News & views

Supramolecular chemistry

Molecules self-assemble into nanoscale chains

Guillaume De Bo

Non-covalent interactions can assemble molecules into complex architectures, but with limited control of the resulting topology. A method for assembling nanoscale chains shows how specific architectures can be targeted. **See p.400**

Complex molecular architectures are usually constructed by connecting a variety of building blocks together in a stepwise manner. But sometimes, complex structures emerge from the self-assembly of a single constituent. On page 400, Datta *et al.*[1] show how polycatenanes – chains made of interlocked nanometre-scale rings – can be formed by the remarkable self-assembly of a simple molecular building block.

Catenanes are molecules in which two or more molecular rings are entangled like the links of a chain[2]; indeed, their name derives from *catena*, the Latin word for chain. The rings are not connected by a covalent bond, but instead form a different kind of linkage called a mechanical bond, in which the connected rings can move freely around each other. This dynamic property makes them useful as components of artificial molecular machines[3]. Many catenanes reported so far consist of only two rings. The construction of molecular chains made of several rings is a major challenge for synthesis, and has been achieved only in the past few years, for small molecular rings (with a radius of approximately 1 nanometre)[4].

The construction of larger systems is limited by the efficiency of the catenation step, in which a preassembled toroid precursor forms a ring that interlinks through another toroid; moreover, a large number of covalent bonds must be formed in the preassembled structure. Synthetic routes that involve non-covalent assembly techniques are therefore preferred[5]. In supramolecular polymerization, for example[6], simple molecular building blocks self-assemble in a single step through non-covalent interactions to form large-scale structures of varied geometries. Unfortunately, the gain in size of the assemblies that are made in this way often comes at a price: chemists have less control of the final construct's architecture, compared with a multistep covalent strategy.

Datta and co-workers have combined aspects of covalent and non-covalent strategies to form their complex polycatenane structures. The authors started with a monomer composed of a polar head and a non-polar tail, separated by a rigid section consisting of benzene rings (Fig. 1). Six of these monomers can self-assemble in an appropriate solvent to form a star-shaped 'rosette'. The polar heads form a hexagonal core that is held together by hydrogen bonds – in much the same way that DNA helices are held together by hydrogen bonds in nucleotide base pairs – and the rigid sections point outwards from the core like arms.

Once formed, the rosettes self-assemble by stacking on top of each other – a process driven by the formation of interactions (known as π–π interactions) between the rigid regions of neighbouring rosettes. Because each rosette added to the stack is slightly offset from its predecessor, the resulting assembly grows with an intrinsic curvature that produces various geometries: random coils, helicoids and toroids[7]. The type of geometry that forms depends on the rate of cooling of the initial monomer solution. Slow cooling (about 1 kelvin per minute) favours the formation of helical fibres; faster cooling (about 10 K min^{-1}) generates random coils; and abrupt cooling adds toroids into the mix.

Datta and colleagues noticed that rapid cooling also produced traces of catenanes consisting of two interlocking toroids. This suggested that individual toroids could act as secondary sites from which another ring could grow, thereby forming the catenated dimers. The authors took advantage of this fortuitous process to devise a protocol for making large, self-assembled polycatenanes by using a solution of toroids as 'seeds' for catenation.

The authors rapidly cooled a solution of the monomer in a solvent mixture that was chosen to facilitate toroid formation,

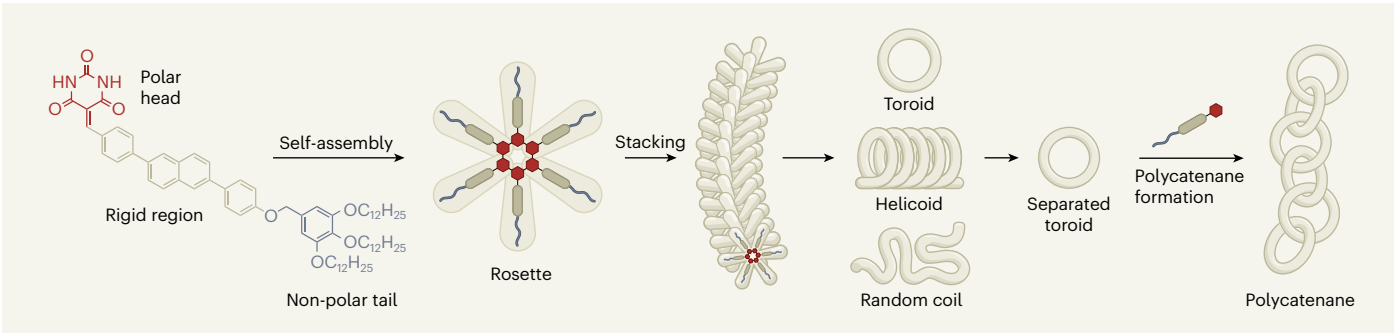

Figure 1 | Self-assembling polycatenanes. Datta *et al.*[1] report that molecules consisting of a polar head, a rigid central region and a non-polar tail self-assemble into 'rosettes', which then stack together into fibres that form various nanoscale structures, such as toroids, helicoids and random coils. The authors devised a protocol in which they separate the toroids, and use them to 'seed' the formation of new catenated rings – thereby producing polycatenane structures in which up to 22 toroids are connected in linear chains or branched systems.

and thereby produced a solution in which approximately half of the monomer molecules were incorporated into toroids; the remaining monomers self-assembled into randomly coiled linear structures. Because the toroids are more stable to heat than are their linear counterparts, the authors could selectively disassemble the coils back into monomers by heating the solution. Subsequent slow cooling promoted the formation of long, helical supramolecular assemblies from the monomers, leaving the toroids intact. Datta *et al.* then filtered the mixture to remove the long helical structures, thus producing a solution that predominantly contained toroids.

