Mechanical stereochemistry

Chirality makes a move

Interlocked molecules can exhibit chiral stereogenic elements that are not found in covalently bound systems. Now the shuttling of the ring in a [2]rotaxane has been shown to result in enantiomeric co-conformations that selectively bind chiral guests.

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Chirality is found throughout nature but it occupies a special place in chemistry, perhaps initially for historical reasons[1] but mainly as a result of the beneficial properties of chiral molecules in diverse areas from medicine to materials science. Writing in the *Journal of the American Chemical Society*[2], Alberto Credi, Massimo Baroncini and co-workers have now combined molecular chirality with molecular motion within a rotaxane, to create a molecule than can be switched between chiral and achiral states. The system also selectively adopts one enantiomeric arrangement in response to the binding of a chiral guest.

Chirality in molecular structures can usually be traced to covalent chirotopic stereogenic elements — molecular subunits that are themselves chiral[3]. These stereogenic elements are typically maintained by the rigidity of the covalent bonds that link the atoms, resulting in the classical elements of covalent stereochemistry, namely stereogenic centres, axes, planes and helices[4]. In addition, molecules can also display dynamic stereochemistry, as in the case of bipyridine which adopts enantiomeric conformations as a result of the rotation of the two aromatic rings relative to one another (Figure 1a).

Interlocked molecules — in which two or more molecular fragments are threaded through one another, and which are therefore held together by the so-called mechanical bond[5] — can display stereogenic elements that are not found in simple covalent systems[6]. This is the case for example of rotaxanes, in which an axle is threaded through a ring and kept in place by bulky stopper units. The simplest such stereogenic element is produced when the ring is 'oriented' and the two ends of the dumbbell-shaped axle are different[7]. Such 'mechanically planar chiral' rotaxanes (Figure 1b) have been investigated as sensors for small chiral molecules[8] and recent work has made them much more synthetically available[9]. Furthermore, a dynamic stereogenic element, analogous to the conformational stereochemistry displayed

by bipyridine, can arise even when the two ends of the axle are the same. Even though such molecules are achiral when the ring is perfectly positioned in the middle of the axle (Figure 1c), moving it either side of the centre results in mirror image structures[6]. Given that the stereochemistry of these molecules is extremely similar to that of mechanically planar chiral rotaxanes and depends on the relative position of the two components, their co-conformations, the term 'co-conformationally mechanically planar chiral' has been proposed to describe this stereoisomerism[6].

Co-conformationally mechanically planar chiral [2]rotaxanes have previously been investigated by Saito and co-workers[10], who used the rate of their racemisation to determine the barrier to exchange between enantiomers, but have otherwise largely escaped scrutiny. Credi, Baroncini and co-workers have now designed rotaxane $\mathbf{1}^{2+}$ that comprises an axle containing a central secondary amine and two triazolium stoppers at its ends, and a ring that is desymmetrised by a single substituent. When the central nitrogen is protonated to give $[\mathbf{1}.H]^{3+}$, the ring component — a substituted crown-ether macrocycle — occupies the centre of the axle. It is held there by strong hydrogen bonding between the crown-ether and the central ammonium moiety, and the molecule is achiral (Figure 1d). Deprotonation of the ammonium unit releases the ring from the central nitrogen moiety, causing the ring to shuttle between the two end units. This produces two co-conformations which are chiral and enantiomeric (Figure 1e). Thus, deprotonation results in a switch between an achiral state, $[\mathbf{1}.H]^{3+}$, and a chiral state, $\mathbf{1}^{2+}$, in a manner comparable to the way the coordination of Pd^{II} to bipyridine results in an achiral complex (Figure 1a).

The enantiomeric co-conformations of $\mathbf{1}^{2+}$, dubbed ($R_{co\text{-}mp}$) and ($S_{co\text{-}mp}$), [11] are equally populated, because enantiomers have identical energies in an achiral environment[12]. In a chiral environment, however, (R_{mp})-$\mathbf{1}^{2+}$ and (S_{mp})-$\mathbf{1}^{2+}$ are distinguishable and non-isoenergetic. The position of the equilibrium could therefore, in principle, be perturbed. Indeed, the researchers demonstrated this by replacing the achiral iodide counterion of $\mathbf{1}^{2+}$, which does not interact directly with the rotaxane, with the chiral anion (*S*)-camphor sulfonate ((*S*)-$\mathbf{CS}^-$). In the presence of (*S*)-$\mathbf{CS}^-$, which the team propose interacts directly with the exposed triazolium site (the one that isn't enclosed by the ring), two species were clearly observed by ^{1}H NMR spectroscopy. These were assigned to the anion-bound rotaxane complexes ($R_{co\text{-}mp}$)-$\mathbf{1}^{2+}$.((*S*)-$\mathbf{CS}$)$_2$ and ($S_{co\text{-}mp}$)-$\mathbf{1}^{2+}$.((*S*)-$\mathbf{CS}$)$_2$ (Figure 1f; note: the second (*S*)-$\mathbf{CS}^-$ anion is not strongly bound to the host). Notably, the relative population of these species was found to be

