Interlocked molecules

https://doi.org/10.1038/s44160-024-00655-w

Heterochiral catenanes create robust nanostructures

Josh Phipps & Shengqian Ma

Supramolecular peptide complexes with interlocking heterochiral linkers showcase a route for self-assembled nanostructures with exceptional mechanical stability.

Studying proteins and enzymes provides an understanding of the development of life and allows the leveraging of these biological materials in applications. These materials are typically unstable in various solvents, at certain temperatures and pH ranges. This obstacle has led researchers to investigate alternatives such as self-assembled peptide materials which can mimic protein functions while remaining stable under these typically adverse conditions. The pursuit of this desired stability, coupled with functionality, has led researchers to incorporate concepts from robust mechanically interlocked molecules (MIMs) to create a peptide-based subset of MIM structures[1–3].

Proteins are comprised of peptide chains that fold to form a functional 3D shape. Similarly, MIMs can utilize intermolecular forces, hydrogen bonding, π–π stacking, and metal coordination to ensure structural integrity in these synthetic assemblies. These structures have strong interactions between two or more groups (analogous to peptide chains within proteins), form mechanical bonds, and can interact with one another to extend and form larger structures. While their biological counterparts are stable in a narrow range of conditions, the robust nature imparted to MIMs through their combined interactions renders the structures stable in a range of conditions[4,5].

Now, writing in *Nature Synthesis*, Davis and co-workers report the synthesis of a class of heterochiral MIMs by combining modified diastereomer peptide chains leading to exceptional mechanical stability[6]. Inspired by the selective chirality of biological materials, a pair of peptide chains with two chiral centres at the middle are synthesized. The first chain expresses *laevus* (L) chirality at both chiral centres (termed ^{LL}P) while the other isomer expresses a change in one chiral centre from L to *dexter* (D) chirality to yield ^{DL}P. This chirality change leads to a difference in the angle of the resulting chains, with the former chain having an obtuse bend from its centre of 112°, while the latter has a more acute 47° bend (Fig. 1a). This difference in the peptide chain angle is a consequence of a new intramolecular hydrogen bond formed by the arrangement changing from ^{LL}P to ^{DL}P. Next, these chains are functionalized at their C- and N-terminus to enable coordination with metals. The coordination of Co^{2+} with these peptide chains in separate solutions of either ^{LL}P alone or an equal parts mixture of ^{LL}P and ^{DL}P yields the self-assembled homochiral (^{LL}P, ^{LL}P) or heterochiral (^{DL}P, ^{LL}P) helical peptide nanostructures, named MCP-1 and MCP-2, respectively.

Characterization of MCP-1 and MCP-2 reveals that the peptide chains form intimate pairs with a partner chain interlocking through strong interactions and coordination with Co^{2+} ions, resulting in ring structures called catenanes in both materials (Fig. 1b)[4]. However, there is a noteworthy difference between the two structures. Instead of the linkers stretching across one another and crisscrossing as observed in MCP-1 catenane, the combination of the smaller angle and larger angle peptide chains in MCP-2 allows for orderly entanglement of the

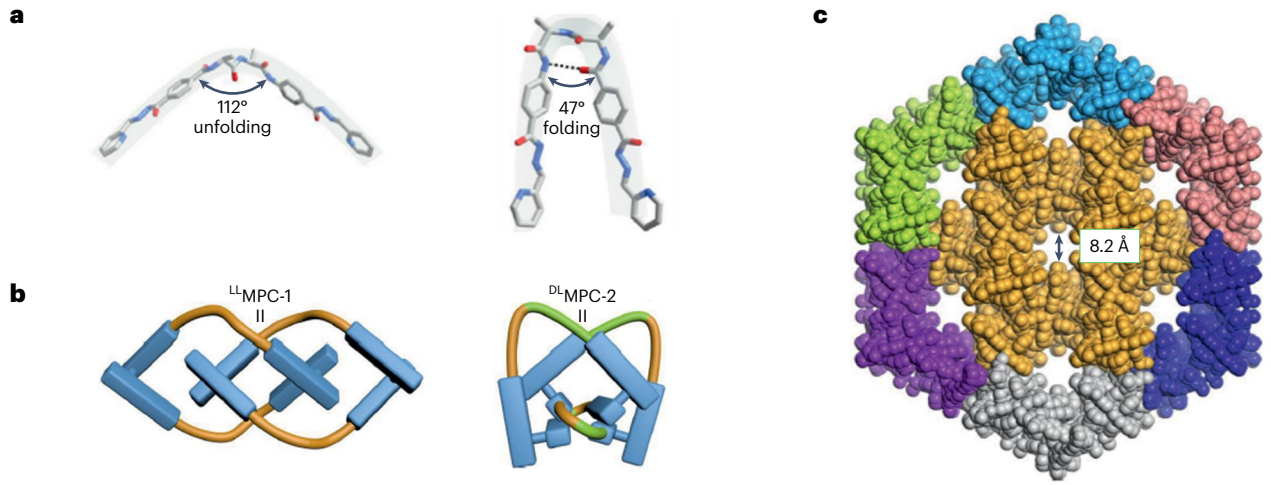

Fig. 1 | Homochiral and heterochiral peptide chains and their combination to create exceptionally stable MIM nanostructures. a, Homochiral (^{LL}P, left) and heterochiral (^{DL}P, right) peptide chains with bond angles and hydrogen bonding expressed. **b**, Knot-like catenane sub-units observed within MCP-1 (^{LL}P, ^{LL}P) and MCP-2 (^{LL}P, ^{DL}P). **c**, An extended view of the porous supramolecular complex, MCP-2.

