Chemical On/Off Switching of Mechanical 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 activate mechanical planar chirality in an appropriately designed rotaxane. 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) – namely, chemical species in which molecular components are held together by mechanical bonds – possess intriguing structures and properties.[1,2] In particular, MIMs such as catenanes and rotaxanes exhibit a unique dynamic behavior that renders them ideal candidates for the construction of molecular mechanical switches, machines and motors.[2,3,4] While the absence of covalent bonds between the components enables facile relative movements, the mechanical constriction limits the possibilities for mutual arrangement of the components, 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 that coincides with the plane of the ring (Figure 1a).[8] When the ring and axle are forced to stay threaded into one another, the improper symmetry operations of the separated components are not symmetry operations of the rotaxane, which therefore becomes chiral.[6] The two enantiomeric forms of such a mechanically planar chiral rotaxane are schematically represented in Figure 1b. The synthesis of mechanically planar chiral rotaxanes was pioneered by Vögtle and coworkers,[9] and further investigated

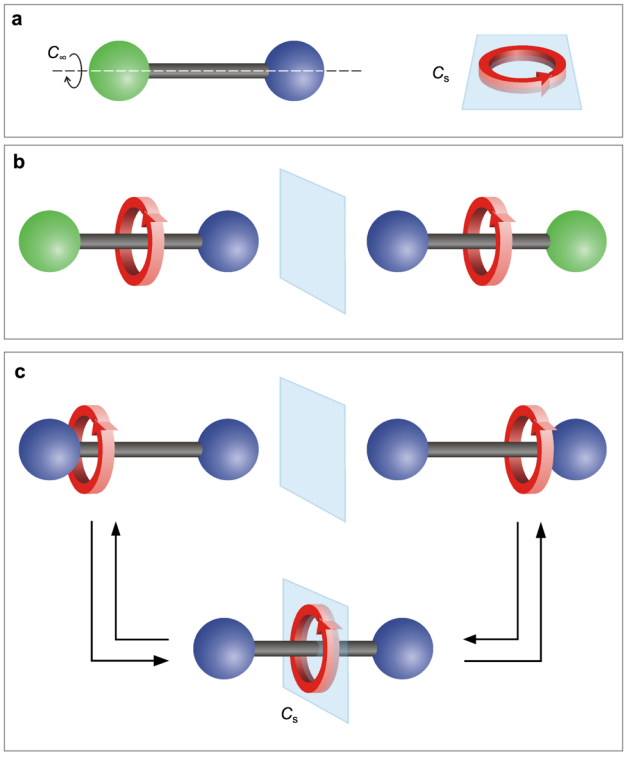


Figure 1. Schematic representation of: a $C_{\infty v}$ symmetric axle and a C_s symmetric ring (a); the two enantiomers of a mechanically planar chiral rotaxane (b); the two enantiomers of a co-conformationally mechanically planar chiral rotaxane and their interconversion by ring shuttling through an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

in more recent times,[10,11,12,13] when efficient and stereoselective synthetic methodologies have enabled the preparation of highly enantiopure rotaxane samples.[14,15] The exploitation of mechanically planar stereogenic elements of MIMs for the development of novel chiroptical materials, enantioselective sensors and asymmetric catalysis, is a fascinating research topic that has just begun to be explored.[6,16]

