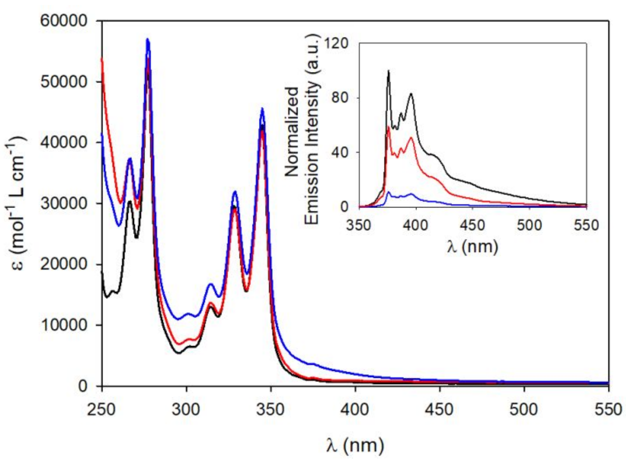


Figure 3. Absorption and fluorescence (inset, λ_{exc} = 328 nm) spectra of the free macrocycle (black), $\mathbf{1}H^{3+}$ (blue) and $\mathbf{1}^{2+}$ (red). Air equilibrated CH_2Cl_2, 20°C.

Having confirmed that $\mathbf{1}^{2+}$ exists as a dynamic racemic mixture of (S_{mp}) and (R_{mp}) forms, we investigated the possibility to induce an enantiomeric excess. Since the triazolium stations are positively charged, an interesting option is ion pairing with an optically active anion.[25] In such a case, two diastereomeric salts would be formed, which can have different energies and thus exhibit unbalanced populations of the macrocycles on the stations (Figure 4a).

Upon addition of the enantiopure anion (1*S*)-(+)-10-camphorsulfonate [(+)-CS] (tetrabutylammonium salt) to $\mathbf{1}^{2+}$ in CD_2Cl_2 at 223 K, the NMR signal of the H_{Tr}^{u} proton – that appears as a singlet at 9.14 ppm in the iodide salt – splits into two singlets with different intensities ($\Delta\delta$ = 0.02 ppm; Figure 4b, left), assigned to the two different diastereomeric ion pairs (analysis of other resonances also supports this interpretation; see the SI). Deconvolution of these peaks affords a diastereomeric ratio of 85:15, which corresponds to a difference in stability of the two diastereoisomers of 3.2 kJ mol^{-1}. Titration data show that the diastereomeric ratio does not depend on the CS/$\mathbf{1}^{2+}$ stoichiometry. Moreover, the spectra recorded upon addition of the opposite enantiomer [(–)-CS] display identical resonances and integral ratio, in full agreement with the formation of a diastereomeric pair that is enantiomerically related to that observed upon addition of (+)-CS (see the SI). In all cases the signal of H_{Tr}^{u} shifts downfield from 9.14 ppm to 9.58 ppm (major diastereoisomer), confirming that the sulfonate anion is coordinated by the free triazolium unit of the rotaxane.[25] Conversely, the fact that the signal of H_{Tr}^{c} is almost unaffected by the presence of the anion indicates that the macrocycle wrapped around the triazolium prevents a tight ion pairing.

Taken together, these observations (see also the SI) suggest that the ring-axle arrangement in $\mathbf{1}^{2+}$ creates a nonsymmetric environment around the unencircled triazolium such that enantioselective anion recognition can take place. The encircled triazolium site does not effectively compete for anion binding and it does not contribute to the stereodifferentiation. The fact that the recognition occurs relatively far away from the site of the mechanical entanglement – where the stereogenic unit is formally located – is quite remarkable.[26] A possible explanation is that the molecule folds to create a 'chiral pocket' similar to that of an enzyme, suggesting that such MIMs can have significant potential in chiral sensing.

The addition of tetrabutylammonium Δ-TRISPHAT[27] to $\mathbf{1}^{2+}$ in toluene-d_8 at 243 K[28] also causes a splitting of the NMR singlet corresponding to the H_{Tr}^{u} proton into two overlapping singlets ($\Delta\delta$ = 0.02 ppm; Figure 4b, right). Integration of these signals, however, revealed that the two diastereoisomers have the same concentration within errors. Thus, Δ-TRISPHAT plays the role of a chiral shift reagent[27] by ion-pairing with $\mathbf{1}^{2+}$ in an apolar solvent, but enantioselective molecular recognition does not occur. Presumably, the large and soft TRISPHAT anion, being loosely bound to the triazolium site, is unable to 'read' the mechanical chirality of $\mathbf{1}^{2+}$ and determine an imbalance of its two co-conformations.