heterochiral peptide linkers, resulting in the interlocking of two of the smaller ^{DL}P within the two outer ^{LL}P. This combination forms the knot-like subunit of MCP-2. These knotted subunits then extend to form supramolecular coordination complexes (Fig. 1c).

Although MCP-1 is highly stable, the sub-unit of MCP-2 endows its complex with superior mechanical stability as a result of extensive π–π stacking within and between the sub-units. This is evident by the high Young's modulus of MCP-2 (an average of 157.6 GPa). This outperforms MCP-1 by over 50 GPa and surpasses the stability observed by comparable materials including metal–organic frameworks (MOFs), covalent–organic frameworks (COFs), polymers, biological materials, and most other peptide assemblies.

Another attribute of MCP-2 is revealed on investigation of the chirality of the complexes using circular dichroism. These findings show that the optical rotation per mole of MCP-1 is 7.2 times greater than that of its linker molecule, while for MCP-2 this value is 17.5 times greater. This increased optical activity coupled with the accumulation of charged centres across MCP-2 (positive internally and negative on the exterior) creates a good environment for acceptor–donor interactions compared to MCP-1, which has a more even charge distribution. These characteristics combined with the porous nature of the complex create potential binding pockets with exceptionally strong chiral amplification.

Finally, the interaction of the complexes with biological materials is probed. There is an interesting trend of antibacterial effects towards Gram-negative bacteria in the order of ^{DL}P<^{LL}MCP-1<^{LD}MCP-2<^{DL}MCP-2. While the linker and MCP-1 showed almost no activity, the comparison between ^{LD}MCP-2 and ^{DL}MCP-2 indicates that there is an enantioselective preference for the latter. Similarly, MCP-2 shows an increased effectiveness compared to MCP-1 towards Gram-positive bacteria. This observation is likely due to the specific arrangement and presence of the D-isomeric structure of MCP-2 which is common among prokaryotes and their cell membranes and shows the power of enantiomeric selection toward interactions with biological substrates.

Davis and co-workers show, with great ingenuity, that by leveraging mixed chiral centres in peptide chains, it is possible to synthesize extended supramolecular coordination complexes with exceptional stability that outperform many conventional materials. By combining the most robust attributes observed in proteins and other materials, such as metal coordination from MOFs, π–π stacking often found in COFs, and intermolecular interactions from peptide assemblies, Davis and co-workers unveil a class of heterochiral MIMs that can be expanded upon in many directions. Notably, the pores of these materials, with their charge density, chiral nature, and ability to be tailored provide an exceptional platform for enzyme-like catalytic reactions with the potential to bestow specific chirality to the selected substrate[7,8]. Similar to COFs, these materials can also serve within membranes as filters in separations. As for biological applications, their organic components, stability, and charged pores make these complexes candidates as tools for drug delivery while the ability to manipulate their attached groups means that they may be surface functionalized toward specific microbes as targeted antimicrobial agents or may serve as a microtubule mimic to observe tau protein aggregation typical in Alzheimer's disease[9]. We foresee that this heterochiral synthesis strategy may expand to enable many of these applications in the future.

Josh Phipps & Shengqian Ma
Department of Chemistry, University of North Texas, Denton, TX, USA.
Twitter / X: @shengqianma
e-mail: Shengqian.Ma@unt.edu

Published online: 20 September 2024

References

1. Horne, W. S. & Grossmann, T. N. *Nat. Chem.* **12**, 331–337 (2020).
2. Capocasa, G., Frateloreto, F., Valentini, M. & Di Stefano, S. *Commun. Chem.* **7**, 116 (2024).
3. Stoddart, J. F. *Angew. Chem. Int. Ed.* **56**, 11094–11125 (2017).
4. Forgan, R. S., Sauvage, J.-P. & Stoddart, J. F. *Chem. Rev.* **111**, 5434–5464 (2011).
5. Zhang, Z.-H., Andreassen, B. J., August, D. P., Leigh, D. A. & Zhang, L. *Nat. Mater.* **21**, 275–283 (2022).
6. Kang, X. et al. *Nat. Synth.* https://doi.org/10.1038/s44160-024-00640-3 (2024).
7. Mitra, R., Zhu, H., Grimme, S. & Niemeyer, J. *Angew. Chem. Int. Ed.* **56**, 11456–11459 (2017).
8. Dong, J., Liu, Y. & Cui, Y. *Acc. Chem. Res.* **54**, 194–206 (2021).
9. Riebe, J. & Niemeyer, J. *Eur. J. Org. Chem.* **2021**, 5106–5116 (2021).

Competing interests

The authors declare no competing interests.