

Toward complex matter: Supramolecular chemistry and self-organization

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As the wind of time blows into the sails of space, the unfolding of the universe nurtures the evolution of matter under the pressure of information. From divided to condensed and on to organized, living, and thinking matter, the path is toward an increase in complexity through self-organization.

Thus emerges the prime question set to science, in particular to chemistry, the science of the structure and transformation of matter: how does matter become complex? What are the steps and the processes that lead from the elementary particle to the thinking organism, the (present!) entity of highest complexity?

And there are two linked questions: an ontogenetic one, how has this happened, how has matter become complex in the history of the universe leading up to the evolution of the biological world, and an epigenetic one, what other and what higher forms of complex matter can there be to evolve, are there to be created?

Chemistry provides means to interrogate the past, explore the present, and build bridges to the future.

Molecular chemistry has created a wide range of ever more sophisticated molecules and materials and has developed a very powerful arsenal of procedures for constructing them from atoms linked by covalent bonds.

Beyond the molecule, supramolecular chemistry aims at developing highly complex chemical systems from components interacting by noncovalent intermolecular forces (1, 2). It has over the last quarter of a century grown into a major field and has fueled numerous developments at the interfaces with biology and physics, thus giving rise to the emergence and establishment of supramolecular science and technology, as a broad multidisciplinary and interdisciplinary domain providing a highly fertile ground for the creativity of scientists from all origins. The breadth and depth of its scope is evidenced and illustrated by the wide selection of many of the major players in the field gathered in the Special Feature in this issue of PNAS.

Rather than adding another facet to this already breathtaking panorama, it appeared appropriate here to emphasize perspectives

and provide a vision. This essay therefore will not be extensively documented (numerous reviews and books are available) but rather outline some conjectures for the future, mainly based on, illustrated by, and extrapolated from work performed in the author's laboratories. Looking toward the horizon of supramolecular chemistry, and more generally of supramolecular science (1, 3), special attention will be given to exposing the forest(s) rather than to describing the trees!

Supramolecular Chemistry and the Information Paradigm

One of the major lines of development of chemical science resides in the ever clearer perception, deeper analysis, and more deliberate application of the information paradigm in the elaboration and transformation of matter, thus tracing the path from merely condensed matter to more and more highly organized matter toward systems of increasing complexity. In chemistry, like in other areas, the language of information is extending that of constitution, structure, and transformation as the field develops toward more and more complex architectures and behaviors. It will profoundly influence our perception of chemistry, how we think about it, how we perform it.

Supramolecular chemistry has paved the way toward apprehending chemistry as an information science through the implementation of the concept of molecular information with the aim of gaining progressive control over the spatial (structural) and temporal (dynamic) features of matter and over its complexification through self-organization, the drive to life (4–6).

Supramolecular chemistry has developed as the chemistry of the entities generated by intermolecular noncovalent interactions (1, 2). Through the appropriate manipulation of these interactions, it became progressively the chemistry of molecular information, involving the storage of information at the molecular level, in the structural features, and its retrieval, transfer, and processing at the supramolecular level, by interactional algorithms operating through molecular recognition events based on well-defined interaction

patterns (hydrogen bonding arrays, sequences of donor and acceptor groups, ion coordination sites, etc.). This venture involved the design and investigation of more or less strictly preorganized molecular receptors of numerous types, capable of binding specific substrates with high efficiency and selectivity.

Three overlapping phases may be considered in the development of supramolecular chemistry, each exploring a main theme.

The first is that of molecular recognition and its corollaries, supramolecular reactivity, catalysis, and transport; it relies on design and preorganization and implements information storage and processing.

The second concerns self-assembly and self-organization, i.e., self-processes in general; it relies on design and implements programming and programmed systems.

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.

From Preorganization Toward Self-Organization and Programmed Systems: Design

Supramolecular chemistry has first relied on preorganization for the design of molecular receptors effecting molecular recognition, catalysis, and transport processes (1, 2).

Supramolecular preorganization also has provided new ways and means to chemical synthesis (1, 7–9). Supramolecular, noncovalent synthesis, i.e., the construction of the supramolecular entities themselves, rests on the making and breaking of noncovalent bonds following an Aufbau strategy incorporated into the design of the molecular components. On the other hand, supramolecular assistance to synthesis provides a powerful tool involving first the noncovalent synthesis of a supramolecular architecture, which positions the components, followed by post-assembly modification through covalent bond formation. Both areas will continue

Abbreviations: CDC, constitutional dynamic chemistry; DCC, dynamic combinatorial chemistry.