Finally, the authors produced polycatenanes by adding monomers to the solution of toroids, which seeded the formation of new catenated rings, as had been hoped. The non-polar tails were originally incorporated into the monomers to improve monomer solubility, but Datta and colleagues found that they also have a crucial role in the seeding process: unfavourable interactions between the tails and the solvent makes it more likely that rosette self-assembly will initiate on the surface of existing toroids.

Atomic force microscopy revealed that polycatenanes of various sizes form in the reactions, and that the toroids have a radius of 12.5 nm. The authors found that addition of monomers in small portions favours the initiation of self-assembly processes that lead to catenation and were thus able to produce linear and branched polycatenanes containing up to 22 rings. This is close to the number previously achieved using covalent assembly (up to 26 rings in linear polycatenanes)[4], and further demonstrates the effectiveness of Datta and colleagues' approach for synthesizing complex, non-covalent structures.

The authors' protocol also shows that a multistep approach, borrowed from the covalent-synthesis playbook, can be used to produce large and complex self-assembled architectures in a controllable way. This is an important step in the development of non-covalent synthesis, and it can be expected that their protocol will inspire the field to tackle more-challenging targets[5]. It would be interesting to see, for example, whether the monomer can be adapted to obtain catenated rings of various sizes, or whether hetero-catenanes can be made, in which the seed toroid consists of a different type of monomer from the one from which the catenated macrocycles are assembled.

It remains to be seen how the mechanical and dynamic properties of the self-assembled polycatenanes compare with those of their smaller covalent counterparts. A main appeal of covalently assembled catenanes is that, if the relative motion and position of the rings can be controlled, it opens up potential applications for molecular machines. The possibility of achieving the same level of control over large, self-assembled structures would bring us a little closer to what nature achieves with cellular machinery.

Guillaume De Bo is in the Department of Chemistry, University of Manchester, Manchester M13 9PL, UK.
e-mail: guillaume.debo@manchester.ac.uk

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Neuroscience

Young brains welcome protein

Roeben N. Munji & Richard Daneman

The discovery that larger quantities of blood-borne proteins enter the brains of young, healthy mice than enter those of aged animals will alter our understanding of the blood–brain barrier, and how it changes with age. **See p.425**

The blood vessels in the brain have properties that limit their permeability to blood-borne ions, molecules and cells[1]. This blood–brain barrier (BBB) is crucial for proper neuronal function and for protecting the brain from harm, but it is also a major impediment to drug delivery[1]. It has been proposed that the BBB becomes more permeable with age, but on page 425, Yang *et al.*[2] find something quite different. They show that the BBB allows blood-borne proteins to enter the healthy brain at a much higher rate than previously thought, and that the overall amount of plasma proteins entering the brain actually decreases with age. The authors' work could help researchers to understand how the brain responds to systemic protein signals, and the role of the BBB in age-related cognitive decline. It might also lead to improved approaches for delivering drugs into the brain.

The BBB is sometimes thought of as a static, impenetrable barrier. In reality, it has many dynamic properties — physical, transport, immune and more — that together tightly regulate the movement of molecules between the blood and the brain, thus controlling the brain's molecular environment. A key question is s what exactly gets across the BBB?

Yang *et al.* addressed this by examining how the proteins found in blood plasma enter the brain. Whereas previous studies[3–5] have traced the movement of injected, exogenous proteins (those not native to the organism), Yang and colleagues labelled endogenous mouse plasma proteins and injected them back into mice. In this way, they could track the movement of proteins that normally interact with the mouse BBB. They found that, in healthy young adult mice, a much higher quantity of plasma proteins than was previously thought enters the brain, and therefore has the potential to interact with the neuronal circuitry. This finding suggests that a wide variety of neural functions, including mood and behaviour, could be modulated by systemic protein signals.

The authors went on to show that the amount of plasma protein that permeates the brain is lower in old than in young mice. This was surprising because multiple studies that used exogenous tracers have shown that BBB permeability increases with age, and have highlighted this increase as a contributing factor to age-related cognitive decline[6,7].

Yang *et al.* reconciled these seemingly disparate results by demonstrating age-related changes in the mechanism by which proteins are transported across the endothelial cells that line blood vessels of the BBB (Fig. 1). In young adults, the predominant method of transport involves the binding of specific proteins to plasma-membrane receptors on endothelial cells. These receptors become incorporated into vesicles and are transported across the cells – a process called receptor-mediated transcytosis. In aged mice, receptor-mediated transcytosis is significantly reduced and non-receptor-mediated (nonspecific) transcytosis increases, leading to nonspecific entry of a larger variety of plasma proteins into the brain. Previous studies that used exogenous molecules probably measured only nonspecific transcytosis, thus missing the vast majority of plasma-protein permeation into the young brain. The finding that the specificity of protein entry