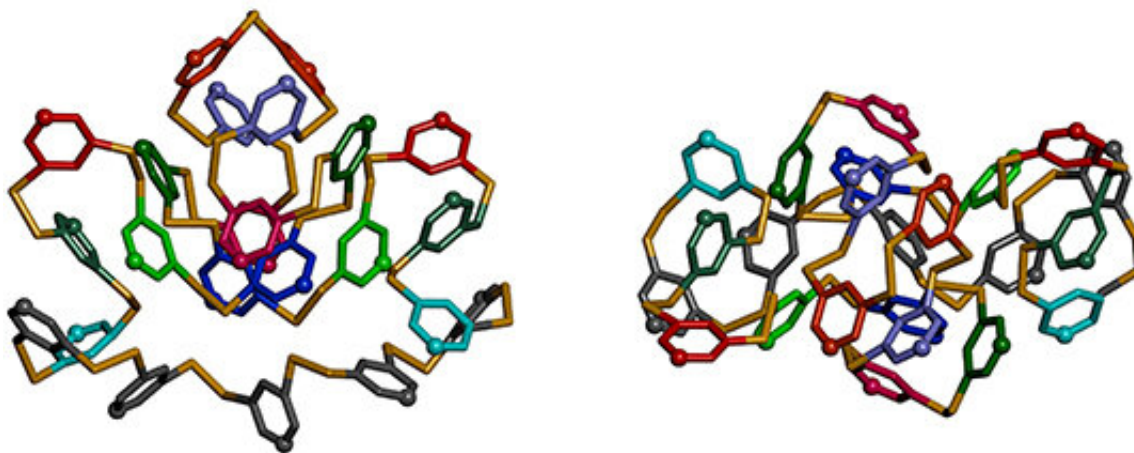


Creating self-constructed folded macrocycles with low symmetry

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Two views of the main chain of the crystal structure of a perfectly unimolecular 23mer that spontaneously forms from a single monomer. Credit: Huc Group

The synthesis and self-organization of biological macromolecules is essential for life on earth. Ludwig Maximilian University of Munich chemists now report the spontaneous emergence of complex ring-shaped macromolecules with low degrees of symmetry in the laboratory.

Monomers, molecules that are made up of multiple repeating subunits that may vary or not in their [chemical structure](#), are classified as macromolecules or polymers. Examples exist in nature, including proteins and nucleic acids, which are at the heart of all biological systems. Proteins not only form the basis of structural elements in cells,

they also serve as enzymes—which catalyze essentially all of the myriad of chemical transformations that take place in living systems.

In contrast, nucleic acids such as DNA and RNA serve as informational macromolecules. DNA stores the cell's genetic information, which is selectively copied into RNA molecules that provide the blueprints for the synthesis of proteins. In addition, long chains composed of sugar units provide energy reserves in the form of glycogen, which is stored in the liver and the muscles. These diverse classes of polymeric molecules all have one feature in common: They spontaneously fold into characteristic spatial conformations, for example the famous DNA double helix, which in most cases are essential for their biochemical functions.

Professor Ivan Huc (Department of Pharmacy, LMU) studies aspects of the self-organization processes that enable macromolecules to adopt defined folded shapes. The molecular structures found in nature provide him with models, whose properties he tries to reproduce in the laboratory with non-natural molecules that are neither proteins, [nucleic acids](#) or sugar-like. More specifically, he uses the tools of synthetic chemistry to elucidate the underlying principles of self-organization—by constructing molecules that are expressly designed to fold into predetermined shapes. Beginning with monomers that his group has developed, he sets out to produce what he calls 'foldamers,' by assembling the monomers one by one to generate a folded macromolecule.

Structures with low degrees of symmetry

"The normal way to get the complex structure of proteins is to use different types of monomers, called [amino acids](#)," as Huc reports. "And the normal method to connect different amino acids in the the correct order is to link them one by one." The sequence of amino acids contains

the folding information that allows different protein sequences to fold in different ways.

"But we discovered something unexpected and spectacular," says Huc. He and his colleagues in Munich, Groningen, Bordeaux and Berlin used organic, sulfur-containing monomers to spontaneously get cyclic macromolecules with a complex shape, as illustrated by their low degree of symmetry, without requiring a specific sequence. The macromolecules self-synthesize—no further conditions are necessary. "We only put one monomer type in a flask and wait," Huc says. "This is typical for a polymerization reaction, but polymers from a single [monomer](#) usually don't adopt complex shapes and don't stop growing at a precise chain length."

To further control the reaction, the scientists also used either a small guest molecule or a metal ion. The regulator binds within the growing macromolecule and causes monomers to arrange themselves around it. By choosing a regulator with the appropriate characteristics, the authors of the new study were able to produce structures with a predetermined number of subunits. The cyclic macromolecules exhibited low levels of symmetry. Some consisted of either 13, 17 or 23 subunits. Since 13, 17 and 23 are prime numbers, the corresponding folded shapes exhibit low degrees of symmetry.

A model for biological and industrial processes

Interest in the elucidation of such mechanisms is not restricted to the realm of basic research. Huc and his colleagues hope that their approach will lead to the fabrication of designer plastics. Conventional polymers usually consist of mixtures of [molecules](#) that vary in length (i.e. the number of monomers they contain). This heterogeneity has an impact on their [physical properties](#). Hence, the ability to synthesize polymer chains of an exact length and/or geometry is expected to lead to materials with

novel and interesting behaviors.

Furthermore, foldamers like those that have now been synthesized show close structural resemblances to biopolymers. They therefore offer an ideal model system in which to study the properties of proteins. Every protein is made up of a defined linear (i.e. unbranched) sequence of amino acids, which constitutes its "primary structure." But most amino-acid chains fold into local substructures such as helically coiled stretches, or parallel strands that can form sheets. These units represent the [protein](#)'s secondary structure. The term 'tertiary structure' is applied to the fully folded single chain. This in turn can interact with other chains to form a functional unit or quaternary [structure](#).

Huc's ultimate goal is to mimic complex biological mechanisms using structurally defined, synthetic precursors. He wants to understand how, for example, enzymes fold into the correct, biologically active conformation following their synthesis in cells. Molecules whose properties can be precisely controlled in the laboratory provide ideal models with which to work out the answers and perhaps to go beyond enzymes themselves.

The study is published in *Nature Chemistry*.

More information: Charalampos G. Pappas et al. Emergence of low-symmetry foldamers from single monomers, *Nature Chemistry* (2020). [DOI: 10.1038/s41557-020-00565-2](https://doi.org/10.1038/s41557-020-00565-2)

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