approximately ~85:15, although it is not clear which co-conformational state is preferred on anion binding. This relative population was maintained at all ratios of **1**$^{2+}$ and (*S*)-**CS**$^{-}$, as would be expected for such a stereodynamic system.

Looking at the simple structural representation of **1**$^{2+}$, the significant bias between the co-conformational diastereomers observed is in the first instance surprising as the mechanical stereogenic element — which would typically be considered localised on the macrocycle — is far from the proposed binding site, the exposed triazolium station. However, in reality, the macrocycle does not sit perpendicular to the axle and its substituent, a large aromatic pyrene moiety, can be projected along the axle. Taken together, the authors rationalised their result using a proposed binding mode in which the pyrene unit encroaches on the unbound triazolium, creating a well-expressed chiral space around the counter-anion (Figure 1f here, based on Figure S38 in the original manuscript) that could account for the observed selectivity.

These results suggest that systems such as rotaxane **1**$^{2+}$ are potential scaffolds for the development of stereodynamic probes for the enantiopurity of small chiral molecules[13], an important challenge in the era of high-throughput reaction analysis where chiral methods are often a bottleneck[14]. In particular, co-conformational biasing in co-conformationally chiral rotaxanes could lead to the appearance of a circular dichroism (CD) response to guests that are otherwise CD-silent, allowing their stereochemistry and enantiopurity to be analysed indirectly[15]. Unfortunately, in the case of **1**$^{2+}$, no CD effect was observed to arise from the host upon guest binding. Furthermore, in order for such systems to be developed, more information is needed as to how the stereoselectivity arises so that rational design can be used to optimise the bias. With this report however, it is clear that such molecules have significant promise.

Furthermore, mechanically interlocked molecules such as rotaxanes and catenanes can display many other unique stereogenic units, some of which prepared through selective synthesis[16]. Others, in particular where stereochemistry arises as a result of co-conformational motion, have yet to receive significant attention, or have only recently been recognised (Figure 2).[6] The system presented by Credi, Baroncini and co-workers, together with previous reports of covalently co-conformationally chiral rotaxanes in catalysis[17] and molecular machines[18], are important steps towards understanding the potential applications of the somewhat peculiar area of mechanical chirality.

