Toward Self-Organization and Complex Matter

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Beyond molecular chemistry based on the covalent bond, supramolecular chemistry aims at developing highly complex chemical systems from components interacting through noncovalent intermolecular forces. Over the past quarter century, supramolecular chemistry has grown into a major field and has fueled numerous developments at the interfaces with biology and physics. Some of the conceptual advances and future challenges are profiled here.

Noncovalent interactions play critical roles in the biological world. Thus, with just a few building blocks, strands of nucleic acids allow huge amounts of information to be stored, retrieved, and processed via weak hydrogen bonds. Similarly, a large array of signaling molecules within cells recognize subtle differences in protein surfaces. Supramolecular chemistry has implemented these principles of molecular information in chemistry. Through manipulation of intermolecular noncovalent interactions, it explores the storage of information at the molecular level and its retrieval, transfer, and processing at the supramolecular level via interactional algorithms operating through molecular recognition events based on well-defined interaction patterns (such as hydrogen bonding arrays, sequences of donor and acceptor groups, and ion coordination sites). Its goal is to gain progressive control over the complex spatial (structural) and temporal (dynamic) features of matter through self-organization (1–5). This has first involved the design and investigation of preorganized molecular receptors that are capable of binding specific substrates with high efficiency and selectivity.

Three main themes outline the development of supramolecular chemistry. (i) Molecular recognition between artificial receptors and their substrates relies on design and preorganization and implements information storage and processing. (ii) The investigation of self-organization relies on design for inducing the spontaneous but controlled assembly of sophisticated supramolecular architectures. It implements programming and programmed systems. (iii) The third, emerging, phase introduces adaptation and evolution. It relies on self-organization through selection in addition to design, and implements chemical diversity and "informed" dynamics.

Molecular Recognition

Supramolecular chemistry first harnessed preorganization for the design of tailor-made molecular receptors effecting molecular recognition, catalysis, and transport on a variety of substrates, from metal ions to anions and chiral molecular substrates (1, 2). It also opened new vistas to chemical synthesis, establishing procedures for the construction of supramolecular entities and providing supramolecular assistance to synthesis in which noncovalent positioning of the components is followed by covalent bond formation (1, 6–8). Both areas will continue to provide access to highly sophisticated noncovalent and covalent entities.

Self-Organization

Beyond preorganization lies the design of programmed systems that self-organize through explicit manipulation of molecular recognition features, thereby directing the buildup from their components of supramolecular species and devices (1, 9–15). Such

molecular recognition–directed self-organization has given access to a range of supramolecular entities of truly impressive architectural complexity, making use of hydrogen bonding, donor-acceptor interactions, and metal coordination interactions for controlling the processes and holding the components together. Examples are inorganic and hydrogen-bonded multicomponent entities (6–15) and interlocked mechanically linked compounds (11, 16) that would otherwise have been too difficult to construct. In these programmed systems, the components must contain the information required for their assembly into a well-defined supramolecular entity through the operation of specific recognition algorithms. Understanding, inducing, and directing such self processes are key to unraveling the progressive emergence of complex matter. Self-organization is the driving force that led to the evolution of the biological world from inanimate matter (4, 5). The inclusion of dissipative nonequilibrium processes, like those present in the living world, constitutes a major goal and challenge for supramolecular chemistry.

More or less strict programming of the output species may be achieved depending on the robustness of a given directing code (such as hydrogen bonding or metal coordination); that is, on how sensitive it is to internal factors (such as secondary metal coordination or van der
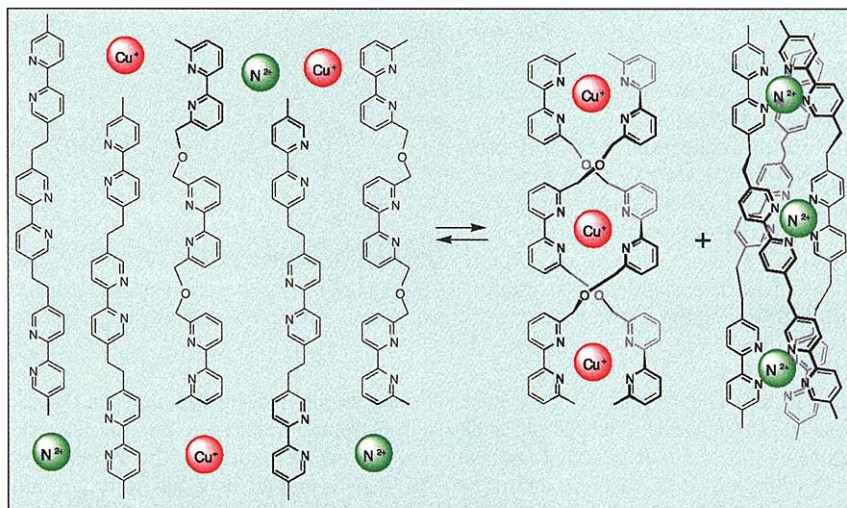