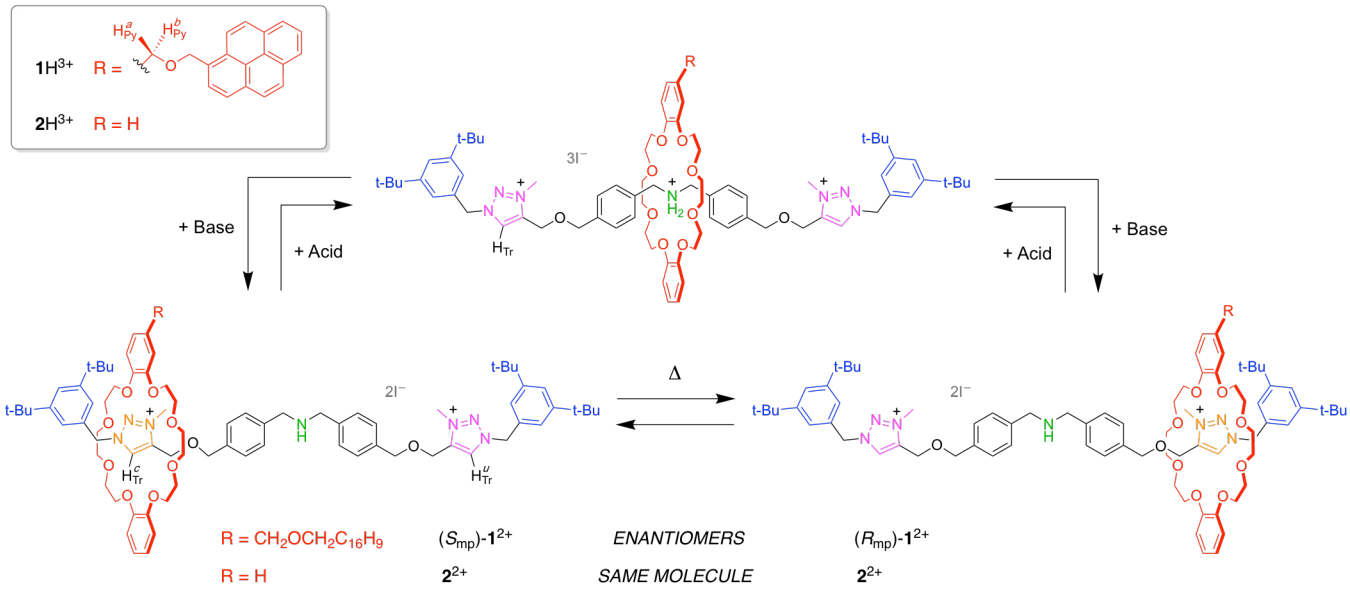
Mechanically planar chiral rotaxanes can also be obtained by interlocking a C_s symmetric macrocycle with an axle that has identical extremities, provided that the ring is located on either side of the mirror plane at the center of the axle (Figure 1c).[6,17] In other words, it is the position of the macrocycle that desymmetrizes the axle component such that, in combination with an oriented ring, yields a mechanically planar 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).[17] To our knowledge, only one example of co-conformationally mechanically planar rotaxane has been reported to date, in which however the position of the ring along the axle could not be controlled because of the absence of any recognition site.[17]

The strict 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 activate mechanical planar chirality. Here we describe the synthesis and properties of a [2]rotaxane that can be reversibly switched between a prochiral and a chiral state upon chemical stimulation. The presence of the two enantiomers in the chiral state was probed experimentally, and the inversion of the mechanical planar stereogenic element induced by 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.

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

Rotaxanes $\mathbf{1}H^{3+}$ and $\mathbf{2}H^{3+}$, 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 $\mathbf{1}H^{3+}$ 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 dual aim of (i) enhancing the chiral information with a large aromatic moiety that may interact with the axle, and (ii) having a fluorescent reporter for the switching process. In the symmetric rotaxane $\mathbf{2}H^{3+}$ the ring is plain DB24C8.

Our results indicate that in both $\mathbf{1}H^{3+}$ and $\mathbf{2}H^{3+}$ the ring encircles the ammonium station, in line with literature data.[18–20] We thus treated $\mathbf{2}H^{3+}$ with a polymer-bound phosphazene base in CD_2Cl_2 to afford rotaxane $\mathbf{2}^{2+}$ (Scheme 1, bottom). The ^{1}H NMR signal associated with H_{Tr} in $\mathbf{2}H^{3+}$ (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



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

timescale. Total line-shape analysis of H^{c}_{Tr} and H^{u}_{Tr} at temperatures varying from 303 K to 222 K (Figure 2a) allowed us to estimate the activation parameters for the shuttling process: $\Delta H^{\ddagger}$ = 27.9 kJ mol^{-1}, $\Delta S^{\ddagger}$ = –105 J mol^{-1} K^{-1}. These results confirm that the crown ether encircles one of the two equivalent triazolium sites, and moves between the two.