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to provide in the future a range of highly sophisticated noncovalent as well as covalent entities. A particularly impressive illustration of the latter is the synthesis of interlocked compounds (see below).

Beyond preorganization lies the design of systems undergoing self-organization, i.e., systems capable of spontaneously generating well-defined, organized, and functional supramolecular architectures by self-assembly from their components, thus behaving as programmed systems (1, 10). Chemical programming requires the incorporation into molecular components of suitable instructions for generation of a well-defined supramolecular entity. The program is molecular, the information being contained in the covalent structural framework; its operation is supramolecular, making use of recognition algorithms based on specific interaction patterns. Understanding, inducing, and directing self-processes is key to unraveling the progressive emergence of complex matter. Self-organization is the driving force that led up to the evolution of the biological world from inanimate matter (4–6).

Whereas self-assembly may be taken as simple collection and aggregation of components into a confined entity, we shall here consider self-organization as the spontaneous but information-directed generation of organized functional structures in equilibrium conditions. A relevant biological example is for instance the formation of a virus particle from its components, genomic nucleic acid and coat proteins. The inclusion of dissipative, non-equilibrium processes, as present in the living world, constitutes a major goal and challenge for the future (4–6).

A self-organization process may be considered to involve three main stages: (i) molecular recognition for the selective binding of the basic components; (ii) growth through sequential and eventually hierarchical binding of multiple components in the correct relative disposition; it may present cooperativity and nonlinear behavior; and (iii) termination of the process, requiring a built-in feature, a stop signal, that specifies the end point and signifies that the process has reached completion.

Suitable encoding by manipulation of structural subunits and processing through interactional algorithms should give access to a variety of systems. More or less strict programming of the output species may be achieved depending on the robustness of a given directing code (for instance, of hydrogen bonding or metal coordination nature), i.e., on the extent to which it is sensitive to perturbations. In a robust system the instructions are strong enough for ensuring the stability of the process, i.e., the self-organization is resistant, stable toward interfering interac-

tions (such as secondary metal coordination, van der Waals stacking, etc.) or toward modifications of parameters (such as concentrations and stoichiometries of the components, presence of foreign species, etc.). When the assembly occurs only in a narrow range of conditions, the system is unstable and presents a singularity; it may also display a bifurcation or a switching point between different assemblies. On the other hand, sensitivity to perturbations, while limiting the operation range, introduces diversity and adaptability (3) in the self-organization process.

Self-selection with self-recognition occurs when the structural instructions are sufficiently strong, as is the case in the “correct” pairing of strands of different lengths in the assembly of helicates, inorganic double helices (11). The process bears relation to the implementation of combinatorial chemistry in its “dynamic” version (see below). It reveals a broader perspective with a paradigm shift, from “pure compounds” to “instructed mixtures”, from “unicity” to “multiplicity + information” (11). Rather than pursuing mere chemical purity of a compound or a material, one seeks to design instructed components, which, as mixtures, allow the controlled assembly of multiple well-defined supramolecular species, following specific programs and interactional algorithms. The implementation of this instructed mixture paradigm is crucial for the development of complex chemical systems, as witnessed by the build-up of organized species and the execution of highly integrated functions that take place side-by-side in the assembly and operation of the machinery of the living cell.

Intense activity has been devoted to the explicit application of molecular recognition to control the formation, from their components, of organized supramolecular entities presenting specific physical and chemical properties. Three main types of investigations have been pursued, based on the use of hydrogen bonding, donor acceptor, and metal coordination interactions for controlling the processes and holding the entities together (12–18). The latter have been instrumental in the initial introduction of the notions of self-assembly into supramolecular chemistry (1, 10). The clever exploitation of templating and self-organization has given access to a range of molecular and supramolecular entities of truly impressive structural complexity, which otherwise would have been considered impossible to construct, such as interlocked entities, whose components are mechanically held together (15, 19) and multicomponent organic or inorganic architectures (1, 12–18).

