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VIEWPOINT

Synthesis Beyond the Molecule

D. N. Reinhoudt* and M. Crego-Calama

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 ofmolecules, 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).

Laboratory of Supramolecular Chemistry and Technology; MESA$^+$ Research Institute and Faculty of Chemical Technology, University of Twente, Post Office Box 217, 7500 AE Enschede, Netherlands.

*To whom correspondence should be addressed. E-mail: d.n.reinhoudt@ct.utwente.nl

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

separations via membrane transport (*9*).

Often, host-guest interactions are of vital importance for the effective synthesis of macrocyclic hosts. For example, large macrocycles such as crown ethers cannot be easily synthesized, because intermolecular reactions compete with intramolecular cyclization. However, when a complementary guest species (template) is present in the preparation of these macrocyclic strucutures, noncovalent interactions between the linear precursor molecule and the template strongly favor macrocyclization. Template synthesis is a special case of synthesis, because it takes advantage of noncovalent interactions and can be defined as "supramolecular-assisted covalent synthesis" (*10*). Template synthesis is extremely useful for the synthesis of a special class of organic molecules in which two or more parts of the molecule are not covalent but are mechanically linked. These interlocked catenane and rotaxane structures owe their simple synthesis to noncovalent interactions between reactants during the macrocyclization reaction. These molecules are prototypes for molecular switches or machines (*11*).

Noncovalent Synthesis

With increasing understanding of the individual interactions that govern the molecular recognition process, the focus is now shifting to supramolecular chemistry as a tool for noncovalent synthesis. Cooperative, weak interactions are used for the spontaneous formation of large aggregates that have well-defined structures (helicates, grids, molecular containers, capsules, cyclic arrays, and the like), in which the individual components are not connected through covalent but through noncovalent bonds.

In this emerging field of noncovalent synthesis, one might expand the definition of a molecule to "a collection of atoms held together by covalent and noncovalent bonds." Contrary to the classical definition of a molecule, these supramolecules may be highly dynamic on the human time scale. On the other hand, noncovalent and covalent synthesis are not fundamentally different; both have as the objective to introduce specific connectivities between atoms. The advantage of noncovalent synthesis is that noncovalent bonds are formed spontaneously and reversibly under conditions of thermodynamic equilibrium, with the possibility of error correction and without undesired side products. Furthermore, it does not require chemical reagents or harsh conditions.

Supramolecular chirality. In biosynthesis, chemical transformations are highly stereoselective with only one of the many possible stereoisomers (compounds with the same molecular formula that differ in the way their atoms are arranged in space) being formed. With the current state of chemical synthesis, a comparable stereocontrol over covalent bond formation is possible for many types of reactions as well. In the synthesis of noncovalent systems, this control over stereochemistry is much more difficult, because bonds between individual components are kinetically labile and are continuously broken and formed. However, in noncovalent synthesis, the stereochemistry of reaction products (regioselectivity, diastereoselectivity, and enantioselectivity) must also be controlled.

Rebek *et al.* have demonstrated that certain symmetrical molecules dimerize through hydrogen bonding to form molecular capsules with dissymmetrical cavities. In the presence of symmetrical guest, the capsule exists as an equal (racemic) mixture of two mirror-image forms (enantiomers). Nevertheless, with the presence of a chiral (nonsymmetrical) guest inside the cavity, theses noncovalent assemblies preferentially form one of the two possible diastereomeric complexes (stereoisomers that are not mirror images) (*12*).

Stereochemical selectivity in noncovalent synthesis can also be illustrated in the assembly of building blocks with complementary melamine-isocyanuric acid (CA) (or melamine-barbituric acid, BAR) H-bonding motifs (Fig. 1A). Whether finite (rosette) or polymeric (tape) structures are formed in the self-aggregation process of these two compounds depends on entropy and steric interactions (*13, 14*). This type of self-assembled structure expresses supramolecular chirality, nonsymmetrical arrangement of molecular components in a noncovalent assembly (*15*), because the building blocks are arranged in a helical nonsymmetrical fashion.