Fig. 1. Parallel formation of a double helicate and a triple helicate by self-selection with self-recognition from a mixture of two different suitably instructed ligands and two different types of metal ions that present specific processing/coordination algorithms. Cu^I (red) and Ni^{II} (green) have tetrahedral and octahedral coordination, respectively (17).

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Waals stacking) or external factors (such as concentrations and stoichiometries of the components or the presence of foreign species). Sensitivity to perturbations limits the operation range but introduces diversity and adaptability (3) into the self-organization process.

Self-selection with self-recognition occurs when the structural instructions are sufficiently strong, as is the case in the "correct" assembly of helicates (inorganic double helices) from different ligands strands and metal ions (Fig. 1) (17). Instructed components can be designed that, as mixtures, allow the controlled assembly of multiple well-defined supramolecular species. The implementation of this "instructed mixture" paradigm is crucial for the development of complex chemical systems, as witnessed by the buildup of organized species and the execution of highly integrated functions taking place side by side in the assembly and operation of the living cell.

Because it is a time-dependent process, self-organization also involves temporal information and may display kinetic control, as in the initial assembly of a triple helical complex that evolves toward a circular helicate (18). Multilevel hierarchical self-organization enables the progressive buildup of more and more complex systems in a sequential temporally ordered fashion. Such is the case in the formation of discotic liquid crystals by the assembly of "sector"-shaped components into disks, which thereafter organize into columns (19), and in the template-induced wrapping of molecular strands into helical disk-like objects, which then aggregate into large supramolecular assemblies (20).

Multiple Self-Organization Processes

Beyond single-code assembly programs, systems of higher complexity operate in multimode fashion through the implementation of several codes within the same overall program, resulting in multiple self-organization processes (3, 21). Thus, different metalloarchitectures may be generated from the same ligand when different sets of metal ions are used to read the binding information. For example, two different helicates can be generated from the same strand (3, 22), and ligands containing two different subunits can code for the formation of a helicate or of a 2 × 2 grid-type complex (Fig. 2) (23). Similarly, differential processing of hydrogen bonding information contained in a molecular strand may yield different supramolecular structures (20).

The multiple processing of the same ligand information by different interaction algorithms allows the controlled generation of different output architectures, resulting in multiple expression of molecular information (21). Such a one code/several outputs scheme could also play an important role in biology. The combination of different recognition/instruction features in a molecular program opens a door to the design of self-organizing systems capable of performing molecular computation (24–26). Recent studies described the use of biomolecules and DNA-based protocols to solve computational problems (25, 26). An approach making use of specifically designed nonnatural components could provide higher diversity, better resistance to fatigue, and smaller size.

Self-Organization Through Selection

Supramolecular chemistry is dynamic by nature because of the lability of the interactions that connect the molecular components of a supramolecular entity. The reversibility of the associations allows a continuous change in constitution, either by internal rearrangement or by exchange, incorporation, and extrusion of components. Thus, supramolecular chemistry is a constitutional dynamic chemistry (CDC) generating constitutional diversity. It enables selection of a given constituent, made up of a well-defined set of components, from a pool of compounds with all possible constitutions, under the pressure of internal factors [intrinsic stability of the species, as in helicate self-recognition (17)] or external factors [interaction with species in the environment, as in anion binding by circular helicates (27)]. CDC may also be molecular; in this case, the components of the molecular entity are linked by covalent bonds that may form and break reversibly.