Because it is a time-dependent process, self-organization also involves temporal

information and may display kinetic control, generating kinetic products before reaching the thermodynamic one(s). This is the case in the initial assembly of a triple helical complex that evolves toward a circular helicate (20). Such a process may either be sequential, if the kinetic product is an intermediate located on the pathway toward the final product, or it may be bifurcated, if this is not so.

A sequential process may be either commutative, if given steps may be interchanged along the overall pathway leading to the final superstructure, or it may be noncommutative if its progressive build-up occurs through a defined sequence of molecular instructions and algorithms, where the generation of a given intermediate depends on the previous one and sets the stage for the next one. For example, discotic liquid crystals form by the assembly of “sector”-shaped components into disks, which thereafter organize into columns (21), and template binding by molecular strands induces wrapping into helical disk-like objects, which then aggregate into large supramolecular assemblies (22).

The generation of supramolecular architectures and materials through a non-commutative sequence of steps amounts to multilevel hierarchical self-organization, along primary, secondary, tertiary, etc. structures. Such conditional processes enable the progressive build-up of more and more complex systems in a directed, temporally ordered fashion; they also offer the intriguing possibility to intervene at each step so as either to suppress the following ones or to reorient the subsequent evolution of the system into another direction, toward another output entity.

Multiple Self-Organization Through Multiple Processing/Expression of Molecular Information

The generation of a given superstructure through self-organization results, in its simplest form, from the operation of a single-code assembly program. A step beyond consists in devising systems of higher complexity that operate in multimode fashion through the implementation of several codes within the same overall program, resulting in multiple self-organization processes (3, 23).

Such behavior may take place in the generation of different metallo-architectures from the same ligand when using different sets of metal ions/coordination algorithms for reading the binding information, as in the generation of two different helicates from the same strand (3, 24) and in the assembly of ligands containing two different subunits coding, respectively, for the formation of a helicate and a $[2 \times 2]$ grid-type complex (25). Similarly, the differential expression of

hydrogen bonding information contained in a molecular strand may yield different supramolecular structures depending on the processing mode (angular or linear) defined by the recognition algorithm of the bound effector (22). These considerations lead to conjectures that may have far-reaching implications and open novel perspectives within the general framework of self-organizing, programmed chemical systems (23).

The processing of the same ligand information by different interaction algorithms (e.g., through the use of different sets of metal ions or of different H-bonding effectors) allows the controlled self-organization of different output architectures, resulting in multiple expression of molecular information, through postinformational (postgenomic!) operations. Such a one code/several outputs scheme, in addition to the one code/one output (product) mode, also has in principle significant implications in biology.

Multisubroutine self-assembly may display three types of behavior: (i) it may behave as a linear combination of the subprograms, each running independently to generate its own encoded output; self-recognition (11) is a related process; (ii) it may present crossover, when the subprograms operate in a combined fashion; or (iii) it may also be of dominant/recessive type, one of the subprograms imposing its own output over the other one(s) (26).

Multiple processing capacity represents a further step in the design of programmed chemical systems of increasing complexity capable of producing a variety of more and more complex architectures as outputs.

Parallel processing, extending eventually to massively parallel systems, would involve the simultaneous operation of multiple self-organization processes toward the generation of a single functional entity or several different ones. The side-by-side formation of different helicates (11) or helicates and inorganic grids (D. Funeriu and J.-M.L., unpublished work) in a mixture of the corresponding ligands and suitable metal ions may be seen as prototypes on a simple level.

Multiple processing of a single set of instructions allows the generation of diversity, because multiple outputs may either coexist, or be potentially accessible (virtual diversity) (27). It thus meets dynamic combinatorial chemistry (DCC) (see below).

Conversely, such chemical systems also open perspectives for information science, inasmuch as they raise the question of going beyond the usual one-to-one correspondence, established by a given program, between the input information and a single output, toward multiple outputs

generated by different modes of processing the same information.

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. Computing by self-assembly may yield a powerful alternative to conventional models (28, 29). Recent studies described the use of biomolecules and DNA-based protocols to solve computational problems (30–32). An approach making use of specifically designed non-natural components could provide higher diversity, better resistance to fatigue, and more compact/smaller size. Such potential is latent in the coordination-controlled assembly of double helicates (3, 24) and metallo-supramolecular architectures (25), as well as in the differential folding processes induced by effector H-bonding (22). Numerous types of interactions and recognition units, be they of inorganic or organic nature, are available for exploring these avenues.

