

COMMENTARY

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A focus on a complex abiotic tertiary structure

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In contrast to the many well-defined helical secondary structures of foldamers reported thus far, examples of tertiary molecular structures of foldamers remain rare with the development of such folded structures being still in its infancy. While the direct design of foldamer tertiary structures still presents a daunting challenge, a realistic strategy for developing unimolecular tertiary structures of foldamers involves covalently linking the molecular components of known quaternary structures of foldamers that have been reported in recent years. Wang *et al.* (S. Wang, J. Sigl, L. Allmendinger, V. Maurizot and I. Huc, *Chem. Sci.*, 2025, 16, 1136–1146, <https://doi.org/10.1039/D4SC07336C>), by starting from a C_3 -symmetrical, hydrogen-bonded homochiral parallel bundle of three aromatic helices, used rational principles and molecular modeling to convert the trimolecular object into a unimolecular helix-turn-helix-turn-helix tertiary structure that represents the most complex abiotic tertiary structure known to date.

The folding and assembly of biomacromolecules have inspired the creation of various foldamers, artificial oligomers that fold into well-defined three-dimensional structures. Efforts over the past three decades have led to the creation of numerous foldamers that adopt well-defined secondary structures, most of which are helices.^{1–6} The availability of these discrete secondary structures has prompted efforts to design higher-level structures inspired by the tertiary and quaternary structures of proteins. Similar to those exhibited by peptides and proteins, including designed protein structures, the availability of tertiary and quaternary structures in foldamers should significantly expand the diversity of functions that can only be expressed at these structural levels, with applications in a range of fields including chemistry, biology, biomedical science, and materials science.

An early observation by Gellman *et al.* on the assembly of a β -peptide provided the first indication of a helical bundle, a quaternary structure of a foldamer.⁷ Indeed, in the solid state or in solution, for foldamers, many more examples of

well-defined quaternary structures than tertiary structures have been observed. Most known foldamer quaternary structures consist of secondary structures, primarily various helices. An intriguing approach for developing tertiary structures of foldamers is to covalently link the secondary structural components of known quaternary structures. DeGrado *et al.* subsequently reported a two-helix bundle consisting of β -peptide helices linked *via* a disulfide bond.⁸ Other examples of foldamer tertiary structures include, but are not limited to, the peptoid helix bundles by Zuckermann and Dill,⁹ the β -peptide bundles reported by Schepartz,¹⁰ the sequence-guided backbone alteration by Horne,¹¹ the AApeptide zipper by Cai,¹² and the oliguria helix bundles by Guichard.¹³

Despite ongoing efforts, the development of protein-like tertiary structures with foldamers remains a significant challenge and is still in its infancy due to several reasons: (1) protein tertiary structures depend on a highly complex network of non-covalent interactions, whereas foldamers often lack the precise combination and tunability of such interactions, which are essential for achieving complex folding and assembly; (2) the synthesis of proteins is highly efficient, thanks to evolutionary

advantages developed over millennia. In contrast, the synthesis of abiotic foldamers is limited by fewer available synthetic strategies and presents considerable challenges; (3) while protein tertiary structures are both dynamic and stable, it is still difficult to synthetically balance the rigidity and flexibility of foldamers.

The Huc group has been leading the development of tertiary structures for aromatic foldamers composed of aromatic rings in their main chain.¹⁴ Many aromatic foldamers, especially aromatic oligoamide foldamers,^{4,6} offer stably folded conformations, which enables the construction of higher-order structures with unique properties and functions that otherwise are unattainable with biomacromolecules.

The current work by Wang *et al.* involves the design of a unimolecular, three-helix bundle consisting of covalently linked aromatic helices that engage in hydrogen-bonding interactions (<https://doi.org/10.1039/D4SC07336C>).¹⁵ Starting from the known crystal structure of a C_3 -symmetrical homochiral, parallel bundle consisting of three aromatic helices that are held together by intermolecular hydrogen bonds,¹⁴ the authors, based on rational principles and molecular modeling, are able to

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Examining the folding of oligomers **7b** and **8b**, which differs by having linkers T6f and T6r, respectively, revealed the folding of **8b** into an abiotic unimolecular three-helix bundle in CD₂Cl₂.

The current contribution presents a systematic and easy-to-follow approach based on rational principles, molecular modeling, and meticulous structural characterization. The developed method should be generally applicable for converting other known quaternary structures of foldamers into tertiary molecular structures by carefully considering the alignment of secondary structural components and by designing appropriate covalent linkers.

Author contributions

B. G. wrote the manuscript with input and assistance from Y. L. Z.

Conflicts of interest

There are no conflicts to declare.

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