A specific expression of CDC is dynamic combinatorial chemistry (28–30). It rests on the dynamic generation of molecular and supramolecular diversity through the reversible connection of covalently or noncovalently linked building blocks, which gives access to the full set of all combinations that may potentially exist. Addition of a receptor displaces the dynamic equilibrium toward the preferential formation of the best-binding constituent, in a target-driven selection of the fittest. This approach opens wide perspectives in a variety of areas of science and technology, such as the discovery of biologically active substances and of new materials.

CDC introduces a paradigm shift with respect to constitutionally static chemistry. The latter relies on design for the generation of a target entity, whereas CDC takes advantage of dynamic diversity to allow variation and selection (31, 32).

The implementation of selection in supramolecular chemistry introduces a fundamental change in outlook. Whereas self-organization by design strives to achieve full control over the output supramolecular entity by explicit programming, self-organization by selection operates on dynamic constitutional diversity in response to either internal or external factors to achieve adaptation in a darwinistic fashion.

Functional Devices

Functional supramolecular entities may be discrete species or extended assemblies in one dimension (polymolecular chains and fibers), two dimensions (layers and membranes), and three dimensions (solids). Functional devices performing energy, electron, or ion exchange or transfer processes form the core of molecular and supramolecular photonics, electronics, and ionics (1, 2, 33–35). Controlling the transfer of photons, electrons, and ions sets the stage for "semiochemistry" (1, 9), which is the chemistry of signal generation and processing. This is of particular interest for the development of supramolecular technologies, such as sensors and other optical or electronic devices, and may be of interest for setting up logic functions and molecular computing (1, 2, 33–37). Mechanical devices producing triggered molecular motions give access to intriguing processes such as shift registers and circular displacements that are related to the design of molecular machines (38, 39).
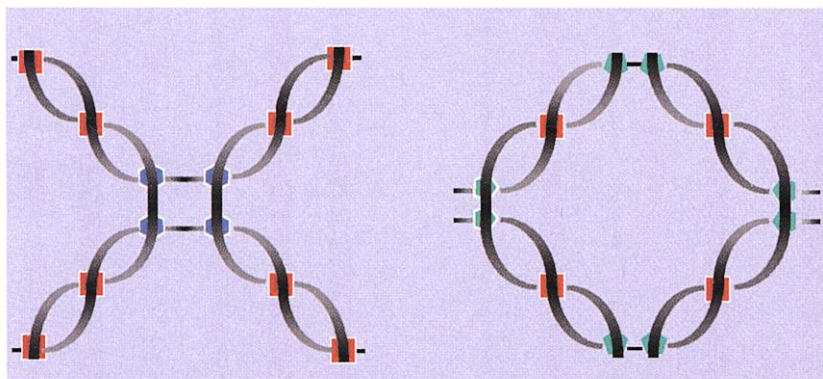
Chemically reactive self-organized enti-

Fig. 2. Schematic representation of the two different coordination architectures obtained by enforced processing of the same ligand binding information by two different sets of metal ions with specific coordination geometries/algorithms; squares, pentagons, and hexagons represent tetra-, penta-, and hexa-coordinated metal ions, respectively (23).

ties are formed when the assembly brings together components that bear reactive functional groups. Given the appropriate disposition of specific subunits, they may perform efficient and selective reactions and catalysis, and in particular may result in replication and self-replication processes (*32*, *40*). The controlled self-organization of functional systems displaying reactivity and catalysis is crucial for the development of chemical systems of both structural and reactional complexity. It has played a key role in biological evolution (*4*, *5*) and presents a major challenge to chemistry.

Supramolecular Materials

The properties of a material depend both on the nature of its constituents and on the interactions between them. Supramolecular chemistry may thus be expected to have a strong impact on materials science through the manipulation of the noncovalent forces that hold the constituents together, leading to the design of "smart" functional supramolecular materials whose buildup and properties are controlled through the self-assembly of suitable units. The connections between the constituents may undergo assembly/disassembly/exchange processes. These constitutionally dynamic materials (CDMs) may in principle select their constituents in response to external stimuli or environmental factors, behaving as adaptive materials (*3*).

