the sensitivity of NMR detection using this technique is likely to be high and should also be free of signal interference from other molecules. Incorporating trifluoromethyl moieties as part of the lipophilic portion of the amphiphile provides the required NMR-active label. Furthermore, the sharpness of the ^{19}F NMR signal is sensitive to the apparent molecular weight of the system, and when part of a 200–500 nm assembly, it is rather broad and not realistically observable. However, when the protein–ligand part of the amphiphile is bound to the protein, the aggregate is disassembled, resulting in a sharp ^{19}F NMR signal. Interestingly, the system is reversible, and when an inhibitor specific to the target protein is added, it displaces the amphiphilic probe, aggregation results, and the ^{19}F NMR signal disappears again.

The versatility of the method has been demonstrated with three different ligand–protein combinations. Furthermore, selective binding and signal generation have been demonstrated in a mixture of proteins. Perhaps the most impressive results involve the detection of human carbonic anhydrase (hCA) inside live red-blood cells. As benzenesulfonamides are known to be good ligands for hCA, amphiphilic assemblies containing this functionality were used to image hCA using ^{19}F MRI. Furthermore, they were able to demonstrate that the signal generation is indeed due to ligand–hCA binding by showing that the MRI signals were not obtained in the presence of inhibitors for the enzyme. This demonstrates that the reversibility of the protein-induced disassembly can also be achieved inside the cells. The apparent ability of these small molecules to be transported across the lipid bilayer and then to reassemble inside cells is both surprising and exciting. One would expect that such small-molecule-based amphiphilic assemblies would simply disassemble on encountering the lipid bilayer. The fact that these reassemble inside the cells is intriguing. Exploring the fundamental factors that control the intracellular delivery and reassembly inside the cells would be very interesting.

As the Kyoto team points out, ^{19}F MRI is still in its infancy, and the practical implications of this finding could take some time to be realized. Moreover, the sensitivity reported in these systems is in the micromolar range. It is important that the detection limits are improved to nanomolar or subnanomolar range, and a variety of approaches could be taken to potentially achieve this. Nonetheless, this exciting work shows that the emerging concept of supramolecular-disassembly-based sensing holds great promise in biosensing and medical diagnostics. ❐

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SUPRAMOLECULAR CHEMISTRY

Form leading to function

In a Dutch city famous for the treaty that led to the creation of the European Union, delegates gathered at a conference to discuss recent advances in the chemistry of macrocyclic and supramolecular systems.

Oren A. Scherman

Whereas the twentieth century witnessed the synthetic chemist ably assembling atoms into complex molecules, the twenty-first century is primed to see synthesis move towards the construction of complex multicomponent systems. But, just "how far can we push self-assembly[1]?" This question is at the root of many of the research problems being tackled by those who attended the Fourth International Symposium on Macrocyclic and Supramolecular Chemistry in Maastricht, the Netherlands, at the end of June. The meeting, organized by Roeland Nolte and Alan Rowan, spanned the entire spectrum of supramolecular chemistry. Key players in the field presented their latest results, a few of which are highlighted below.

A clear theme that ran through many of the lectures and much of the discussion in Maastricht was the topic of functional self-assembled systems. Bert Meijer suggested that the accomplishments of the previous century that enabled synthetic chemists to progress from Wöhler's nitration of benzene to Pederson's macrocycles and beyond have set the backdrop for today's supramolecular chemists to make systems that rival the complexity of cells. Once target functional architectures have been defined, this lofty goal will undoubtedly require multistep supramolecular synthesis and perhaps even new methodologies, such as the use of supramolecular protecting groups[2]. What is clear is that our understanding of self-assembly in relatively simple systems must be developed for self-organizing assemblies that possess much higher degrees of complexity.

Understanding the way in which a functional supramolecular polymer forms — either through an isodesmic, step-growth-like mechanism or a nucleation-growth cooperative self-assembly process — and controlling such processes will be critical

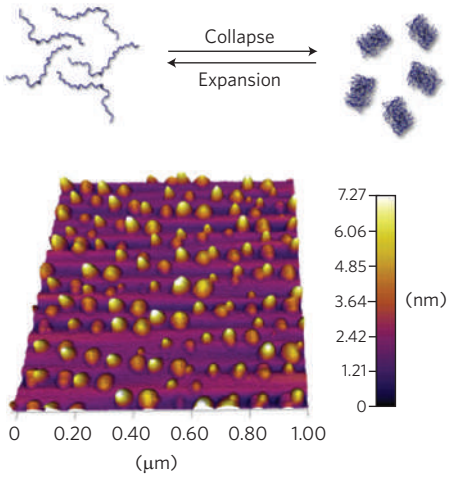

Figure 1 | Collapse and expansion of single polymer chains into nanoparticles. On dilution and subsequent deprotection of the UPy moiety, single polymer chains collapse into metastable nanoparticles. Image courtesy of Bert Meijer.

in developing new synthetic systems with complexity we have yet to engage. Meijer discussed his recent work in nucleated-growth polymerization, describing how he could take a system of non-chiral molecules and arrive at a fully chiral self-assembled structure[3]. He finished his talk with some very novel ways of introducing single-chain collapse into a folded and compartmentalized structure through a combination of protection/deprotection steps and dilution.