In the absence of other elements of chirality, the assembly $\mathbf{1}_3 \cdot (DEB)_6$ forms as a racemic

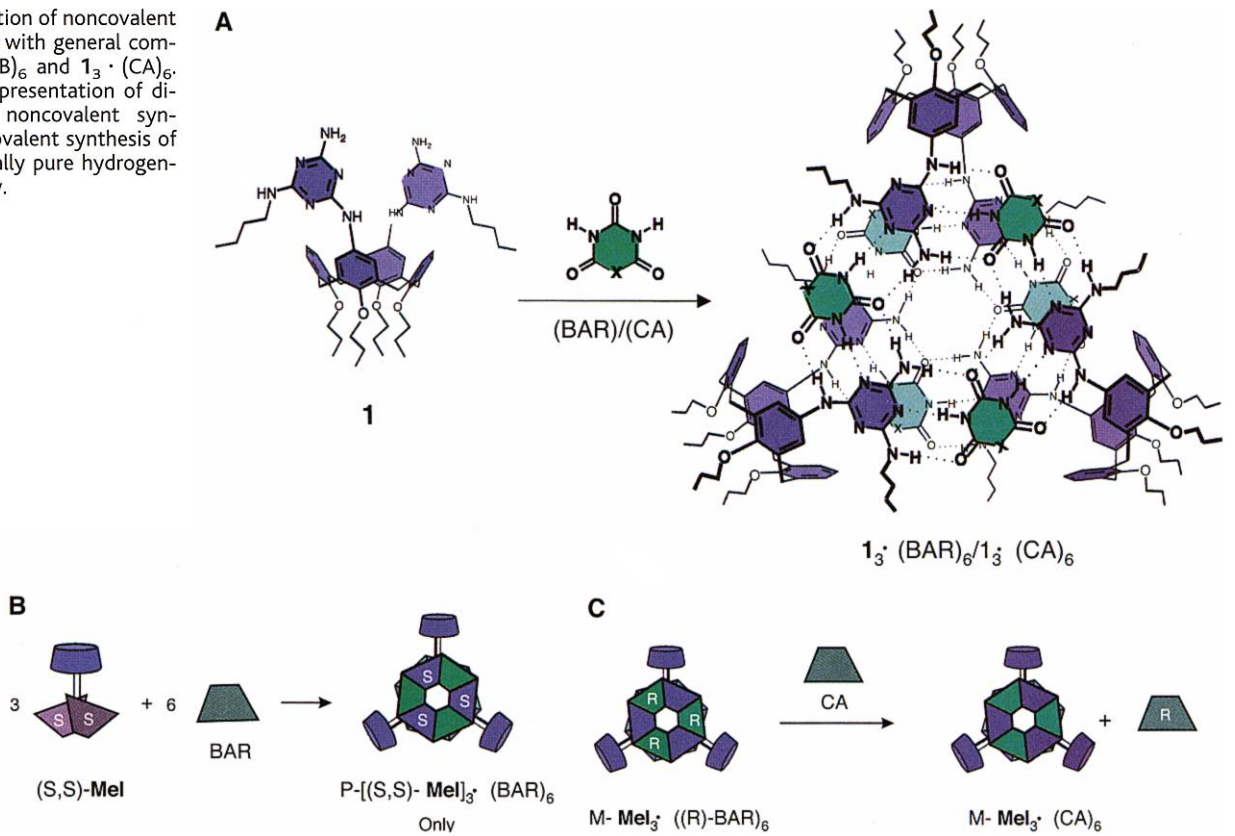

Fig. 1. (**A**) Formation of noncovalent chiral assemblies with general composition $\mathbf{1}_3 \cdot (DEB)_6$ and $\mathbf{1}_3 \cdot (CA)_6$. (**B**) Schematic representation of diastereoselective noncovalent synthesis. (**C**) Noncovalent synthesis of an enantiomerically pure hydrogen-bonded assembly.

mixture of M- and P-enantiomers. When one of the components (melamine or BAR) is chiral, they can assemble in two diastereomeric forms with either P- or M-helicity (Fig. 1B). This assembly process is remarkably sensitive for the chirality of one of the components and in most cases the chiral centers render the assembly process completely stereoselective (*16*). If in each of these diastereoisomeric assemblies all chiral barbiturates [(R)-BAR] are substituted for achiral isocyanurates (CA), the helicities of the assemblies are not affected (Fig. 1C). Pure enantiomers M or P are formed in which the assembly is optically active although none of the individual constituents contain a chiral element (chiral memory) (*17*). In polar solvents, the P- and M- enantiomers racemize slowly at room temperature ($t_{1/2} > 4$ days).