The combination of polymer chemistry with supramolecular chemistry defines a supramolecular polymer chemistry (*1*, *2*, *41*, *42*). Here, molecular interactions (hydrogen bonding, donor-acceptor effects, etc.) and recognition processes are used to generate main-chain (or side-chain) supramolecular polymers through the self-assembly of complementary components. Supramolecular polymers are reversible CDMs, displaying constitutional diversity determined by the nature and variety of the different monomers.

The exploration of supramolecular versions of the various species and procedures of molecular polymer chemistry gives access to a wealth of novel entities and functionalities.

Molecular recognition may be used to induce and control self-organization in two and three dimensions in order to perform supramolecular engineering of polymolecular assemblies (such as layers, films, membranes, micelles, gels, and liquid crystals) on surfaces, at interfaces, and in the solid state (*43*). Vesicles are of special interest, because compartmentalization must have played a major role in the self-organization of complex matter and the evolution of living cells and organisms. The controlled buildup of architecturally organized and functionally integrated polyvesicular systems may lead to the design of artificial cells and polymolecular systems of tissue-like character based on specific intra- and intervesicular processes (*44–46*). For example, liposomes decorated with recognition groups (recosomes) present features such as selective interaction with molecular films, aggregation, and fusion (*45*).

Nanoscience

Self-organization offers to molecular nanotechnology (*47–49*) a powerful alternative to both top-down miniaturization and bottom-up nanofabrication approaches. It strives for self-fabrication by the controlled assembly of ordered, fully integrated, and connected operational systems by hierarchical growth, bypassing the implementation of tedious fabrication and manipulation procedures (*1*, *3*). It may take advantage of both design and selection and finds inspiration in the integrated processes of biological systems.

In the long run, the goal is complex organization and collective operation rather than small size and individual addressing. Self-organization offers the full range of self processes that determine the internal buildup, the functional integration, and the operation of

the entity (such as self-selection or self-wiring), as well as its external connection to the environment (self-connection for addressing and sensing). The most complex object we know, the brain, builds up by self-organization and is self-wired and self-integrated, as well as self-connected through our senses.

Outlook

The combined features of supramolecular systems—information and programmability, dynamics and reversibility, constitution and diversity—are leading toward the emergence of adaptive/evolutive chemistry (*3*). Adaptive chemistry implies selection and growth under time reversibility. It becomes evolutive chemistry when acquired features are conserved and passed on. Harnessing the power of selection for adaptation and evolution on the molecular scene is ushering in a darwinistic era of chemistry. The ultimate goal is to merge design and selection in self-organization to perform self-design, in which function-driven selection among suitably instructed dynamic species generates the optimal organized and functional entity, in a post-darwinian process.

Beyond programmed systems, the next step in complexity consists in the design of chemical "learning" systems, which are not just instructed but can be trained. The incorporation of time irreversibility implies the passage from closed systems to open and coupled systems that are connected spatially and temporally to their surroundings.

Supramolecular chemistry provides ways and means for progressively unraveling the complexification of matter through self-organization. Together with the corresponding fields in physics and biology, it leads toward a supramolecular science of complex, informed, self-organized evolutive matter (Fig. 3). Through progressive discovery, understanding, and implementation of the rules that govern the evolution from inanimate to animate matter and beyond, we will ultimately acquire the ability to create new forms of complex matter.
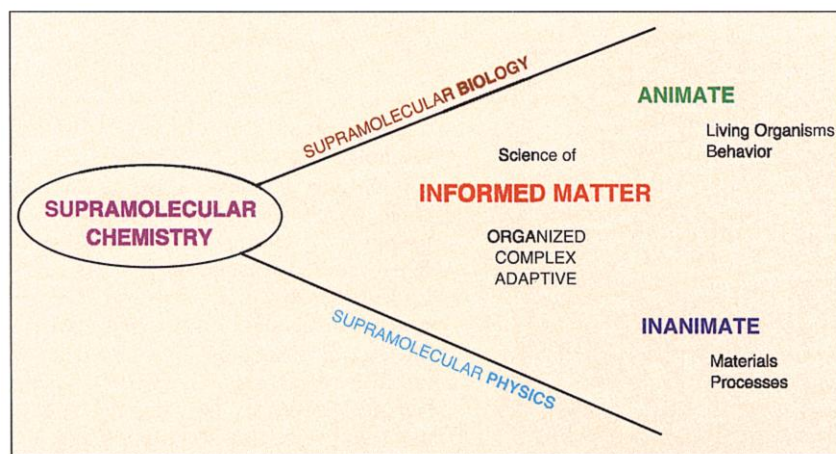
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Fig. 3. Supramolecular science as the science of informed matter at the interfaces of chemistry with biology and physics.