The combination of multiple expression with reversible diversity generation suggests the notion of dynamic computing through dynamic information generation and processing, defining adaptive/evolutionary programmed systems. Evolutionary computation may be envisaged with biomolecules (28, 32, 33), but entirely synthetic molecular systems or mixed abio/bio ones should in the future be amenable to similar feats, with probably advantages in design, control, and diversity.

Dynamic Chemistry and Constitutional Diversity: Selection

Supramolecular chemistry is by nature a dynamic chemistry in view of the lability of the interactions connecting the molecular components of a supramolecular entity. The reversibility of the associations allows a continuous change in constitution, which may be either internal, by rearrangement of the components with modification of the connectivity between them, or external, by exchange, incorporation, or extrusion of components, therefore conferring constitutional plasticity to the system. Thus, supramolecular chemistry is a constitutional dynamic chemistry (CDC).

Dynamic chemistry also can be just morphological, involving reversible changes in shape through molecular or supramolecular conformational or configurational modifications, without change in (internal or external) constitution and resulting in motional processes.

CDC may be molecular as well as supramolecular when the components of the molecular entity are linked by covalent bonds that may form and break reversibly. This ability to undergo continuous and reversible change by reorganization, deconstruction, and reconstruction (alike or different) generates constitutional dy-

namic diversity. It allows us to perform selection of a given constituent, made up of a well-defined set of components in the pool of compounds having all possible constitutions, under the pressure of either internal [intrinsic stability of the species, as in helicate self-recognition (11)] or external [interaction with species in the environment, as in anion binding by circular helicates (34, 35)] factors.

CDC constitutes thus a general area of which one specific expression, when under combinatorial conditions, is DCC that has actively developed in recent years (27, 36, 37). It relies on the dynamic generation of molecular and supramolecular diversity through the reversible combination of covalently or noncovalently linked building blocks (components). Whereas combinatorial chemistry itself is based on extensive libraries of prefabricated molecules, DCC implements the reversible connection of pools of basic components to give access to virtual combinatorial libraries (VCLs) whose constituents comprise the full set of all possible combinations that may potentially be generated in dynamic equilibrium. The constituents actually expressed among all those accessibles are expected to be those presenting the strongest interaction with a given target, i.e., the fittest. DCC bypasses the need to actually synthesize the library constituents and lets the target select the optimal partner by inducing its preferential assembly from its components, eventually with a facilitation of the connecting reaction. It is thus a target/function-driven self-organization, i.e., a self-design process (see below). The basic features of the DCC/VCL approach have been presented together with its implementation in different fields and the perspectives it offers in a variety of areas of science and technology, such as the discovery of biologically active substances, new materials, and catalysts, etc. (27).

CDC introduces a profound change in paradigm and opens a range of novel perspectives with respect to constitutionally static chemistry (see also refs. 38 and 39). Whereas the latter relies on design for the generation of a target molecule or supermolecule, CDC takes advantage of dynamic diversity to allow variation and implements selection to achieve adaptation in a darwinistic fashion.

Self-Organization by Design and Selection: Self-Design

Whereas preorganization relies entirely on design, supramolecular self-organization introduces in addition the possibility to let the system build up by selection.

Self-organization by design has been pursued with the goal to achieve full control over the output supramolecular entity by means of correctly instructed components, specific interaction algorithms, and (as

much as possible) strict programming. Design is knowledge-based and has an explicit information content.

Self-organization by selection requires dynamic diversity (constitutional and/or morphological) on which to operate. This is made possible by the implementation of CDC responding to the pressure of either internal or external factors. Selection has an implicit information content. It is also truly a supramolecular process, because it occurs in relation to interactions with surroundings (which may be either the medium or a more or less distant part of a folded macromolecule).

The introduction of the selection paradigm into (supramolecular) chemistry brings about a fundamental change in ways, means, and outlook. Of course, the question is not to replace the deliberately planned linear process of design by a multipronged trial-and-error process of selection. Design and selection are not mutually exclusive but are complementary for reaching systems of higher complexity through self-organization. The ultimate goal is to merge design and selection in self-organization to perform self-design, where function-driven selection among suitably instructed dynamic species generates the optimal organized and functional entity. In fact, self-recognition in helicate self-assembly from mixtures of ligand strands (11), the selection of monomers in the synthesis of molecular helices under the pressure of folding (40) as well as the formation of dynamic helical polymers (J.-L. Schmitt and J.-M.L., unpublished work) may be perceived as such internally driven systems.