More interestingly these systems also exhibit amplification of chirality (*18*). Thus, the achiral components "follow" the helicity induced by the chiral components even when the chiral molecules are present in very small fractions, far less than equimolecular amounts. From a philosophical point of view this amplification of chirality is also regarded as essential for the explanation of homochirality in nature (i.e., only L–amino acids and D–sugars) (*19*).

Synthesis of nanostructures. One of the areas where noncovalent synthesis has a great advantage over covalent synthesis is the bottom-up (chemical) assembly of nanostructures. Large-scale nanometer fabrication will be a requirement for future molecular electronic devices, high-density data storage, or drug delivery. Covalent synthesis has been proven to be extremely fruitful for the synthesis of compounds with molecular weights in the range of 100 to 3000 daltons such as palytoxin, norbrevetoxin, and taxol (*20*). Nevertheless, with the exception of the sequential methodologies for the synthesis of biopolymers (or oligomers), there are no simple covalent strategies for the synthesis of pure molecules that have molecular weights between 10^4 and 10^6 kilodalton (kD). Such molecules have dimensions between 3 and 20 nm and fill the gap between small molecules and larger nano-objects that are now accessible by top-down (physical) fabrication methods, mainly based on lithography. This is also the size range where quantum confinement influences the electronic and optical properties of matter.

Consequently, noncovalent synthesis is increasingly being considered as an alternative for the construction of chemical well-defined nanostructures incorporating high degree of complexity. One example is the formation of dendrimers, a group of highly branched polymers, which are very interesting as soluble heterogeneous catalysts, carriers for the transfer of biomolecules into cells, or magnetic resonance imaging (MRI) agents (*21*). Traditionally, these large polymers are obtained by laborious sequential covalent multistep synthesis and the higher generations generally have structural defects. Recently, Zimmerman *et al.* have synthesized a defect free hydrogen-bonded dendrimer (MW = 34 kD) via self-assembly using the hexameric isophthalic acid motif (*22*). Also, coordination chemistry can be used to assemble noncovalently large metallodendrimers (MW ~ 100 kD) (*23*).

The degree of complexity and sophistication of noncovalent synthesis has now progressed to a level where it is possible to control the self-assembly of 27 individual components via 144 hydrogen bonds (*24*). These self-assembled structures have a size of 3.3 nm by 3.3 nm by 5.5 nm and a molecular weight of ~20 kD, comparable to those of small proteins like cytochrome *c* (~12 kD) and myoglobin (~16 kD).

Self-Replication and Amplification Processes (Supramolecular Evolution)

In nature, the immune system (antibodies) is an impressive example of biological machinery, with elements of recognition, selection, optimization, and amplification. In principle, equilibrating mixtures of supramolecular structures [dynamic combinatorial libraries (DCL)] have the ability to adapt to a given guest species and so to mimic the evolution that is exhibited by antibodies. This unique property of noncovalent assemblies, compared to covalent systems, is the direct result of their reversible nature.

Crego-Calama *et al.* (*25*) showed that chemical evolution in such a noncovalent dynamic combinatorial library is possible. Using a basis of a melamine-barbiturate (BAR) motif as the constant region of the receptor, they introduced binding sites (Zn-porphyrins) for a trispyridine guest in the variable region. Upon addition of the guest, the equilibrium between individual stronger and weaker binding receptors is shifted, and the most effective binder in the library is amplified. Similarly, Lehn and Huc reported a DCL of bipyridine ligands that, upon coordination to Pd^{2+} ions, exposes different H-binding motifs. In the presence of a barbituric acid derivative, the composition of the DCL undergoes a shift so that more of the DAD · DAD (D, hydrogen bond donor; A, hydrogen bond acceptor) array, which is complementary to barbiturate (ADA · ADA), is generated (*26*). Recently, Sanders *et al.* reported a covalent but still dynamic pseudopeptide library (*27*). The library is generated by macrocyclization of a proline derivative that has both a hydrazide and masked aldehyde functionality. In the presence of acetylcholine, the complex mixture of cyclic oligomers shifts to a composition almost exclusively containing the trimeric compound.

At present, the noncovalent synthesis of DCLs is in its infancy, but it has great promises for the development of artificial receptors and especially for drug discovery; it combines the advantages of combinatorial chemistry with molecular evolution (*28*). DCLs can take advantage of evolution through the recognition process and ultimately, through amplification of the optimal receptor. This could be considered a self-screening process capable of accelerating the identification of active compounds.