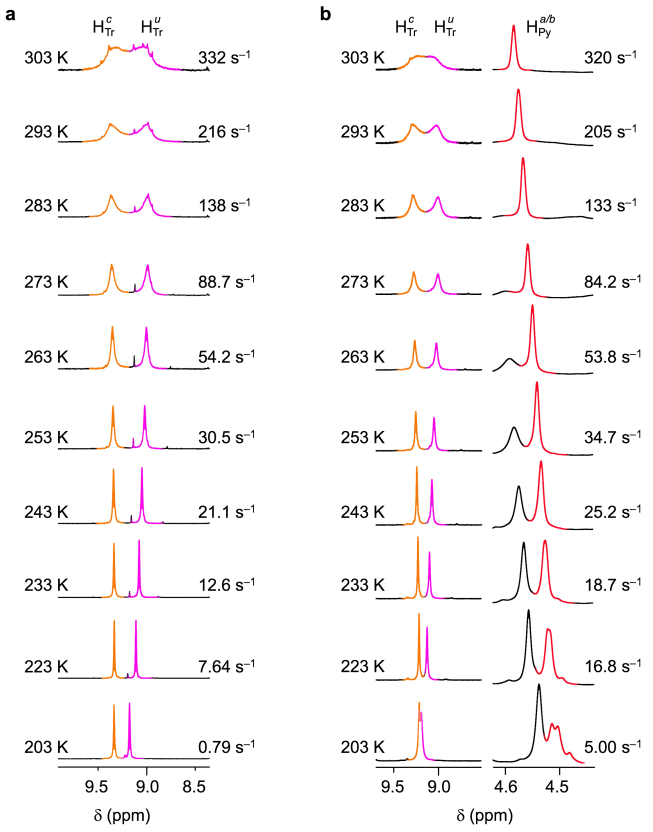


Figure 2. (a) Variable temperature (VT) ^{1}H NMR spectra (500 MHz, CD_2Cl_2) of rotaxane $\mathbf{2}^{2+}$ in the region of the triazolium protons (H^{u}_{Tr}, H^{c}_{Tr}). (b) VT ^{1}H NMR spectra (500 MHz, CD_2Cl_2) of rotaxane $\mathbf{1}^{2+}$ in the regions of the triazolium protons (H^{u}_{Tr} and H^{c}_{Tr}, left) and of the methylene protons in the pyrenyl tether of the macrocycle, adjacent to the dioxybenzene unit (H^{a}_{Py} and H^{b}_{Py}, right). See Scheme 1 for proton labeling.

Similar results were obtained upon deprotonation of $\mathbf{1}H^{3+}$ to yield $\mathbf{1}^{2+}$. The analysis of the NMR signals H^{c}_{Tr} and H^{u}_{Tr} at variable temperatures afforded activation parameters in line with those previously determined for $\mathbf{2}^{2+}$: $\Delta H^{\ddagger}$ = 26.1 kJ mol^{-1}, $\Delta S^{\ddagger}$ = –112 J mol^{-1} K^{-1} (Figure 2b). Such results show that the pyrenyl tether of the macrocycle does not affect the kinetics of the co-conformational equilibrium.

In contrast with $\mathbf{2}^{2+}$, however, the ring shuttling in $\mathbf{1}^{2+}$ generates a 50:50 population of two mirror image co-conformations, that is, a racemic mixture of two enantiomers (R_{mp})-$\mathbf{1}^{2+}$ and (S_{mp})-$\mathbf{1}^{2+}$.[21] In this regard, $\mathbf{1}^{2+}$ 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 mechanically planar enantiomers of $\mathbf{1}^{2+}$ 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} in Scheme 1). These protons are enantiotopic – and thus isochronous – in $\mathbf{1}H^{3+}$, while they become diastereotopic in $\mathbf{1}^{2+}$. We therefore envisioned that in the deprotonated rotaxane they should resonate at different frequencies and form a coupled spin system.[23]

The ^{1}H NMR spectra of $\mathbf{1}^{2+}$ 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 $\mathbf{1}^{2+}$ ring shuttling and inversion of the mechanically planar 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 $\mathbf{2}^{2+}$ (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.

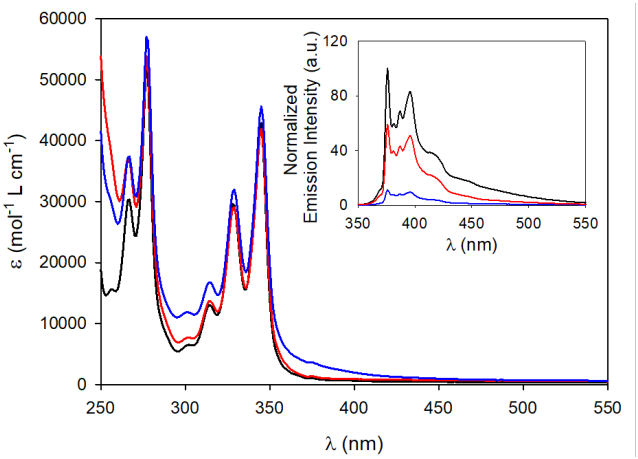


Figure 3. Absorption spectra of the free pyrenyl-containing macrocycle (black), $\mathbf{1}H^{3+}$ (blue) and $\mathbf{1}^{2+}$ (red). The inset shows the corresponding fluorescence spectra obtained on absorbance-matched solutions at the excitation wavelength (λ_{exc} = 328 nm). Conditions: air equilibrated CH_2Cl_2, 20°C.

