Mechanical Chirality

A chiral catalyst with a ring to it

A chiral [2]rotaxane in which the asymmetry is derived from the way in which the two components are mechanically interlocked — rather than being encoded in the covalent connectivity of the components themselves — has been shown to act as an enantioselective organocatalyst.

Stephen M. Goldup

Rotaxanes are a class of mechanically interlocked molecules, the simplest examples of which consist of a macrocycle encircling a linear, dumbbell-shaped axle component. Although there is no direct covalent bond between the macrocycle and axle, if the end groups of the dumbbell are large enough to prevent the macrocycle from escaping, the two components cannot separate and the link between them is termed a 'mechanical bond'. These compounds, initially somewhat of a chemical curiosity, have been developed as prototypical molecular machines and are now receiving increased attention as catalysts.

Although early studies focused on using the sterically crowded environment created by the mechanical bond to influence the enantioselectivity of a catalytic process[1], the majority of recent reports have used the machine-like movement of the macrocycle along the axle to produce catalysts with unusual reactivity[2] or stimuli-responsive behaviour[3]. Now, writing in the *Journal of the American Chemical Society*, David Leigh and co-workers have taken advantage[4] of one of least explored structural properties of the mechanical bond — the ability of rotaxanes to display molecular asymmetry even in the absence of any covalent chiral information — in order to create a new class of enantioselective catalyst.

Leigh and colleagues synthesised rotaxane (*S*)-**1** (Fig. 1a) and compared its catalytic behaviour with that of the corresponding non-interlocked axle, **2** (Fig. 1b). Importantly, the covalent structure of **2** (which is identical to the axle component of **1**) is achiral — the amine organocatalytic moiety (yellow) is bonded to a carbon bearing to two identical succinamide (green) substituents. The presence of the macrocycle in **1** desymmetrizes the structure, meaning that the rotaxane exists in two mirror-image forms depending on which of the succinamide binding sites the macrocycle encircles. Moreover, because the amine

substituent is too large for the macrocycle to pass over, these two enantiomers are stable and can be separated. This form of chirality is dubbed ‘mechanical point chirality’ by analogy with the much more common covalent point chirality. The absolute configuration of **1** was assigned as *S* by treating the macrocycle as a substituent of the right-hand portion of the axle where it is localized and applying the familiar Cahn–Ingold–Prelog rules for stereogenic centres.

To demonstrate the potential of such 'mechanochiragenesis' in catalyst design, Leigh and co-workers prepared (*S*)-**1** in highly enantioenriched form (84% e.e.) with the stereochemical information derived from a chiral-pool starting material, namely D-asparagine. The ^{1}H NMR spectrum of (*S*)-**1** clearly showed the desymmetrization of the axle component caused by the position of the macrocycle and the circular dichroism spectrum of the compound also exhibited a large Cotton effect. Rotaxane (*S*)-**1** and the non-interlocked axle **2** were then investigated separately in two different, yet well-understood, organocatalytic reactions (Fig. 1c) — one that proceeds through the formation of an iminium species and one that involves an enamine mode of activation. As expected, when either reaction was performed in the presence of the achiral axle (**2**), no enantioselectivity was observed. In contrast, rotaxane (*S*)-**1** catalysed both the Michael addition and α-amination reactions with reasonable levels of enantioselectivity — 36% (corresponding to a 67 : 33 ratio between the major and minor enantiomers of the product) and 42% e.e. (71 : 29), respectively, in the best cases reported.

This is the first time that an enantioselective catalyst that is chiral solely as a result of a mechanical bond has been demonstrated. In this context, the e.e. values achieved in this proof-of-concept study are certainly respectable. Because the catalyst itself is not enantiopure, it should be noted that the values reported under-estimate the underlying selectivity; if the catalyst were enantiopure the e.e. values would be expected to rise to 43% and 50% e.e. for the iminium and enamine pathways, respectively, assuming that the catalyst is acting monomerically. It is somewhat surprising, however, that the enantioselectivities observed are not higher, given that the difference in steric bulk between the encircled and free succinimide units is significant.

One possible explanation is that although the macrocycle is a very large ‘substituent’, it may be positioned too far from the amine organocatalyst to exert the maximum influence on the reaction. If this were the case, rigidifying and/or shortening the link between the stereogenic

centre bearing the amine and region of the axle where the macrocycle is localised could be expected to enhance the enantioselectivity of the catalyst. Alternatively, projecting the steric bulk of the macrocycle back towards the catalyst by adding large groups to the flanking *p*-xyxlyl aromatic rings of the macrocycle could achieve the same effect. It may also be that rotaxane (*S*)-**1** is less active than other highly enantioselective secondary-amine catalysts[3]. If the reactions investigated in this study can also take place via non-selective uncatalysed pathways, then low catalyst activity may enable these to compete with the desired rotaxane-catalysed process thus lowering the observed enantioselectivity.