Altogether, harnessing the power of selection for adaptation and evolution on the molecular scene is ushering in a darwinistic era into chemistry, where the fittest species survive.

Self-Organization of Functional Supramolecular Systems

The self-organization of functional supramolecular entities concerns either discrete species or, on the other hand, extended assemblies in one (e.g., polymolecular chains, fibers), two (e.g., layers, membranes), and three (e.g., solids) dimensions.

Functional supramolecular devices are based on the structural organization and functional integration of active components operating with photons, electrons, and ions or presenting chemical reactivity.

Photoactive and electroactive devices performing energy or electron exchange/transfer processes form the core of molecular and supramolecular photonics and electronics (41–45). They have, for instance, led to labeling and detection procedures of interest for biological studies and medical diagnostics based on energy transfer. Redox

processes have been used for developing prototypes of molecular electronic components, such as molecular wires, batteries, and rectifiers. The combined operation of photo- and electro-effects gives rise to photoinduced electron transfer and charge separation, so that a major thrust has been toward the mimicking of the first steps of photosynthesis (45). The search for artificial ion carriers and ion channels provides the basis for (supra)molecular ionics (41, 42, 46, 47). Controlling the transfer of photons, electrons, and ions sets the stage for semiochemistry (10), the chemistry of signal generation and processing, of interest for instance in devising sensing and logic functions (48, 49). Developments toward supramolecular technology have been actively pursued, concerning in particular sensors and other optical or electronic devices, possibly of interest for “molecular computing” (42, 50).

Mechano-devices, effecting triggered molecular motions, belong to a general area of dynamic devices. Molecular motions and changes in molecular shape may be produced through external stimuli in various systems, e.g., cis-trans isomerization in azobenzene derivatives and optical changes in photochromes are accompanied by large geometric variations. Interlocked and intertwined structures have been used for the photochemical or electrochemical induction of relative motion between the mechanically linked components. They have given access to a range of intriguing processes (e.g., shift registers, circular displacements) related in particular to the design of “molecular machines” and the induction of directional motion (51–53).

While the above devices present physical functionality, chemically reactive self-organized entities are formed when the assembling brings together components bearing reactive functional groups. Through the appropriate disposition of specific subunits in an organized pattern, they may be amenable to perform efficient and selective reactions and catalysis. Such supramolecular processes involve first a substrate recognition step followed by a chemical transformation on the bound entity (1), resulting in an activity of artificial enzyme type. When the reactions occur within the self-assembled entity, they amount to self-transformation and may in particular result in replication and self-replication processes (39, 54, 55). They may present autocatalysis, a behavior that together with the establishment of networks of reactions and coupled catalytic cycles amounts to self-organization on the chemical reactivity level, presenting features such as self-regulation, feedback, and amplification. The controlled self-organization of functional systems displaying reactivity and catalysis is cru-

cial for the development of chemical systems of both structural and reactional complexity. It has played a key role in biological evolution (4) and presents a major challenge to chemistry.

Functional Supramolecular Materials

The properties of a material depend both on the nature of its constituents and the interactions between them. Supramolecular chemistry may thus be expected to have a strong impact on materials science by means of the explicit manipulation of the noncovalent forces that hold the constituents together. These interactions and the recognition processes that they underlie allow the design of materials and the control of their build-up from suitable units by self-organization. Thus, supramolecular chemistry opens new perspectives in materials science toward an area of supramolecular materials, “smart” materials whose features depend on molecular information. For instance, liquid-crystalline polymers of supramolecular nature have been obtained by the self-assembly of complementary subunits (56–58).

Supramolecular materials are by nature dynamic materials, materials whose constituents are linked through reversible connections and which may undergo assembly/deassembly processes in specific conditions. Because of this intrinsic ability to exchange their constituents, they are constitutionally dynamic materials and may in principle select their constituents in response to external stimuli or environmental factors. Supramolecular materials thus are instructed, dynamic, and combinatorial and behave as adaptive materials (3).

