Recent advances in functional supramolecular nanostructures assembled from bioactive building blocks

Abstract:
Supramolecular nanostructures covered with bioactive functional molecules have been actively explored as promising materials in the field of biotechnology. Recent advances in nano-sized chemistry have made it possible to fabricate various kinds of nanostructures with tailor-made nanostructural properties. This, combined with appropriate bioactive functionalization, has led to the successful utilization of supramolecular nanostructures in diverse biomaterials applications. This tutorial review describes the concept, current developments, and prospects of self-assembled bioactive nanostructures, which are assembled directly from bioactive supramolecular building blocks.

Molecular hydrogels of therapeutic agents

Abstract:
This tutorial review aims to introduce a new kind of biomaterials—molecular hydrogels of therapeutic agents. Based on the molecular self-assembly in water, it is possible to transform therapeutic agents into analogues that form hydrogels without compromising their pharmacological efficacy. This transformation can be beneficial in three aspects: (i) the therapeutic agents become “self-deliverable” in the form of hydrogels; (ii) the self-assembly of hydrogelators of drugs might confer new and useful properties such as multivalency or high local densities; (iii) the exploration of molecular hydrogels of drugs may ultimately lead to bioactive molecules that have dual or multiple roles. By summarizing the reports on the molecular hydrogels made from clinical used drugs or other bioactive molecules, this article presents representative molecular hydrogels of therapeutics and outlines the promises and challenges for developing this new class of biomaterials.

Hydrogen-Bonded DeUG-DAN Heterocomplex: Structure and Stability and a Scalable Synthesis of DeUG with Reactive Functionality

Abstract:
A convenient, scalable synthesis of the supramolecular building block 7-deazaguanine-based urea (DeUG) is reported. Incorporation of reactive moieties (DeUG azide 10 and alkyne 11 for copper-catalyzed azide-alkyne cycloadditions, “click chemistry”) and a demonstration of transesterification (DeUG glycol, 12) highlights the versatility. X-ray structures of DeUG and a DeUG∙DAN heterocomplex were obtained. Kassoc for the 1∙2 heterocomplex was estimated to be $2 \times 10^8 \text{ M}^{-1}$ in chloroform.

- Photoswitchable Sexithiophene-Based Molecular Wires
  Abstract:
  Photochromic sexithiophenes were prepared by oxidative electrochemical coupling of terthiophenes. The redox properties in the open state are typical of sexithiophenes. Ring closure of both photochromic units leads to a decrease in the energy of the LUMO orbitals with little affect on the energy of the HOMO orbitals. The photochemical tuning of the conjugation of a molecular wire is achieved by combining dithienylethene units with a sexithiophene.

- Metal Nanoparticles Functionalized with Molecular and Supramolecular Switches
  Abstract:
Weakly protected metal nanoparticles (MNPs) are used as precursors for the preparation of catenane- and pseudorotaxane-decorated NPs of various compositions (gold, palladium, platinum). When attached to the surface of MNPs, the molecular switches retain their switching abilities. The redox potentials of these switches depend on and can be regulated by the composition of the mixed self-assembled monolayers covering the MNPs.

- **Nucleobase-Templated Polymerization: Copying the Chain Length and Polydispersity of Living Polymers into Conjugated Polymers**
  **Abstract:**

Conjugated polymers synthesized by step polymerization mechanisms typically suffer from poor molecular weight control and broad molecular weight distributions. We report a new method which uses nucleobase recognition to read out and efficiently copy the controlled chain length and narrow molecular weight distribution of a polymer template generated by living polymerization, into a daughter conjugated polymer. Aligning nucleobase-containing monomers on their complementary parent template using hydrogen-bonding interactions, and subsequently carrying out a Sonogashira polymerization, leads to the templated synthesis of a conjugated polymer. Remarkably, this daughter strand is found to possess a narrow molecular weight distribution and a chain length nearly equivalent to that of the parent template. On the other hand, nontemplated polymerization or polymerization with the incorrect template generates a short conjugated oligomer with a significantly broader molecular weight distribution. Hence, nucleobase-templated polymerization is a useful tool in polymer synthesis, in this case allowing the use of a large number of polymers generated by living methods, such as anionic polymerization, controlled radical polymerizations (NMP, ATRP, and RAFT) and other mechanisms to program the structure, length, and molecular weight distribution of polymers normally generated by step polymerization methods and significantly enhance their properties.

