News & views

Supramolecular chemistry

Self-assembly of molecules triggered by electricity

Robert Francke

The options for controlling molecular self-assembly processes have been limited. A fresh approach uses electrons to facilitate self-assembly, and thereby provides precise external control over the process. **See p.265**

Molecular recognition is the formation of specific interactions between two or more molecules through non-covalent bonding, and has a crucial role in biological systems. Chemists have long been working to achieve molecular recognition between synthetic molecules under non-biological conditions: when molecules with specific properties are brought together, they self-assemble spontaneously until an equilibrium ratio between the number of free and assembled molecules is reached. However, so far, only a few options have been available for steering the time course of the process. On page 265, Jiao *et al.*[1] present a method that uses electrochemical reduction of the components to trigger molecular assembly. This ground-breaking approach enables assembly to be switched on and off at will, allows the assembly rate to be tuned, and can generate stable solutions containing almost any possible ratio of assemblies and free molecules.

The countless examples of molecular recognition in biological systems include the interactions between ligands and receptors on enzymes, the docking of antibodies on antigen molecules and the binding between DNA and proteins. Molecular recognition is therefore a cornerstone of metabolic processes, the immune system and various drug therapies. Unsurprisingly, chemists have been inspired by the fascinating and intricate recognition mechanisms in nature, and have worked for decades to recreate them with non-biological molecules in the laboratory[2,3]. The study of such self-assembly processes and the resulting structures is referred to as supramolecular chemistry.

The prerequisite for the self-assembly of two molecules is that the binding partners, often referred to as the host and the guest molecules, are equipped with compatible binding sites in a complementary spatial arrangement — analogous to a lock with a matching key. Molecules must therefore be carefully designed and synthesized to enable molecular recognition under artificial conditions. Non-covalent interactions such as hydrogen bonding, van der Waals forces and π–π interactions then serve as the glue that holds the host and the guest together.

Molecular assembly usually proceeds spontaneously on preparation of a solution of two or more suitable components in a flask. The degree of assembly — that is, the ratio of the unbound molecules and assembled architectures — is determined by the chemical properties of the host–guest couple and by the medium (the solvent, pH and temperature). It follows that, for a specific set of conditions, neither the rate of the assembly process nor the composition of the mixture can be adjusted.

To control the course of the process, a mechanism is needed that switches the interactions between binding sites on and off using an external stimulus. This is the capability that Jiao *et al.* have accomplished in their proof-of-concept study. The authors used a macrocycle (a large, ring-shaped molecule) as a host and a dumb-bell-shaped molecule as a guest. Both molecules initially carry two positive charges (Fig. 1a), which prevents the formation of host–guest complexes as a result of repulsion between the charges (Coulombic repulsion).