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VIEWPOINT

Synthesis Beyond the Molecule

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Weak, noncovalent interactions between molecules control many biological functions. In chemistry, noncovalent interactions are now exploited for the synthesis in solution of large supramolecular aggregates. The aim of these syntheses is not only the creation of a particular structure, but also the introduction of specific chemical functions in these supramolecules.

Molecules are collections of atoms that are connected by a continuous network of strong chemical bonds. They are synthesized from smaller molecules by the selective formation of kinetically stable covalent bonds. Molecules can also interact without forming such strong bonds through much weaker and kinetically labile noncovalent interactions (electrostatic and van der Waals forces or hydrophobic effects, π-π stacking interactions, metal coordination, and hydrogen bonding). In biology, such interactions are responsible for the transduction of signals, the selective transport of ions and small molecules across membranes, enzymatic reactions, or the formation of larger aggregates. In chemistry, such weak noncovalent interactions determine the physical properties of molecules, e.g., the properties of liquids, the solubility of solids, or the organization of amphiphilic molecules in larger aggregates such as membranes, micelles, and vesicles. In the late 1960s, Pedersen (*1*), Lehn (*2*), Cram (*3*), and others published the synthesis of macrocyclic molecules (crown

ethers, cryptands, spherands, and so forth) that are able to selectively bind ions or small organic molecules via noncovalent interactions. Although the synthesis of these molecular receptors involves the formation of covalent (molecular) bonds, the objective of the synthesis is the specific recognition function (binding and selection) that these receptors display. Lehn (*2*) coined the term "supramolecular chemistry" or "chemistry beyond the molecule" for this field. It should be emphasized that long before the name supramolecular chemistry was introduced, there were already fields rich with this type of chemistry, e.g., coordination chemistry where noncovalent interactions are very important. The difference is that in supramolecular chemistry, molecules (hosts) are designed and synthesized for their ability to interact specifically with other molecules (guests) or to form larger aggregates. The concepts developed in supramolecular chemistry are also increasingly used in fields like material science, surface science, sensor technology, and nanotechnology. In this viewpoint, we will describe how basic supramolecular concepts are now applied for noncovalent synthesis of supramolecular entities, the ultimate objective being the introduction of functions in such noncovalent structures (functional devices and superstructures).

Synthetic Receptors

Early work in supramolecular chemistry focused on molecular recognition, i.e., on the selective recognition of substrate molecules (guest) by synthetic receptors (host). The mimicry of selective recognition processes in biological systems was a major source of inspiration for the early researchers. The field of supramolecular chemistry has reached such a level of control that crown ether receptors rival the K^+/Na^+ selectivity of the antibiotic valinomycin (*4*) and synthetic anion receptors preferentially select $H_2PO_4^-$ over HSO_4^- or Cl^-, similar to natural phosphate-binding proteins. The selective complexation of biologically interesting neutral molecules such as barbituric acid, creatine, steroid (*5*), and many others has also been achieved.

The need for multiple binding sites in the aforementioned molecular receptors is evident, because the individual noncovalent interaction is weak. This principle of multisite interaction is very common in living systems, e.g., binding of the antibodies and macrophages to cells or cell-cell recognition (*6*). Using this principle, molecular recognition of complex biomolecules such as cytochrome *c* (cyt *c*) by synthetic receptors has been accomplished (*7*). These receptors based on calix[4]arene scaffolds decorated with four cyclic peptidic loops bind cytochrome *c* with a strength similar to that of natural cytochrome *c* oxidase. This type of polyvalent receptor can be further developed for drug design and discovery, because it can identify specific binding areas in biomolecules. Synthetic receptors are applied for the selective recognition of analytes by sensors (*8*) and for

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