Chiral macrocycle formation within chiral capsules

Chiral macrocycles are of interest for various applications, including drug discovery, but are challenging to synthesize. Now, a method for enantiocontrolled macrocyclization is demonstrated, involving the confinement of a linear substrate within a self-assembled chiral capsule. This method shows good substrate scope and affords chiral macrocycles with high enantioselectivities and conversions.

This is a summary of:
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The problem

Chiral macrocycles exhibit intriguing properties that can be attributed to their unusual molecular structure and the conformational rigidity of their cyclic skeletons. In particular, their binding affinity to and selectivity for biological targets are higher than those of their linear analogues, making them of interest as drug leads and prospective pharmaceuticals[1]. Thus, the development of efficient macrocyclization methods is an important goal in the quest for identifying new drug leads. However, most synthetic methods face the formidable challenge of having to form rigid macrocycles — overcoming the entropic penalty due to restriction of the conformational flexibility of a linear chain — while simultaneously inducing chirality with control of the enantioselectivity[2]. This challenge is partially due to the difficulty of achieving the folding constraints with the substrate in a fixed chiral conformation, which is a prerequisite for chiral macrocyclization. Although specific binding to an enzyme[3] or a synthetic chiral auxiliary[4] has been applied to induce chirality during macrocycle formation, these synthetic methods are not widely generalizable and lack the capability of chirality switching. Thus, universal chirality induction with enantiocontrol in macrocyclization remains largely unexplored.

The solution

One approach to addressing this challenge is to tightly confine a linear substrate within a chiral environment. However, tight confinement requires a rigid chiral environment that is not adaptable to substrates of different sizes and lacks switching capability. We hypothesized that a way to overcome this limitation would be to encapsulate a linear substrate in a flexible chiral capsule self-assembled from a precursor molecule with a chiral side chain followed by stepwise self-assembly of the flexible capsule into a rigid two-dimensional (2D) nanostructure (Fig. 1).

We selected a precursor molecule that comprises an aromatic pyridine-based segment and a hydrophilic chiral dendron. Addition of a hydrophobic substrate to a solution of the precursor molecule triggers capsule formation, entrapping the substrate. The flexibility of the chiral capsule arises from the non-specific aromatic interactions in the capsule wall: the aromatic segments of the precursor molecules can slide with respect to each other, enabling the capsule to change size to adapt to different substrates and making it possible to switch the chirality through application of an external stimuli. Following formation, the flexible chiral capsules are 'frozen' through self-assembly into a 2D nanostructure, which serves as a template in which each of the entrapped linear substrates is tightly held in a chiral conformation, providing the preorganized structure required for chiral macrocyclization. Subsequently, the macrocyclization in the confined state affords an enantiopure macrocycle product (with enantioselectivities of >99%) with quantitative conversions.

To show that the substrate encapsulation process is amenable to substrates of different sizes, we applied our macrocyclization method to substrates decorated with a wide range of functional groups, yielding various chiral macrocycles. Furthermore, we showed that the chirality of the flexible chiral capsules can be collectively switched to the opposite form using sonication and the original chirality recovered with heat treatment (Fig. 1), enabling precise control of the enantioselectivity of macrocycle formation.

The implications

The high efficiency and precision of our capsule assembly for chirality induction in macrocyclizations could be attributed to the fixation of the flexible chiral capsules into a 2D nanostructure in which the entrapped linear substrates adopt a chiral conformation in the chiral interiors. This macrocyclization strategy, could provide access to a universal synthesis method for guiding the formation of complex chiral macrocycles with excellent stereocontrol. We envisage that such a general method could be used in the identification of new therapeutic leads and for potential applications in catalysis, sensing and as chiroptical switches.

Nevertheless, although our strategy provides an efficient chiral macrocyclization method, there is still room for improvement. One challenge is how to achieve self-separation of the macrocycle products out of the fixed 2D nanostructure; this is the focus of ongoing work in our group.

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EXPERT OPINION

"It is typically not trivial to carry out macrocyclization in a controlled manner. Now, the authors of this study have discovered a strategy to promote stereoselective macrocyclization, which goes one step further than inducing macrocyclization, and is no small feat." **Nathalie Katsonis, University of Groningen, Groningen, the Netherlands.**

FIGURE

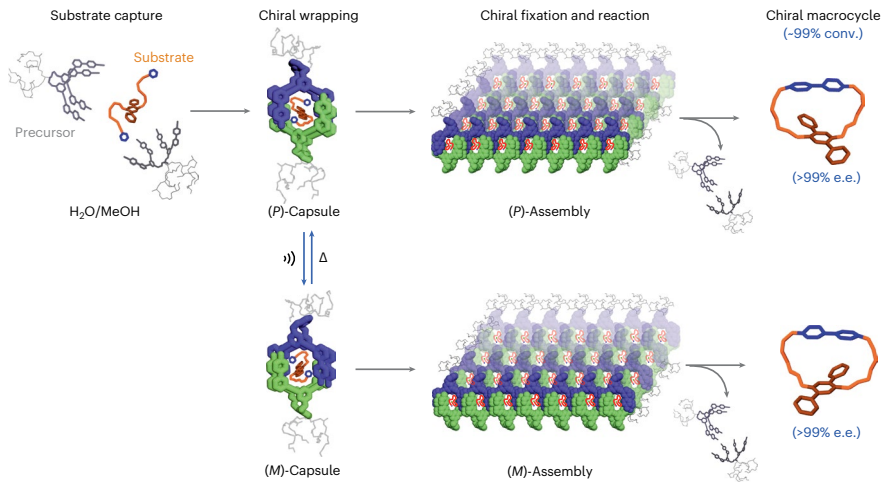

Fig. 1 | Schematic showing our method for enantiocontrolled macrocyclization. Addition of a linear substrate to a solution of the host precursor leads to formation of a chiral capsule, which traps the linear substrate. The chiral capsules subsequently self-assemble into a rigid 2D nanosheet structure. Chemical reaction of the substrate within the confined environment of the chiral capsules generates a highly enantiopure macrocycle. The chirality of the capsule structure can be switched into the opposite form through sonication, enabling control of the macrocycle enantioselectivity. e.e. enantiomeric excess. © 2023, Tan, L. et al.

BEHIND THE PAPER

After performing experiments to encapsulate a linear substrate using an amphiphilic precursor with chiral side chains in aqueous environments, we were excited to discover that not only did addition of the achiral substrate induce a strong signal in the circular dichroism (CD) spectrum, but also that the CD signal inverted upon sonication. On the basis of these observations, we reasoned that following self-assembly of the capsules, the linear substrates were confined in a chiral environment with a folded chiral conformation, thus providing a preorganized structure for chiral macrocyclization. Consequently, we were able to achieve enantiocontrolled macrocyclizations through control of the chirality of the 2D self-assembly. After repeating the experiment under identical conditions to confirm this result, we were confident in the findings and set out to comprehensively demonstrate the concept of precise enantiocontrolled macrocyclizations. **M.L.**

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FROM THE EDITOR

"The chiral interior of a molecular capsule is used to carry out different macrocyclization reactions with high yields and good stereoselectivities. A useful feature of the capsules is their flexibility, which enables different substrates to be accommodated, at the same time as preserving the rigidity required to provide a chiral space." **Alison Stoddart, Chief Editor, *Nature Synthesis*.**