These points notwithstanding, based on Leigh's preliminary results it can be argued that such mechanically chiral molecules have a bright future in catalysis. Furthermore, in addition to the mechanical point chirality exploited in rotaxane (*S*)-**1**, rotaxanes and catenanes can exhibit other forms of mechanical chirality in the absence of covalent chirality (Fig. 2) when there is a directionality associated with the covalent frameworks of the sub-components[5,6,7] Looking to the future, by combining elements of mechanical chirality with the well-developed chemistry of rotaxane molecular shuttles[3] it may be possible to create switchable catalysts[8] that can generate either mirror-image form of a chiral target in response to external stimuli. Perhaps more prosaically, but no less exciting from the point of view of catalyst development, given that the crowded environment of the mechanical bond has been demonstrated to influence challenging catalytic processes such as gold(I)-mediated reactions[9,10], it seems likely that chiral reaction fields generated by the mechanical bond in rotaxanes and catenanes could be used to address existing challenges asymmetric catalysis.

Steve Goldup is in the Department of Chemistry, University of Southampton, Southampton, SO17 1BJ, UK. Email: s.goldup@soton.ac.uk; Twitter: @sgoldup

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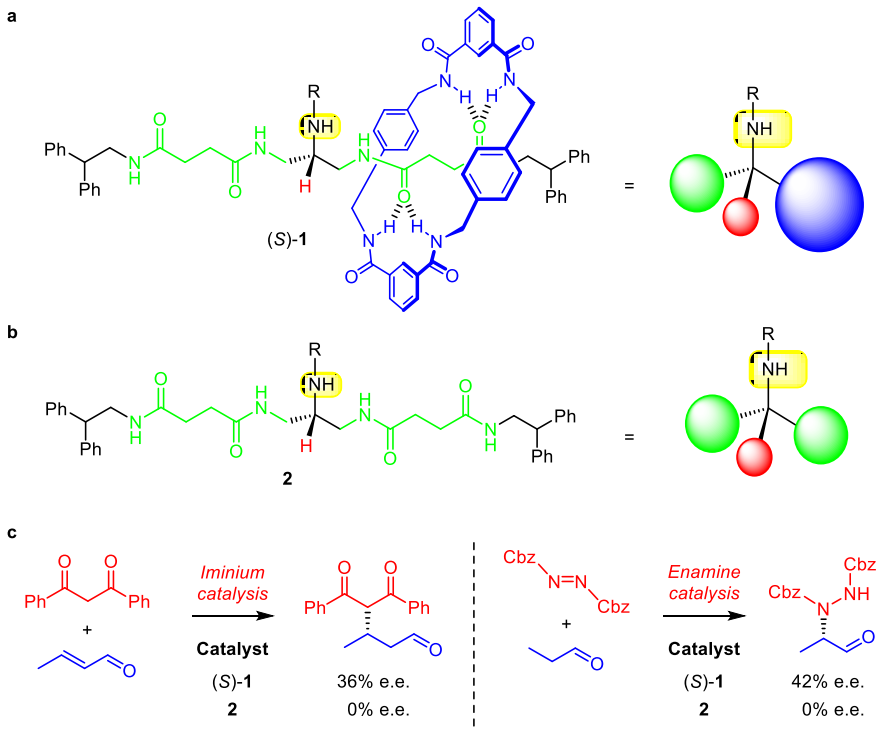

Figure 1 | A mechanically point chiral organocatalyst. **a,** the (*S*) enantiomer of the mechanically point chiral organocatalytic rotaxane **1**; **b,** the achiral amine organocatalyst (**2**) which is the same as the axle in rotaxane **1**; **c,** organocatalytic reactions that occur via iminium and enamine intermediates used to compare the stereoselectivity of rotaxane (*S*)-**1** with axle **2**.

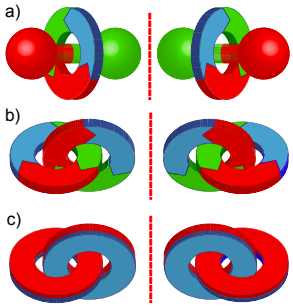

Figure 2 | Examples of mechanical chirality exhibited by rotaxanes and catenanes. **a,** Enantiomeric rotaxanes comprised of a macrocycle that lacks rotational symmetry and an axle with two different ends; **b,** enantiomeric catenanes comprised of macrocycles that lack rotational symmetry; **c,** enantiomeric catenanes containing two macrocycles that are facially non-symmetrical. In each case the dotted line represents a mirror plane.