A rich domain emerges from the combination of polymer chemistry with supramolecular chemistry defining a supramolecular polymer chemistry (56–58). It involves the designed manipulation of molecular interactions (hydrogen bonding, donor-acceptor effects, etc.) and recognition processes to generate main-chain (or side-chain) supramolecular polymers by the self-assembly of complementary monomeric components (or by binding to lateral groups). In view of their lability, these associations present features of reversible, “living” polymers capable of growing or shortening, of rearranging or exchanging components. Supramolecular polymers are thus constitutionally dynamic materials, based on dynamic polymer libraries whose members possess constitutional diversity determined by the nature and variety of the different monomers. The components effectively incorporated into the polyassociations depend in particular on the nature of the recognition and core groups, internal structural compatibility, as well as the interactions with the environment. These features give access to higher levels of behavior such as healing, adaptability, response to external stimulants (heat, light,

additives, etc.) by association/growth/dissociation sequences.

The selective, recognition-controlled incorporation of components presenting specific functional properties (energy transfer, electron transfer, ion binding, etc.) allows us to envisage applications for such diverse purposes as drug delivery, gene transfer, mechanical action (e.g., triggered changes in shape or size), viscosity adjustment, hydrophilicity/hydrophobicity modulation, optical and electronic effects, etc.

Supramolecular versions of the various species and procedures of molecular polymer chemistry may be imagined and implemented, providing a wide field of future investigation that may offer a wealth of novel entities and functionalities. Similar considerations apply to the generation of supramolecular liquid crystals (56–58).

Molecular recognition may be used to induce and control self-organization in two and three dimensions for performing supramolecular engineering of polymeric assemblies and materials, layers, films, membranes, micelles, gels, mesophases, and solids as well as on surfaces or at interfaces.

Surfaces modified with recognition units may display selective surface binding on the microscopic level and recognition-controlled adhesion on the macroscopic scale. Intermolecular interactions may be brought to induce the controlled assembly of macroscopic objects as is the case with capillary forces (59).

Self-organization of polymeric assemblies reaches a second level in the self-organization of objects that are themselves self-organized. Vesicles are of special interest in this respect, because compartmentalization must have played a major role in the self-organization of complex matter and thus in the evolution of living cells and organisms. One may envisage the controlled build-up of architecturally organized and functionally integrated polyvesicular systems toward the design of artificial cells and polymeric systems of tissue-like character, implementing specific intravesicular and intervesicular processes (60, 61). The manipulation of the features of vesicles and their behavior is a step in this direction; thus, liposomes decorated with recognition groups, reosomes, present features such as selective interaction with molecular films, aggregation, and fusion (62, 63).

Molecular recognition interactions also provide a powerful entry into solid-state chemistry and crystal engineering. The increasing ability to control the way in which molecules associate gives means for the designed generation of supramolecular architectures in the solid state (64).

The generation of self-organized nanostructures, organized and functional spe-

cies of nanometric dimensions, defines a supramolecular nanochemistry.

Supramolecular Nanochemistry and Nanomaterials

Nanoscience and nanotechnology are receiving great attention in view of both their basic interest and their potential applications (65, 66). Here again, supramolecular chemistry and self-organization contribute a fundamentally novel outlook of deep impact. Three approaches to these areas may be considered.

(i) The miniaturization, top-down “size-shrinking” approach, mainly pursued up to now, has led to the tremendous achievements of the microelectronics technology and is pushing down the limits of size and compactness of components and devices.

(ii) The nanofabrication and nanomanipulation bottom-up approach to molecular nanotechnology, takes advantage of novel nanolevel materials and methods (e.g., near-field scanning microscopies) to generate nanoentities presenting intriguing potential, such as electrical devices built on carbon nanotubes (for two recent examples, see refs. 67 and 68) or optical devices like optical sieves (69).

(iii) The supramolecular self-organization approach, where the goal is not smaller size or individual addressing but complexity through self-processing, strives for self-fabrication by the controlled assembly of ordered, fully integrated, and connected operational systems by hierarchical growth.

The first two approaches rely on design and implement physical procedures. Self-organization may take advantage of both design and selection, through its informed, dynamic and adaptive features, and finds inspiration in the integrated processes of biological systems.

