[3]Rotaxane Host Selects Between Stereoisomers

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Thanks to the Nobel Prize winning work of Knowles, Noyori and Sharpless,[[[1]](#endnote-2)] and many others since, man-made catalysts have come to challenge the gold-standard set by nature’s enzymes in terms of enantioselectivity. More importantly, artificial catalysts allow transformations that enzymes have not evolved to carry out and, whereas for the most part a distinct enzyme is required for each pair of substrates, modern synthetic catalysts often exhibit broad substrate scope and high stereoselectivity. Conversely, artificial systems still struggle to compete with the other well-known function of proteins, the selective binding of small molecule guests and the transduction of this binding event into a measurable signal, with discrimination between subtle changes in molecular structure such as stereochemistry.

The exquisite selectivity of nature’s hosts is linked to the high stereoselectivity of enzymes; both are manifestations of the size and shape selectivity embodied by Emil Fischer’s lock-and-key hypothesisand rely on a well-defined cavity within the protein that discriminates between guests or substrates. However, application of nature’s sensors in a non-natural context suffers from the same challenges as enzymatic catalysts in that recognition typically must take place under aqueous conditions and, for the most selective examples, a specific host is required for each guest. These drawbacks limit the application of protein hosts to the recognition of non-biological analytes, and in particular, to the non-invasive determination stereochemical purity, a contemporary challenge with the advent of high-throughput reaction screening, in which enantiomeric excess (*ee*) determination by chiral stationary phase HPLC is often the limiting analytical step.[[[2]](#endnote-3)] As a result, a number of artificial strategies have been developed for the selective binding and reporting of stereoisomers,typically involving metal coordination or dynamic covalent chemistry.[[[3]](#endnote-4)]

Writing in *Angewandte Chemie*, Beer and co-workers demonstrate a new approach to the selective binding and reporting of stereoisomers using mechanical bonding to produce a well-defined three-dimensional binding pocket.[[[4]](#endnote-5)] Their strategy builds on their previous work on the use of rotaxanes and catenanes as selective hosts for anionic guests,[[[5]](#endnote-6)] and borrows ideas from asymmetric catalysis and protein hosts.

Chiral [3]rotaxane **1** (Figure 1) was synthesized in good yield using chloride as a template to assemble the precursors. Rotaxane **1** has two binding sites for anions in the form of the mixed hydrogen-bonding/halogen-bonding regions presented by the amide units and polarized C-I bonds brought into coincidence by the macrocycles wrapped around the axle. Accordingly, small anions such as chloride were found by 1H NMR analysis to bind to rotaxane **1** in a 1 : 2 fashion, one within the cavity of each macrocycle. In contrast, and consistent with previous work by Beer and co-workers with sulphate and nitrate anions,[[[6]](#endnote-7)] bulkier di-anions such as dicarboxylates bound in a 1 : 1 manner to rotaxane **1** with the guest sandwiched between the binding sites, rather than endotopically within the ring cavity. The binding mode of the dicarboxylate anion along the axle requires the guest to be in close contact with the chiral, stereo-differentiating Binol unit and the C2-symmetry of the host ensures that even non-symmetrical guests such as glutamic acid have only one available binding orientation relative to the axle, a strategy that is well-used in the design of enantioselective catalysts. Furthermore, each binding region of the host presents the guest a number of attractive, highly directional (hydrogen- and halogen-bonds; abbreviated to HB and XB respectively) interactions, ensuring strong and structured binding and by sandwiching the guest between the sterically bulky “walls” created by the macrocycles, it is isolated from its surroundings, both features of enzymatic hosts.



**Figure 1.** Structures of [3]rotaxane **1** (PF6 counter anions omitted), and the dicarboxylate guests studied and their binding constants (M-1) with **1** determined by fluorescence titration in CHCl3-CH3OH-H2O 60:39:1 at 293 K.

Analysis of the selectivity of binding reveals that the host is able to differentiate both between geometric isomers, in the case of fumarate *vs* maleate and enantiomers, in the case of (*R*)- vs (*S*)-glutamate. Furthermore, the emission of the binol moiety provides a luminescent response to guest binding, allowing the binding event to be reported optically. Molecular modelling underlines the benefit of using the mechanical bond to engineer a flexible, sterically crowded binding pocket and sheds some light on the observed selectivity. Firstly, all of the guests studied were predicted to interact with both binding sites in a similar manner despite significant differences in the distance between their carboxylate groups. This is due to the flexibility of the Binol unit and the threaded arrangements of the macrocycles, in keeping with previous work from Sauvage and co-workers who showed that the restricted movement of macrocycles along an axle in a [3]rotaxane can provide a flexible binding pocket for different sized guests.[[[7]](#endnote-8)] Secondly, the end walls of the binding pocket, which are formed by the macrocycles, fold around the guest to create a crowded binding pocket that serves to exclude solvent from the hydrophilic carboxylate region, much as the binding pocket of an enzyme ensures controlled solvation of the guest.



**Figure 2.** Modelled structures of the host-guest complexes of [3]rotaxane **1** with a) (*S*)-glutamate and b) (*R*)-glutamate.

Modelling of the binding of fumarate compared with maleate suggests that the discrimination between these guests is due to both to size/shape complementarity and differences in the solvation of the guests bound to the receptor leading to relative binding constants for fumarate *vs* maleate of 4.4 : 1. In contrast, the differentiation between the enantiomers of glutamate appears to be driven largely by shape complementarity; models (Figure 2) indicate that (*S*)-glutamate is embedded more effectively within the cavity formed between the macrocycles than (R)-glutamate leading to a large relative binding constant of 5.7 : 1 for (*S*)- *vs* (*R*)-glutamate. In contrast, the corresponding non-interlocked axle, which contains the same stereo-differentiating Binol unit but lacks the constrained binding pocket provided by the macrocycles underlines the importance of the mechanical bond; the axle does not differentiate between the enantiomers of glutamate, which have essentially the same binding constants.

This work, combined with previous work from the same authors that employed a simpler [2]rotaxane[[[8]](#endnote-9)] and a report from Niememeyer and co-workers who demonstrated a Binol-based [2]catenane host for dianionic guests,[[[9]](#endnote-10)] underlines the unexploited potential of interlocked molecules as scaffolds for the development of enantioselective hosts and related sensors. Furthermore, whereas the stereochemistry of [3]rotaxane **1** can be attributed to the Binol covalent axial stereogenic unit, interlocked molecules have the potential to display chirality purely as a result of their mechanical structure, including mechanical planar[[[10]](#endnote-11)], topological[[[11]](#endnote-12)] or mechanical axial[[[12]](#endnote-13)] chirality.[[[13]](#endnote-14)] These unusual forms of stereochemistry have the potential to generate a well-defined chiral environment in which the molecular chirality is the result of a stereogenic unit that involves the entire structure.

In conclusion, the highly stereoselective binding of the stereoisomers studied to [3]rotaxane **1** suggest that the use of the mechanical bond to engineer a binding pocket has long term potential for the development of stereoselective hosts. Given the relative infancy of stereoselective binding and sensing by interlocked molecules and the wealth of unexplored stereochemical properties available for study, the work by Beer and co-workers suggests a bright future for interlocked molecules in the development of hosts for challenging applications, in addition to the established role of rotaxanes and catenanes in the development of molecular machines.[[[14]](#endnote-15)]



**Figure 3.** Schematic structures of examples of mechanical stereogenic units that lead to molecular chirality even when the covalent subcomponents are achiral: a) mechanical planar chiral rotaxane; b) topologically chiral catenane’ c) mechanically axially chiral catenane.

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