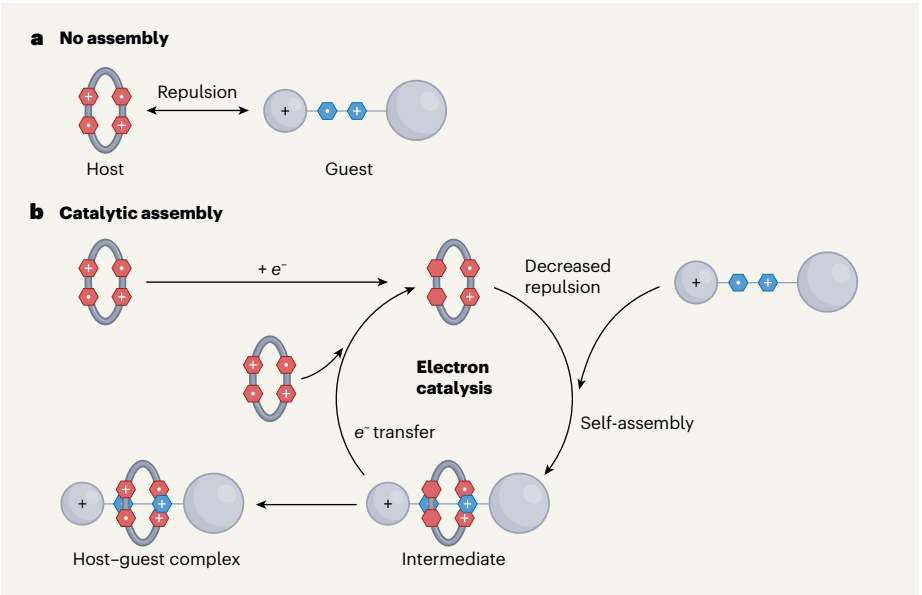

Figure 1 | Electron catalysis for molecular self-assembly. Jiao *et al.*[1] report a system in which electrons drive the self-assembly of a 'host' and a 'guest' molecule. **a**, Initially, the host carries two positive charges and two unpaired electrons (shown as dots; the molecular regions that contain the unpaired electrons are charge neutral). The guest carries two positive charges and one unpaired electron. Charge repulsion prevents the molecules from self-assembling. Hexagons represent potential binding sites for self-assembly. **b**, Transfer of an electron (e^-) into a host (or into a guest, not shown) reduces the positive charge on the molecule and lowers the number of single unpaired electrons. This decreases repulsion between the host and guest, enabling them to self-assemble into an intermediate complex through non-covalent interactions between binding sites. Loss of the electron from the intermediate interlocks the desired host–guest complex. The electron passes to another host molecule, restarting the catalytic cycle with the fresh host. The source of electrons can be either reductant compounds or an electric current.

To initiate assembly, the researchers made use of electron catalysis — a widely used strategy for inducing the formation of covalent bonds in synthetic organic chemistry[4,5]. Introduction of an electron into one of Jiao and colleagues' molecules lowers the Coulombic repulsion to such an extent that the dumb-bell can enter the macrocycle. In other words, the configuration of the key (the guest) is set so that it fits perfectly into the lock (the host) — or vice versa, if an electron is added to the host, rather than to the guest (Fig. 1b).

Once the dumb-bell is situated in the macrocycle, the binding sites in the host and guest can dock with each other through non-covalent interactions. In this case, the interactions are produced by the pairing up of radicals, and of electron donor and acceptor groups. Moreover, the resulting complex can now pass the activating electron on to another unbound molecule. This electron-transfer step locks the dumb-bell into the macrocycle and simultaneously sets off a chain of further transfers, leading to the formation of more complexes.

Jiao *et al*. first demonstrated this catalytic concept by using chemical reagents (reductants) as the electron source, but then went on to replace the reductants with electric current. In the latter approach, electrons are injected into molecules at the cathode surface in an electrochemical cell. Notably, the rate of molecular self-assembly can be conveniently controlled by the current intensity, and the process can be initiated and interrupted as desired by switching the current on and off.

Another advantage of the cathode-driven process is that it is clean — no waste is produced from the electron source, unlike when chemical reductants are used. And, in contrast to conventional molecular-recognition processes, the ratio of molecular assemblies to free molecules can be adjusted at will. A strength of the work is that the authors combined a wide variety of techniques to collect conclusive evidence for the proposed catalytic mechanism.

Electron-catalysed self-assembly is a pivotal addition to the toolbox of supramolecular chemistry, and will inspire chemists to develop new means of controlling non-covalent binding events and to orchestrate molecular assembly at extended length scales. Furthermore, Jiao and colleagues' work might serve as a starting point for the development of new forms of complex matter[6].

One of the current limitations is that the assembly process cannot yet be reversed under the given conditions. A future challenge could therefore be to develop a bidirectional approach, in which two different stimuli (such as positive and negative currents) can be used to switch between assembly and disassembly. This could, for example, eventually enable the synthesis of supramolecular materials whose properties can be controlled by electrical pulses. Exciting developments in the field of electrically stimulated self-assembly are to be expected in the future.