Indeed, the spontaneous but controlled generation of well-defined, functional supramolecular nanostructures through self-organization offers a very powerful alternative to nanofabrication and nanomanipulation, bypassing the implementation of tedious procedures and providing a chemical approach to nanoscience and technology. Rather than having to top-down prefabricate or to stepwise construct nanostructures, more and more powerful methodologies resorting to self-organization from instructed components will give access to highly complex functional architectures (1). Their dynamic features, allowing constitutional modification through exchange of components, confer to them the potential to undergo healing and adaptation, processes of great value for the development of “smart” nanomaterials. Of course, various combinations of self-organization and fabrication procedures may be envisaged and implemented at different stages.

Fabricating, manipulating, and implementing nano-size chemical entities offer a wide range of potential applications of great value for science and technology (70). Reducing size to the nano-object and addressing it are admirable feats that provide entirely new insight into the properties and functioning of chemical as well as biological systems. However, in the long run, the goal is complex organization and collective operation rather than smaller size and individual addressing. And here the path is traced by self-organization, covering a full range of self-processes that determine the internal build-up and the operation of the entity (self-selection, self-wiring), as well as its interaction with the environment (self-connection for addressing and sensing). It follows also a bottom-up scale change by growth from the nanolevel to the meso level and to the macrolevel with internal structural organization, functional integration, and external connection. Indeed, the most complex object around, the brain, builds up by self-organization and is self-wired and self-integrated as well as self-connected through our senses!

Toward Adaptive and Evolutive Chemistry

The combination of the features of supramolecular systems—information and programmability, dynamics and reversibility, constitution and diversity—leads toward the emergence of adaptive/evolutive chemistry (3). It is, by essence, of supramolecular nature because it is determined by interaction with an external entity. It may be constitutional and/or morphological (as occurs in “induced fit” for instance). Adaptive chemistry implies selection and growth under time reversibility.

Implementing both design and selection, self-organization offers adjustability (through self-correction, self-healing under internal dynamics); adjustability leads to adaptation (through reorganization under interaction with environmental effectors); adaptation becomes evolution, when acquired features are conserved and passed on.

Adaptation is illustrated by functionally driven optimization through selection from pools of dynamically interconverting supramolecular species. Evolutive chemical systems suppose multiple dynamic processes with sequential selection/acquisition/fixation steps and undergo progressive change of internal structure under the pressure of environmental factors. But the world of selection is a brutal world, where only the fittest survives. It is ultimately for thought and design to open up a post-Darwinian era by recruiting the forces of information to override the dictate of selection!

Beyond programmed systems and in line with an evolutive chemistry, the next

step in complexity consists in the design of chemical “learning” systems, systems that are not just instructed but can be trained (see for instance ref. 71).

The incorporation of the arrow of time, time irreversibility, leads to self-organization in nonequilibrium, dissipative systems through irreversible processes (4, 5). It implies the passage from closed systems to open and coupled systems that are connected spatially and temporally to their surroundings.

Supramolecular Science, the Science of Informed, Complex Matter

In the long-range perspective, the development of chemical science is toward complex systems, spanning the broadest outlook from divided to condensed matter then to organized and adaptive matter, on to living matter and thinking matter, up the ladder of complexity.

Complexity implies and results from multiplicity of components, interaction between them and integration i.e., correlation, coupling, and feedback (1). The species and properties defining a given level of complexity result from and may be explained on the basis of the species belonging to the level below and of their multibody interaction, e.g., supramolecular entities in terms of molecules, cells in terms of supramolecular entities, tissues in terms of cells, organisms in terms of tissues and so on, up to the behavior of societies and ecosystems along a hierarchy of levels defining the architecture of complexity. At each level of increasing complexity novel features emerge that do not exist at lower levels, which are deducible from but not reducible to those of lower levels.

Supramolecular chemistry provides ways and means for progressively unrav-

eling the complexification of matter through self-organization. The Special Feature in this issue of PNAS takes stock and outlines prospects for many of the activities pursued in the field.

Together with the corresponding areas in physics and biology, supramolecular chemistry builds up a supramolecular science whose already remarkable achievements point to the even greater challenges that lie ahead. They lead toward a science of complex matter, of informed, self-organized, evolutive matter. The goal is to progressively discover, understand, and implement the rules that govern its evolution from inanimate to animate and beyond, to ultimately acquire the ability to create new forms of complex matter. The perspectives opened up become wider and wider as progress is being made and will constitute horizons of the future for quite some time!

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