

# Introduction to the Molecular Recognition and Self-Assembly Special Feature

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**M**olecular recognition is a mature branch of chemical science, and why shouldn't it be? Decades of studies in physical organic chemistry have defined and evaluated the weak intermolecular forces involved when 2 molecules encounter each other. Every bimolecular reaction, whether it occurs in the gas phase, dilute solution, or an enzyme's interior, begins with a recognition event. It is an apt time to explore recognition in a larger context, that of multicomponent assemblies, and this special issue of 14 contributions is a beginning.

Molecules can be made to self-assemble spontaneously into multicomponent, complex structures when they are instructed to do so. The instructions exist in the form of the molecule's shape, its chemical surfaces, and how well it fills space in the phase where the assembly takes place. These instructions are written into the molecule during its synthesis. Each step in the assembly process is reversible and dynamic: the complex product is constantly forming and dissipating, and this feature allows for the correction of errors as the assembly proceeds. Self-assembly implies the distinction between "self" and "nonself," with recognition and selection between the two during assembly. When 2 different self-assemblies are in the same solution they may coexist and remain self-sorted or they may hybridize. This molecular miscegenation occurs when one component prefers to interact with a component other than itself.

Several recent studies have shown many complexes strictly self-sort, and this phenomenon is the subject of the contribution by Jiang and Schalley (1), "Integrative self-sorting is a programming language for high-level self-assembly." The article showcases the application of tandem mass spectrometry for analysis of complex mixtures in the gas phase. Quadruply interlocked species are shown to form specific assemblies with merciless fidelity. Exceptions to self-sorting in reversibly formed capsules appear in the work by Ajami et al. (2), "Disproportionation and self-sorting in molecular encapsulation." A small spherical capsule that binds gases such as methane and a longer, cylindrical capsule that binds molecules such as stilbene do not coex-

ist. On mixing, these 2 capsules form a hybrid, which is more stable than either original capsule. The formation of the hybrid provides places for guests that could not otherwise be accommodated. As in certain schools of architecture, reversible encapsulation is less about the mechanical boundaries of the walls than it is about the spaces they define.

Encapsulation of multiple groups of small molecules is the theme of the article by Yamauchi et al. (3), "Discrete stack of an odd number of polarized aromatic compounds: The importance of net vs. local dipoles." Three guests with polarized aromatics stack up within a capsule held together by metal/ligand interactions. The 3 aromatics arrange themselves, as clearly shown by X-ray diffraction studies, in such a way that the local dipoles cancel. These self-assembled capsules can make use of long or short spacer elements that permit different numbers of aromatic guests to stack within the space.

The electronic environment inside still another capsule is explored in the contribution by Pluth et al. (4), "Encapsulation and characterization of proton-bound amine homodimers in a water-soluble, self-assembled supramolecular host." These capsules are also held together by metal/ligand interactions that result in large overall negative charge in the shell provided by the host and stabilize positively charged guests inside. Using NMR spectroscopy, Pluth et al. show it is possible to capture a proton bound to 2 different amines while inside the capsule. These arrangements cannot be seen in bulk solution where rapid exchange of amine partners at equilibrium averages the signals for the many species present.

A molecular device is at the heart of the article by Kitagawa et al. (5), "Encapsulated guest rotation in a self-assembled heterocapsule directed toward a supramolecular gyroscope." Here, a reversibly formed capsule of some complexity brings together 2 different resorcinarenes, 1 bearing acidic and 1 bearing basic groups. The space inside is probed with disubstituted aromatics that are found to spin along the long axis of the capsule. This "gyroscope" is notional and at the molecular level, but these assemblies provide chemical models

and departures for possible future applications.

A switching device is involved in a calyx[6]arene that offers 2 separate binding sites in the work of Coquière et al. (6), "Multipoint molecular recognition within a calix[6]arene funnel complex." The conformational mobility of the system allows 3 imidazole arms to chelate zinc ions, while 3 aniline nitrogens converge to provide a binding site for a single proton. The space in the calixarene cavity is shown to bind small molecules such as acetonitrile reversibly. The stress in this molecular device resembles the entatic states proposed for certain enzyme activities.