The fascinating idea that a molecule could catalyze its own formation has been associated with the origin of life. Current work in the area of self-replication uses peptides, oligonucleotide analogs, and simple synthetic molecules as templates. Very interesting examples are the oligopeptides reported by Ghadiri *et al.* (*29*), who have demonstrated that chiroselectivity in peptide self-replication is a direct consequence of complementary noncovalent interactions that transfer simultaneously both binding and stereochemical information.

These replicators, based on a 32–amino acid leucine zipper-type sequence, are capable of efficiently amplifying homochiral products from racemic mixtures of peptide fragments. Chiroselective amplification is an autocatalytic process in which a homochiral template instructs the synthesis of a homochiral product of the same handedness (Fig. 2A). The templated strand **T** places the reactive sites **N** (nucleophile) and **E** (electrophile) in close proximity, and ligation between **N** and **E** generates a copy of the original strand. In this particular example, an enantiomeric pair of electrophilic **E** [$\mathbf{E^D}$ (D–amino acids) or $\mathbf{E^L}$ (L–amino acids)] and nucleophilic **N** ($\mathbf{N^D}$ or $\mathbf{N^L}$) peptide fragments was employed in order to probe the relationship between self-replication and homochirality. Starting from a racemic mixture of equal amounts of $\mathbf{E^D}$ and $\mathbf{E^L}$, and $\mathbf{N^L}$ and $\mathbf{N^D}$ fragments, homochiral products $\mathbf{T^{LL}}$ and $\mathbf{T^{DD}}$ are preferentially produced. The observed increasing diastereomeric excess is due to the autocatalytic activity of the homochiral templates, $\mathbf{T^{LL}}$ and $\mathbf{T^{DD}}$.

In combination with functionalized surfaces, von Kiedrowski has shown that oligonucleotide analogs can proliferate exponentially (Fig. 2B) (*30*). Similar processes may also have played a role in the origin of life.

Supramolecular Catalysis

Even though the differences between supramolecular and "normal" catalysis are not always apparent (especially when metal ions are involved), one of the areas where supramolecular chemistry could play an important role is substrate-selective catalysis. Selective recognition of substrates and stabilization of the transition state, as displayed by enzymes, have inspired much of the work in this area. Sanders *et al.* (*31*) reported rate acceleration of a Diels-Alder reaction in ternary complexes, but product inhibition is still a serious problem. Mandolini *et al.* reported a supramolecular catalyst that exhibits the three characteristic properties of an enzyme: substrate specificity, transition state stabilization, and high turnover (*32*). This uranyl

salenophane catalyzes the 1,4-addition of thiols to α,β-unsaturated ketones at room temperature. The complexity of mimicking the catalytic properties of a natural enzyme is well illustrated by the cytochrome P450 model reported by Nolte *et al.* (*33*). The system contains molecular oxygen as the oxidizing agent, a metallophorphyrin as a catalytic center, an electron donor as the reducing agent, and a membrane system that holds all the components together.

Functional Noncovalent Devices and Superstructures

Currently, the priorities in supramolecular chemistry in solution are slowly shifting from structure to the construction of sophisticated functional superstructures and devices.

A very nice example in which supramolecular structures display unexpected biological effects are the peptide nanotubes (*34*). Cyclic D,L-α–peptides self-assemble via H-bonding to tubular open-ended and hollow structures. The in vivo antibacterial efficiency of these cyclic peptides may well be related to the formation of transmembrane channels in bacterial cell walls. These nanotubes can also act as channels for K^+, Na^+, glucose, or glutamate ions in lipid bilayer membranes, similar to naturally occurring channel-forming proteins.

The noncovalent synthesis of photo- and redox-active assemblies combined with the interest in nanotechnology have led to electrochemical or optical devices and primitive prototypes of artificial molecular machines such as light-fueled molecular "piston cylinders," shuttles, switches, and muscles (*11*). Their ability to move arises from interlocking rings (catenanes) or rings threaded by molecular strings (rotaxanes and pseudorotaxanes).

The research groups of J. F. Stoddart and J. R. Heath (*35*) have sandwiched a monolayer of redox-active V-shaped [2]rotaxanes between two metal electrodes (Fig. 3). This molecular junction can be used as switching device, which is read by monitoring current flow as a function of applied voltage (*35*). The linear array of such devices behaves as a logic gate.

The captivating concept of synthetic molecular muscles has been explored by Sauvage *et al.* The system is based on a doubly threaded structure that is capable of contracting or stretching under the action of a chemical signal, in this case, a metal exchange reaction (*36*).

