The construction of supramolecular systems

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The construction of supramolecular systems

Self-assembly must be transformed into multistep synthesis to create complex structures

By Ghislaine Vantomme and E. W. Meijer

Self-assembly by intermolecular noncovalent interactions directed by self-recognition created the field of supramolecular chemistry (1). However, the word “self” appears to limit this field to mixing components in one assembly step where most of the complexity is inherent in the covalently synthesized reactants, rather than the result of a series of assembly steps that build more complex structures in reproducible procedures. The paradigm shift in supramolecular chemistry that we propose is the building of multicomponent systems following a multistep pathway—the emergence of molecular complexity (see the figure). The latter is not only directed by the information stored in the covalent framework of the components, but also controlled by the kinetics and thermodynamics of the reaction pathways selected in processing this information (2).

Although noncovalent synthesis was quoted by Whitesides and Reinhoudt in the 1990s (3, 4), it has never been broadly accepted or used. The main reason comes from the difficulty in manipulating the reactivity of the noncovalent bond, the dynamic nature of the structures formed, and a lack of physical organic characterization of the individual assembly steps. The noncovalent interactions involve forces weaker than their covalent counterparts with a larger participation of entropic energy, which makes the control of the structure-energy balance more delicate.

In the proposed multistep approach, the gradual construction of well-defined hierarchical architectures through multiple steps should not only simplify and accelerate the identification of new architectures, but also make understanding of the interactions involved more logical and effective. In this regard, the toolkit of reported single-step reactions is lacking, in that the rate of formation of the supramolecular entities, the yield, and the manner of purification at each step often are not reported. In addition, synthetic strategies must be identified that include orthogonal directed-assembly methods, compartmentalization mimicking cellular processes, and catalysts that favor one of the possible reaction pathways. Recent progress has shown that a clever combination of sequential noncovalent and covalent reaction steps can modify noncovalent synthetic products and ready them for another round of noncovalent reactions, or stabilize products once they are formed (5).

Both covalent organic chemistry and nature are sources of inspiration for arriving at complex structures. Most organic chemistry reactions do not proceed with 100% atom efficiency because of activation barriers and the need for protective groups. Moreover, they are controlled through kinetics rather than thermodynamics. These aspects are critical to selectively adapt the reactivity of the noncovalent bonds in complex architectures and perform chemical reactions without interfering with the assembled structures.

Nature uses a complex interplay of dissipative molecular networks structured and compartmentalized into highly organized hierarchical architectures coupled with balanced interactions. One fascinating and inspiring example is the formation of the collagen fibrils, beautifully combining covalent and noncovalent synthesis. The mechanism of their formation has been described as a multistep synthetic pathway from the transcription of messenger RNA inside the cell to the exocytosis of triple helices of procollagen, cleaved to form tropocollagen, which assembles into elongated fibril structures. This complex succession of processes is carefully regulated by control mechanisms, which ensure that the components interact correctly, detect the errors of assembly, and repair them.

Although mimicking this level of control is still out of reach for chemists, covalent organic syntheses have achieved a stunning level of efficiency and precision. What aspects can be borrowed for noncovalent synthesis? The ability to target particular sites for covalent reactions on a molecule often involves additional steps where an otherwise reactive site is rendered inert through
the addition of protecting groups. Catalysts are made more selective by the introduction of bulky ligands that favor one reaction outcome over another, especially in stereoselective synthesis. Each chemical reaction goes from a set of reactants to a final kinetic or thermodynamic product and follows a stepwise reaction mechanism selected and controlled by the external conditions (such as temperature, solvent, and reactant concentration) and fueled by a continuous flow of energy (either heating or the internal energy of reactants).

Similar principles can guide molecular assembly in the laboratory. In terms of sample preparation, the synthesis of vesicles by using cosolvents and sonication followed by filtering (6) is an example of noncovalent synthesis in a multistep approach to form hierarchically ordered structures. Because of the weak energies at stake, the forces generated by the experimental techniques during the sample preparation steps have an impact on the architectures formed (such as the forces of solvation by mixing with a cosolvent, or mechanical forces created by sonication, gravitation, and centrifugal forces in vortex tubes and Peltier cooling cells). These tools are frequently used to break kinetically trapped structures and manipulate the energy of competitive interactions (7). However, these forces have not been implemented commonly in noncovalent synthesis and will require the establishment of new experimental protocols to describe and standardize the processes.

In terms of spatial isolation, surfaces offer a platform for directing assembly to create structures with controlled heterogeneity. The layer-by-layer deposition of charged polymers (8) is one example, which has proven to be a powerful method to make functionalized stratified multilayer films with unique properties. Surface structuring by noncovalent synthesis is steered by noncovalent synthesis and will require the establishment of new experimental protocols to describe and standardize the processes.

A paradigm shift to noncovalent synthetic chemistry

Supramolecular chemistry must follow the same trajectory as organic chemistry to make complex structures that mimic those found in nature.

**Single step**

Nitrobenzene

**Covalent synthesis**

Organic chemistry began with single-step reactions of pairs of molecules. Strategies such as the use of protecting groups and catalysts enable the synthesis of complex molecules through multistep reactions.

**Noncovalent synthesis**

Single-step self-assembly of a few components, such as small molecules or polymers (red and blue), must shift to multistep synthetic strategies to mimic complex biological structures such as the extracellular matrix.

REFERENCES AND NOTES