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 that we assign to a charge-transfer interaction between the pyrenyl electron donor and a triazolium electron acceptor. Such a tail disappears upon deprotonation to yield $\mathbf{1}^{2+}$, presumably because the pyrenyl unit cannot interact efficiently with either triazolium unit (the complexed one is surrounded by the crown ether, and the free one is relatively far away). The fluorescence behavior is consistent with this in-

terpretation: 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 the base. Such a luminescence turn-on behavior provides a useful signal to monitor the occurrence of the chiral state, even by the naked eye.

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 chance is offered by 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 tetrabutylammonium salt of the enantiopure anion (1*S*)-(+)-10-camphorsulfonate [(+)-CS] to $\mathbf{1}^{2+}$ in CD_2Cl_2 at 223 K, the NMR signal of the H^u_{Tr} 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), which we assigned to the two different diastereomeric ion pairs (analysis of other resonances also supports this interpretation; see the SI). Deconvolution of these peaks allowed us to estimate a diastereomeric ratio of 80:20, which corresponds to a difference in stability of the two diastereoisomers of about 0.6 kcal mol^{-1}. 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). These results demonstrate that a chiral recognition event is taking place. In all cases the signal of H^u_{Tr} shifts downfield from 9.14 ppm to 9.58 ppm (major diastereoisomer), confirming that a supramolecular interaction occurs between the sulfonate anion and the free triazolium unit of the rotaxane. Conversely, the fact that the signal of H^c_{Tr} 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 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 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 and highlights the potential of the (co-)conformational properties of MIMs for generating chiral 'pockets' that may resemble those of enzymes.

The addition of tetrabutylammonium Δ-TRISPHAT[26] to $\mathbf{1}^{2+}$ in toluene-d_8 at 243 K[27] also causes a splitting of the NMR singlet corresponding to the H^u_{Tr} 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[26] 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.

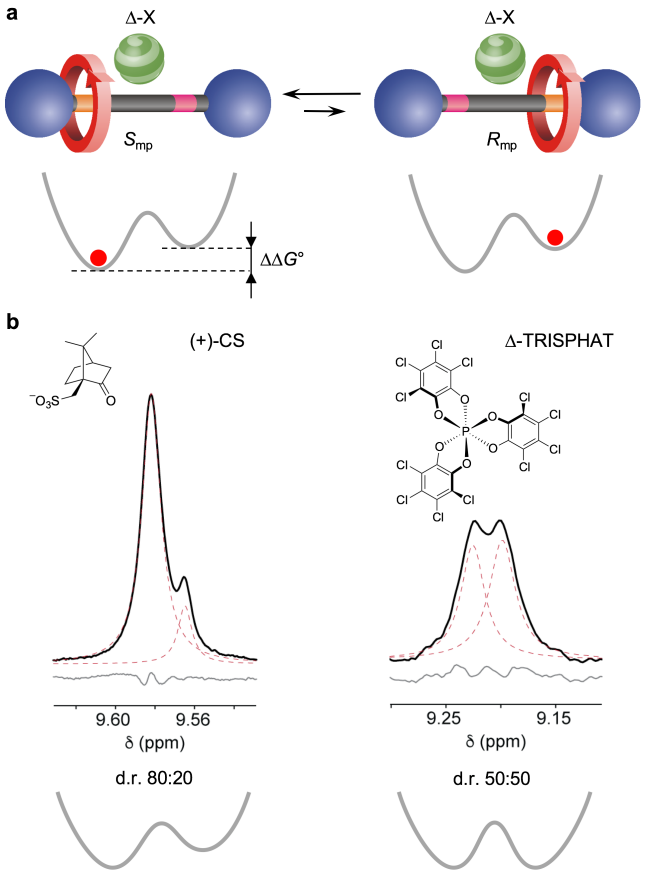


Figure 4. (a) Schematics of the interconversion between two diastereomeric ion pairs composed of a co-conformationally mechanically planar chiral rotaxane cation and a chiral anion (only one anion is represented for clarity). Simplified potential energy curves for the location of the ring along the axle 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^u_{Tr} resonance in $\mathbf{1}^{2+}$ after the addition of 8 equivalents of the tetrabutylammonium salt of either (1*S*)-(+)-10-camphorsulfonate (in CD_2Cl_2 at 223 K, left) or Δ-TRISPHAT (in toluene-d_8 at 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 the design, synthesis and properties of a three-station molecular shuttle that can be switched reversibly between a symmetric prochiral and a 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,[28] or activating molecular machines with a chiral trigger. Considering the central role of chirality in chemistry, 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 catalytic, sensing and optoelectronic 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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