Conclusions and Outlook

In the last 30 years, the way chemists think about synthesis has been strongly influenced by supramolecular concepts. The exploitation of weak forces between molecules for the construction of aggregates with defined composition, shape, and chemical function now offers an alternative for covalent synthesis. The fundamental difference between covalent and noncovalent structures is their different kinetic stability. In noncovalent systems, the individual components exchange rapidly on the human time scale, introducing novel properties such as the chemical evolution of mixtures and the amplification of a specific component in DCLs. The latter can be regarded as primitive analogy of "the survival of the fittest" in biological systems. Because noncovalent structures are formed under thermodynamic equilibrium conditions, error correction is possible, thus expanding the range of chemical synthesis to much larger molecules.

Increasingly, remarkable feats have been accomplished in the field of supramolecular chemistry. Significant advances in this field include the construction of simple prototypes of molecular machinery that may lead the way to molecular computing. Systems that can self-replicate are no longer science fiction. Nevertheless, important challenges remain. More exhaustive control over the stereochemistry of noncovalent systems could produce aggregates for the separation of enantiomers. Despite the fact that there are several examples of supramolecular catalysis, the catalytic efficiency and selectivity of enzymatic catalysis are very difficult goals to achieve. In the coming 5 to 10 years, we may see that evolution and selection processes, such as in combinatorial dynamic libraries, provide the next step toward more effective supramolecular catalysts.

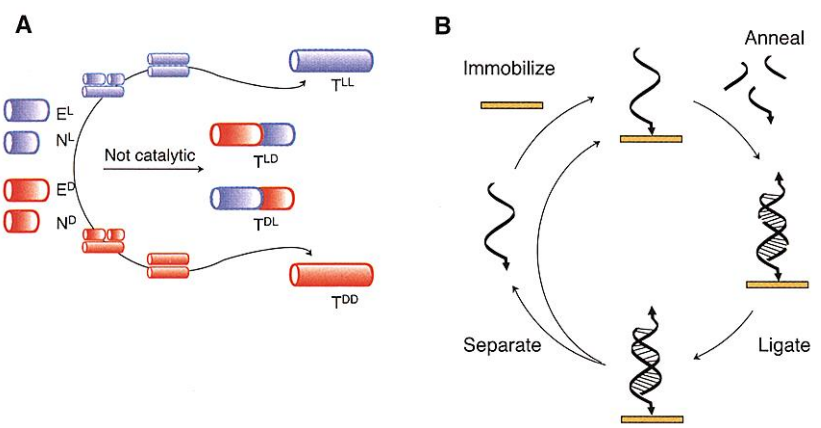

Fig. 2. Self-replicating systems: (**A**) Chiroselective amplification in peptide synthesis. Homochiral peptides T^{LL} and T^{DD} are produced autocatalytically while the heterochiral peptides T^{DL} and T^{LD} result from uncatalyzed condensation reactions. (**B**) General scheme of the surface-promoted replication and exponential amplification of DNA analogs (SPREAD). A template is immobilized onto a solid support and subsequently the template binds complementary fragments from solution, which are then linked together by a chemical reaction. Finally, the copy is released and re-immobilized. This process provides a means to overcome product inhibition.

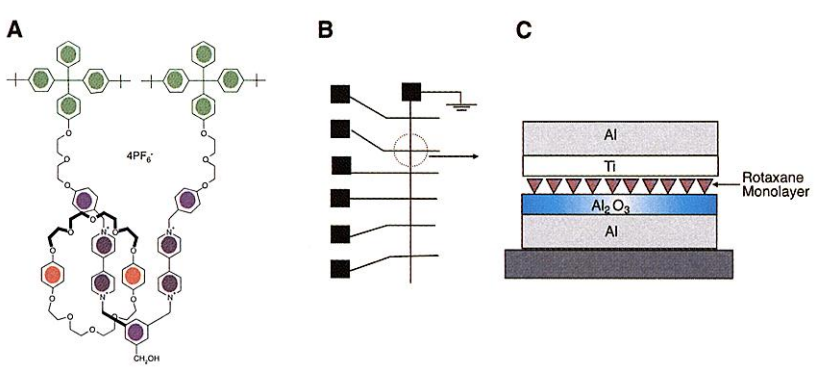

Fig. 3. (**A**) Graphical representation of the [2]-rotaxane molecule used as a part of the molecular switch. (**B**) Linear array (top view) of six switching devices. (**C**) Side view cross section of a single device junction. The rotaxane monolayer sandwiched between the two electrodes contains several millions of molecules.