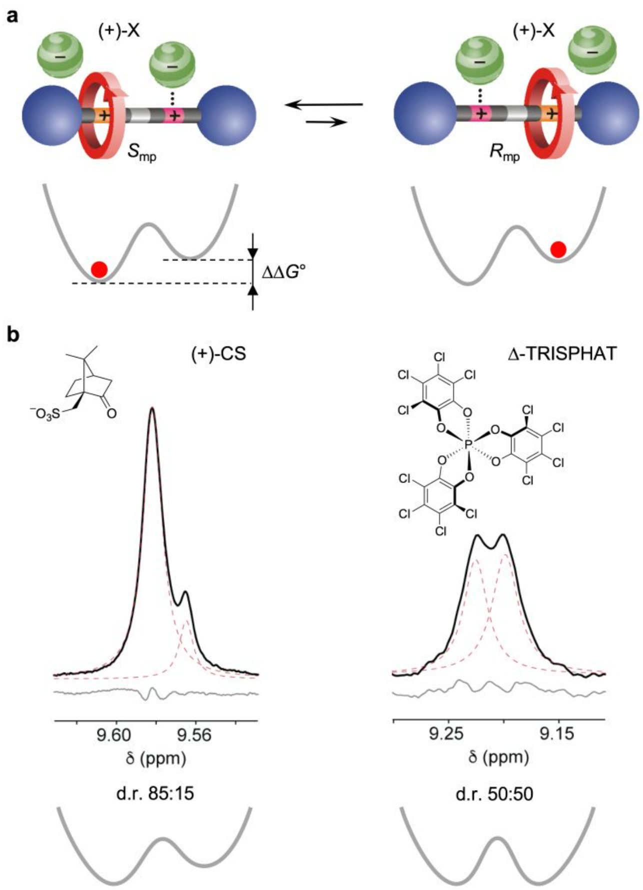


Figure 4. (a) Interconversion between two diastereomeric ion pairs composed of a co-conformationally MP chiral rotaxane dication, such as $\mathbf{1}^{2+}$, and a chiral monoanion. In the proposed structures, one anion is coordinated to the unencircled triazolium, while another is weakly paired with the encircled site. Simplified potential energy curves for the location of the ring along the axle are also shown. As the two ion pairs can have different stabilities [$\Delta\Delta G° \neq 0$], the ring distribution between the two identical stations can become unbalanced. (b) Partial ^{1}H NMR spectra (500 MHz) of the H_{Tr}^{u} resonance in $\mathbf{1}^{2+}$ after the addition of 8 equivalents of the tetrabutylammonium salt of (1*S*)-(+)-10-camphorsulfonate (CD_2Cl_2, 223 K; left) or Δ-TRISPHAT (toluene-d_8, 243 K; right). Black, red and grey traces show respectively the experimental spectrum, the deconvoluted peaks, and the fitting residuals.

In summary, we have described a three-station molecular shuttle that can be switched reversibly between symmetric prochiral and desymmetrized mechanically planar chiral states. The two enantiomers in the chiral state have been observed, and their interconversion – caused by thermally driven shuttling between two identical stations – has been quantitatively characterized. We have established a clear connection between the stimuli-controlled dynamic behavior of rotaxanes (i.e. their molecular machine aspect) and the unique stereochemical features arising from the mechanical bond. Furthermore, we have induced a difference in the population of the stations by interaction with an optically active anion, which is of interest for, e.g., enantioselective sensing and catalysis,[16ab,29] or activating molecular machines with a chiral trigger. Considering the central role of chirality in chemistry, and the fact that mechanical chirality of MIMs is often overlooked,[30] studies of this kind not only have exciting implications for basic science, but can also open new avenues for the development of molecular devices and materials for practical applications.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. General methods and experimental procedures, synthesis, NMR and CD spectra (PDF).

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Author Contributions

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(30) See, e.g., ref. 19i and: (a) Li, J.; Li, Y.; Guo, Y.; Xu, J.; Lv, J.; Li, Y.; Liu, H.; Wang, S.; Zhu, D. A Novel Supramolecular System: Combination of Two Switchable Processes in a [2]Rotaxane. *Chem. Asian J.* **2008**, *3*, 2091-2096. (b) Iwamoto, H.; Yawata, Y.; Fukazawa, Y.; Haino, T. Highly Efficient Synthesis of [3]Rotaxane Assisted by Preorganisation of Pseudorotaxane Using bis(Crown Ether)s. *Supram. Chem.* **2010**, *22*, 815-826. (c) Wang, X.-Y.; Han, J.-M.; Pei, J. Energy Trabfer and Concentration-Dependent Conformational Modulation: A Porpyrin-Containing [3]Rotaxane. *Chem. Asian J.*

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