Placing functional groups on the concave surface of a molecule is a difficult chemical maneuver, but the article by Ballester and Gil-Ramirez (7), "Self-assembly of dimeric tetraurea calix[4]pyrrole capsules," uses assembly to accomplish just that. Moreover, they do so in the much harder environment of the inner surface of a capsule. Two calyx[4]pyrroles are stitched together with a cyclic seam of hydrogen bonds to provide the capsule. In this host, guests are presented with the hydrogen-bond donors of the pyrroles. The interior binding sites impart high thermodynamic and kinetic stability to the host-guest capsule assembly and hint at opportunities for catalysis inside these spaces. These elegant structures are featured on the cover of this special issue.

Supramolecular assemblies that show reactive functions are the subject of the article by Kluwer et al. (8), "Self-assembled biomimetic (2Fe2S)-hydrogenase-based photocatalyst for molecular hydrogen evolution." They describe a catalyst that produces molecular hydrogen by using light as the energy source that is transmitted from chromophores to a diiron-based hydrogenase. This supramolecular approach led to an active catalyst that would have been difficult to prepare by traditional synthetic strategies. Catalysis is an intimate and, because a moving target (the transition state) is involved, perhaps the ultimate form of recognition.

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The study by Au-Yeung et al. (9), “Dynamic combinatorial synthesis of a catenane based on donor–acceptor interactions in water,” takes advantage of the mechanical bond and uses dynamic combinatorial synthesis to assemble a catenane. The symmetrical structure of the catenane contains both electron-rich and -poor surfaces and provides a model for intercalation phenomenon in water. This catenane features a record 5 imbricate and alternating  $\pi$  donor and acceptor units.

The breadth of self-assembly phenomena is expressed in the study by Deutman et al. (10), “Squaring cooperative binding circles.” This modern treatment of binding cooperativity exposes the difficulties in multicomponent receptor–guest systems. They use zinc porphyrin/pyridine interactions that are embedded in another mechanically bound system, a pseudorotaxane. This experimental approach allows apparent cooperativity to be properly related to the intrinsic thermodynamic and kinetic values.

Polymers based on supramolecular phenomenon and self-assembly are the subject of the article by Haino et al. (11), “Supramolecular polymer formed by reversible self-assembly of tetrakisporphyrin.” They use the familiar por-

phyrins coupled with a less familiar electron deficient aromatic to drive the assembly through the tendency of flat molecules to stack on each other. These are characterized in solution by NMR and on a mica surface by atomic force microscopy. The latter revealed a coiled structure of the fibrous filaments.

Biology provides the vehicle and inspiration for the article by Martos et al. (12), “Calix[4]arene-based conical-shaped ligands for voltage-dependent potassium channels.” The  $C_4$  symmetry of potassium channels mapped neatly on a calixarene scaffold. The congruence of the shapes and the spacing allowed the presentation of 4 arginines disguised as guanidinium ions on the calixarene. Salt bridges were formed to carboxylates on the protein tetramer. This process led to the blocking of potassium channels in oocytes and provided a rare application of self-assembly in chemical biology.

The role of neural networks in self-assembled systems in high-throughput screening methods is the subject of the article by Shabbir et al. (13), “A general protocol for creating high-throughput screening methods for reaction yield and enantiomeric excess: Applied to hydrobenzoin.” Shabbir et al. devised a sensor to discriminate between enantiomers of

organic compounds and pair them with indicators that give large optical responses. The 5 steps involved in the process were integrated into a high-throughput screening method for optical analysis.

The article by Macfarlane et al. (14), “DNA-directed colloidal crystal formation: Assembly and reorganization,” applies the recognition involved in dsDNA to the directed assembly of nanoparticles into aggregates. These are used to elucidate processes involved in crystal growth and reveal the mechanism of growth for DNA gold nanoparticles.

In this special issue of PNAS, recognition and assembly appear in a broad spectrum of structural contexts. These include mechanically bonded catenanes and rotaxanes, hydrogen-bonded, and metal/ligand-bound encapsulation complexes, salt-bridged biological macromolecules, and open-ended, reversible polymers held together by aromatic stacking. Throughout, chemically synthesized molecules are central to programmed self-assembly and rely on the intermolecular forces of recognition between molecules. These interactions are weak and short range but their reach is far, because applications can be found in nanoscience, materials, devices, sensors, and chemical biology.

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