Meijer and co-workers accomplished this latter objective by preparing a norbornene-based monomer bearing a nitrobenzyl-protected ureidopyrimidinone (UPy) moiety. Incorporation of this functional monomer into a polynorbornene copolymer was achieved using ring-opening metathesis polymerization (ROMP). While the quintessential quadruple hydrogen-bonding UPy unit was present in a protected form, no inter- or intrachain hydrogen bonding occurred and the polymer adopted a random coil conformation. However, on dilution (to avoid crosslinking between chains) and subsequent light-induced deprotection of the nitrobenzyl group, single chains collapsed individually to form nanoparticles as the UPy moieties formed multiple hydrogen-bonded interactions with each other along the polymer chain. These metastable, shape-persistent nanoscale objects could be observed and characterized both in solution and on a solid support (Fig. 1). One can only presume that subsequent publications on 'metastable single-chain nanoparticles'[4] from the Meijer group, will disclose how to harness function from these unimolecular compartmentalized systems.

Hanadi Sleiman discussed a variety of higher-order three-dimensional (3D) structures that she and her co-workers had prepared from DNA-based components. They recently described a method of preparing a library of discrete 3D structures from a relatively small set of DNA building blocks. Of particular note is the fact that these DNA nanostructures are dynamic and can be altered with an external stimulus or agent, paving the way to new applications where reversible structural control and switching with shape persistence are required[5]. Sleiman then went on to describe how the introduction of metals — such as gold nanoparticles — at the vertices of the 3D DNA structures adds structural rigidity and has enabled the formation of shapes such as cubes, squares and stars. The structure and overall alteration of the geometric shape can be tuned by adding new components 'post-assembly'. In this way, Sleiman hopes to use this newly found control over the assembly of 3D DNA objects to introduce function for different sensing and catalytic applications that have not been possible with previous, less rigid DNA intersections alone[6].

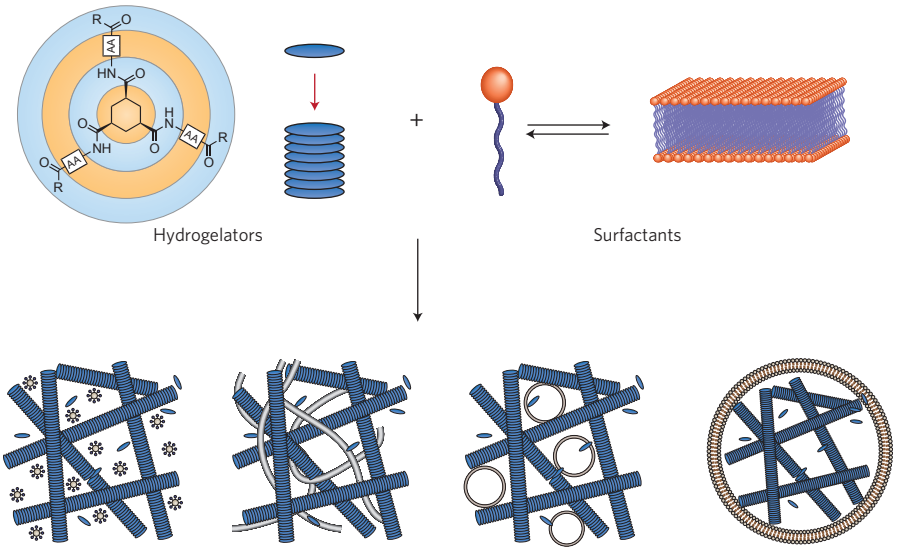

Figure 2 | Formation of hierarchical hydrogels through the orthogonal self-assembly of both hydrogelators and surfactants. The simultaneous self-assembly of trifunctional core-based hydrogelators with surfactants can be controlled over a variety of length scales, allowing for a network to form in the presence of vesicles and spherical or cylindrical micelles. Figure courtesy of Jan van Esch.

Continuing with the theme of functional nanomaterials, Jan van Esch described his recent research in hierarchical hydrogel assemblies. His group aims to prepare such materials through a process that can be referred to as orthogonal self-assembly, in which different structures — each with their own characteristics — are formed independently and can coexist within a single system. In some of the systems described by van Esch, surfactants self-assemble in the presence of low-molecular-weight gelators[7]. The self-assembly of these two disparate classes of molecules enables the formation of new and more complex compartmentalized architectures, such as interpenetrating networks and vesicle configurations that coexist with gel fibres (Fig. 2). He believes that new function will be imparted to these nanomaterials by gaining control over geometric constraints, as well as being able to fine-tune aggregate size and structure.

In one of the final talks of the meeting, Jonathan Nitschke described his work on a hollow tetrahedral self-assembled cage capable of binding white phosphorus (P_4) within its hydrophobic internal cavity, rendering this ordinarily pyrophoric guest air-stable[8]. The air-sensitivity of the encapsulated guest could be turned back on by adding a competing guest, thus enabling an external means of controlling the reactivity of phosphorus. Nitschke's demonstration that extremely reactive reagents can be harnessed and unleashed to perform on command will certainly find use in a variety of new applications in self-organized complex systems.

It is clear that function arising from form and structure, and uncovering new routes to control reactivity will be key areas of research as we tackle just how far we are able to push self-assembly. We are certainly poised to embark on a journey from the small-molecule world to complexity-rich, self-organized supramolecular systems. ❐

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