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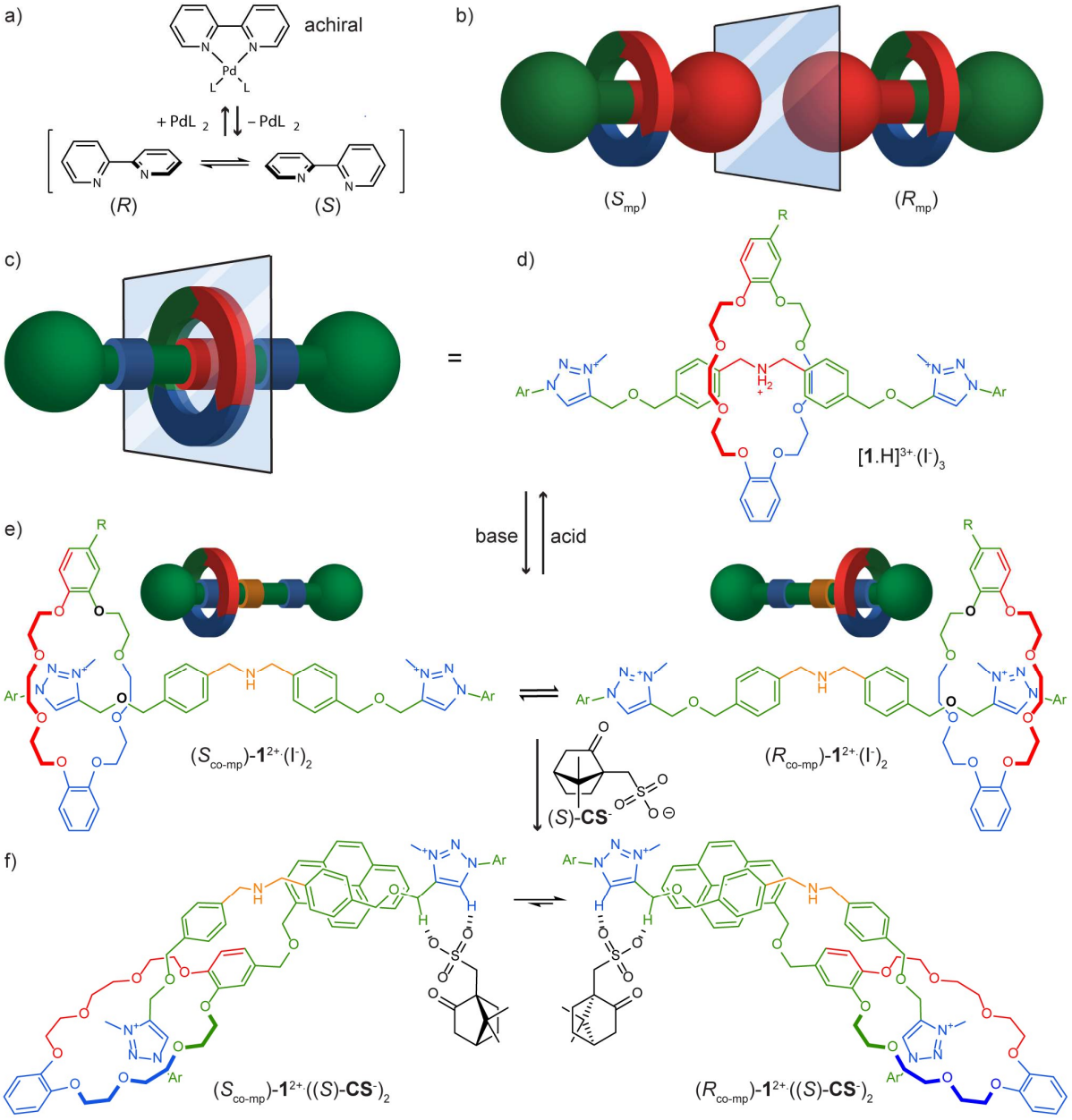

Figure 1 | **a,** the switching of bipyridine between an achiral coordination complex and chiral conformations; **b,** cartoon representation of the enantiomers of a mechanically planar chiral rotaxane (arbitrary stereochemical labels included); **c,** cartoon representation of the achiral co-conformation of a co-conformationally chiral rotaxane; **d,** rotaxane [**1**.H]$^{3+}$, the achiral state of Credi's rotaxane (unbound anions omitted for clarity); **e,** enantiomeric co-conformations of rotaxane **1**$^{2+}$ (stereochemical labels assigned using the highest priority atoms (black, bold) in the axle and ring)[6]; **f,** representation of the diastereomeric complexes of **1**$^{2+}$ with (*S*)-

camphorsulfonate ((*S*)-**CS**$^-$) showing the proposed binding mode of the anion (unbound anions omitted for clarity; arbitrary co-conformational preference shown).

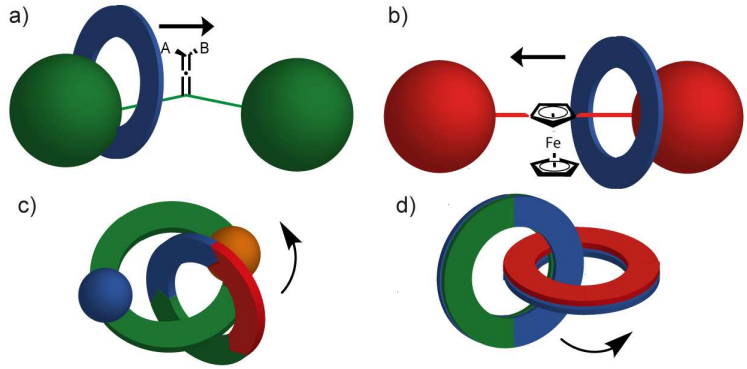

Figure 2 | Examples of recently recognised co-conformational stereogenic units exhibited by rotaxanes and catenanes that have yet to be synthetically realised.[6] The motion that exchanges the enantiomers is indicated. **a,** co-conformationally covalent axially chiral rotaxane; **b,** co-conformationally covalent planar chiral rotaxane; **c,** co-conformationally mechanically topologically chiral catenane; **d,** co-conformationally mechanically axially chiral catenane;