Robert Francke is in the Department of Electrochemistry & Catalysis, Leibniz Institute for Catalysis, 18059 Rostock, Germany.
e-mail: robert.francke@catalysis.de

1. Jiao, Y. *et al. Nature* **603**, 265–270 (2022).
2. Philp, D. & Stoddart, J. F. *Angew. Chem. Int. Edn* **35**, 1154–1196 (1996).
3. Persch, E., Dumele, O. & Diederich, F. *Angew. Chem. Int. Edn* **54**, 3290–3327 (2015).
4. Studer, A. & Curran, D. P. *Nature Chem.* **6**, 765–773 (2014).
5. Francke, R. & Little, R. D. *ChemElectroChem* **6**, 4373–4382 (2019).
6. Aida, T., Meijer, E. W. & Stupp, S. I. *Science* **335**, 813–817 (2012).

The author declares no competing interests.

Medical research

Multiple sclerosis sparked by virus-led autoimmunity

Hartmut Wekerle

Understanding factors that lead to the development of multiple sclerosis might aid efforts to develop new therapies. Clinical data now implicate a viral culprit and immune-system dysfunction as underlying factors in this condition. **See p.321**

Most people who study multiple sclerosis (MS) propose that the factors underlying initiation of the disease enter the central nervous system (CNS) from outside the brain. The debate about the nature of these factors has split researchers into two main camps. Most see autoimmunity as the driving factor for the illness, but a minority invoke viral culprits. On page 321, Lanz *et al*.[1] report evidence that might settle this debate through a compromise solution.

Supporters of the autoimmunity thesis point to compatible evidence such as the particular patterns of inflammatory injuries in MS; genetic risk factors involving immune-related genes; and immunotherapy treatments that help to relieve the condition[2]. However, a universally accepted culprit that could be the prompt for an abnormal immune response leading to MS has been missing until now. For the proponents of a viral origin, analysis of human populations using epidemiological evidence from the clinic provides compelling data coupling MS with the Epstein–Barr virus[3]. But this associative connection lacked a causal, disease-triggering link.

Lanz *et al*. examined antibodies obtained from the cerebrospinal fluid (CSF) of people with MS, and identified antibodies that recognize small regions of protein (antigens) corresponding to proteins of the Epstein–Barr virus. The authors report that such antibodies also recognize the protein GlialCAM, which is a component of glial cells in the brain. This result indicates that GlialCAM can act as a target of these antibodies, providing an 'autoantigen' for self-directed autoimmunity; it also suggests that this contributes to the events leading to MS.

Importantly, Lanz and colleagues' data indicate that these crossreactive antibodies evolve from ones that recognize only the virus, through a process of antibody refinement. In samples of CSF from people with MS, the level of immunoglobulin proteins (which form antibodies) are higher than those in the CSF of healthy people, and this is a diagnostic sign of MS. A technique called electrophoretic separation shows that these immunoglobulins form discrete bands in the electrophoresis analysis, which are produced by individual families (clones) of B cells. These bands, called CSF-specific oligoclonal bands (OCBs), are absent from blood plasma samples. The nature of the antigens that these immunoglobulins recognize is debated. Previous studies indicated that these OCB antibodies bound to various ubiquitous intracellular proteins, but not to CNS-specific autoantigens, raising doubts about whether such antibodies cause disease[4].

Lanz *et al*. revisited this topic taking a straightforward and powerful approach. They isolated antibody-producing B cells of the immune system called plasmablasts from CSF samples of people with early-stage MS (Fig. 1). The authors characterized the cells individually and assessed their antigen receptors; the genes encoding these receptors provide an initial blueprint that is modified to form the antibodies that the mature, activated cells produced. The plasmablasts expressed markers on their surface indicating ongoing activation of these cells, possibly indicating antigen recognition — but they did not express proteins required for cell migration, which qualified them as being CNS residents. Key