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VIEWPOINT

Functional Materials Based on Self-Assembly of Polymeric Supramolecules

Olli Ikkala[1]* and Gerrit ten Brinke[1,2]*

Self-assembly of polymeric supramolecules is a powerful tool for producing functional materials that combine several properties and may respond to external conditions. We illustrate the concept using a comb-shaped architecture. Examples include the hexagonal self-organization of conjugated conducting polymers and the polarized luminance in solid-state films of rodlike polymers obtained by removing the hydrogen-bonded side chains from the aligned thermotropic smectic phase. Hierarchically structured materials obtained by applying different self-organization and recognition principles and directed assembly form a basis for tunable nanoporous materials, smart membranes, preparation of nano-objects, and anisotropic properties, such as proton conductivity.

Recently there has been much effort to develop novel concepts for preparing structures and objects approaching the molecular level. Electronics miniaturization provides a strong motivation because present-day lithography faces fundamental problems in achieving further reduction in feature sizes by orders of magnitude. For example, molecular-level switching elements based on interlocking rings and their use in memory elements in electronics have been studied by the groups of Stoddart and Heath (*1*).

There have also been attempts not only to construct individual nanoscale functional features but also to control bulk materials structures, defects, and anisotropy at all length scales from the macroscopic scale down to the molecular level. Very recently, it was demonstrated that if sufficiently high-quality single crystals can be grown by vapor deposition, even organic oligomers can have high charge-carrier mobilities, as well as showing lasing and luminance (*2*). In polymers, spin-cast self-organized polyalkylthiophenes have recently been shown to have enhanced charge-carrier mobility (*3*) and even superconductivity (*4*). However, although self-organization allows high structural control at the local length scale, the inherent tendency for coiling of polyalkylthiophenes causes folds, as visualized by Bäuerle *et al.* (*5*). In such polymers, it may be fundamentally difficult to achieve a monodomain-like structure with high overall order.

Here, we describe some possibilities for preparing functional polymeric materials using the "bottom-up" route, based on self-assembly of polymeric supramolecules. Directed assembly leads to the control of structure at several length scales and anisotropic properties. The physical bonds within the supramolecules allow controlled cleavage of selected constituents. The techniques constitute a general platform for constructing materials that combine several properties that can be tuned separately.

To achieve enhanced functionalities, the principal periodicity is at ~10 to 2000 Å. There are established ways to accomplish this by using various architectures of block copolymers (*6*), in which the structure formation is based on self-organization (*7*), that is, on the repulsion between the chemically connected blocks. Depending on the architecture, block length, and temperature, it is possible to obtain lamellar, cylindrical, spherical, gyroid, or more complicated structures in the 100 to 2000 Å range. Also, rodlike moieties within the block copolymers can be used (*7*, *8*) to further tailor the structures in terms of shape persistency. However, self-organization renders only the local structures. To fully realize the opportunities offered by the symmetry of the self-organized structures to prepare materials with a strongly directional variation of properties, additional mechanisms and interactions have to be invoked to obtain macroscale order. This may be achieved by flow, by electric or magnetic fields, or by using topographically patterned surfaces (*9*–*12*). One can further extend the structural complexity by mixing block copolymers with additional polymers and inorganic additives, thereby increasing the self-organization periods into the photonic band gap regime (*13*). Block copolymers have also been used as templates for the synthesis of inorganic materials, even allowing the creation of separate ceramic nano-objects (*14*).

To achieve even greater structural complexity and functionality, we can combine recognition with self-organization. Lehn elaborated on the concept of recognition in synthetic materials, whereby two molecules with molecularly matching complementary interactions and shapes recognize each other and form a receptor-substrate supramolecule (*15*). To achieve sufficient bonding, synergism of several physical interactions is often required. Homopoly-

[1]Department of Engineering Physics and Mathematics and Center for New Materials, Helsinki University of Technology, Post Office Box 2200, FIN-02015 HUT, Espoo, Finland. [2]Department of Polymer Science and Materials Science Center, University of Groningen, Nijenborgh 4, 9747 AG Groningen, Netherlands.

*To whom correspondence should be addressed. E-mail: Olli.Ikkala@hut.fi (O.I.); G.ten.Brinke@chem.rug.nl (G.t.B.)