- **Langmuir Monolayer and Langmuir-Blodgett Films Formed by a Melamine-Headed Azobenzene-Derived Amphiphile: Interfacial Assembly Affected by Host-Guest Interaction**
  **Abstract:**
A novel azobenzene-derived amphiphile with a melamine head, 2Azo-2C_{12}H_{25}-melamine, has been synthesized. π-A isotherm measurements displayed that this amphiphile is able to form a stable Langmuir monolayer on both pure water and barbituric acid (BA)- or thymine (T)-containing subphases. The collapse surface pressure and limiting molecular area of its Langmuir monolayer on pure water are 40 mN/m and 0.56 nm², respectively. However, when barbituric acid or thymine was introduced into the subphase, the corresponding π-A isotherms of the monolayers exhibited a lower collapse surface pressure (22 mN/m for BA, 21 mN/m for T) and smaller limiting molecular area (0.54 nm² for BA and 0.52 nm² for T). UV–vis and FT-IR studies of the LB films formed by 2Azo-2C_{12}H_{25}-melamine have also been carried out. The results indicated that the LB films of 2Azo-2C_{12}H_{25}-melamine deposited from pure water undergo distinct collapse of the H-aggregate upon UV irradiation, while the LB films deposited from a BA- or T-containing subphase retain the H-aggregate. The host–guest-interaction-induced blockage of azobenzene photoisomerization should be responsible for the stabilized H-aggregate. A 1:1 host/guest binding mode to form a linear supramolecular polymeric chain has been proposed in the Langmuir monolayers formed on a BA- or T-containing subphase. The current results suggest that the host–guest interaction should be an effective means to manipulate the interfacial assembly of azobenzene-derived amphiphiles.

- **Plasmon-Enhanced Photocurrent Generation from Self-Assembled Monolayers of Phthalocyanine by Using Gold Nanoparticle Films**

**Abstract:**

The effect of localized electric fields on the photocurrent responses of phthalocyanine that was self-assembled on a gold nanoparticle film was investigated by comparing the conventional and the total internal reflection (TIR) experimental systems. In the case of photocurrent measurements, self-assembled monolayers (SAMs) of a thiol derivative of palladium phthalocyanine (PdPc) were prepared on the surface of gold-nanoparticle film that was fixed on the surface of indium-tin-oxide (ITO) substrate via a polyanion (PdPc/AuP/polyion/ITO) or on the ITO surface (PdPc/ITO). Photocurrent action spectra from the two samples were compared by using the conventional spectrometer, and
were found that PdPc/AuP/polyion/ITO gave considerably larger photocurrent signals than PdPc/ITO under the identical concentration of PdPc. In the case of the TIR experiments for the PdPc/AuP/polyion/ITO and the PdPc/AuP/Glass systems, incident-angle profiles of photocurrent and emission signals were correlated with each other, and they were different from that of the PdPc/ITO system. Accordingly, it was demonstrated that the photocurrent signals were certainly enhanced by the localized electric fields of the gold-nanoparticle film.

• Synthesis and Properties of Polyacetylenes Containing Terphenyl Pendent Group with Different Spacers.
Abstract:

Liquid-crystalline, monosubstituted acetylenes containing terphenyl pendent group with varying spacer lengths \([HCtC(CH_2)nO-terphenyl-CN, \text{AnCN, } n \) 1, 6] and its polymers \(\text{PA}n\text{CN}\) were synthesized. Also, the effects of the structural variation on their properties, especially their mesomorphism, UV and photoluminescence behaviors, were studied. The monomers are prepared by simple Suzuki coupling reactions. High yields and high trans-content of polyacetylenes were obtained by polymerization using \([\text{Rh(nbd)Cl}]_2\) catalyst. The polymer with long spacers (hexamethylene), that is, \(\text{PA}6\text{CN}\), formed a nematic mesophase when heated and cooled, however the polymer with short spacers (methylene), that is, \(\text{PA}1\text{CN}\), could not exhibit liquid crystallinity at elevated temperatures. Upon photoexcitation by keep the constant photons of excitation, \(\text{PA}1\text{CN}\) emits ultraviolet emission (\(\lambda_{\text{max}} \sim 311\) nm) but \(\text{PA}6\text{CN}\) gives a stronger emission (\(\lambda_{\text{max}}\sim 308\) nm), indicating that the emission intensity increases with the spacer length due to orientation of main chain by alignment of mesogenic pendant. Short spacer between polyacetylene and mesogens hindered alignment of the main chain, consequently lower fluorescence emission, and loss mesophase of the polymer was induced by short spacer due to disturbance of rigid main chain.

• Radical Entry Mechanisms in Alkali-Soluble-Resin-Stabilized Latexes.
Abstract:
Alkali-soluble resins (ASRs) are random copolymers that contain both hydrophobic groups and a large number of carboxylic acid groups, which are widely used as the sole stabilizers in the production of waterborne dispersed polymers because they remarkably improve the end-use properties of the latexes. However, they reduce the radical entry rate. In this work, the mechanisms for radical entry in ASR-stabilized systems have been investigated. It has been found that the mechanism responsible for the reduction of the rate of radical entry depends on the type of ASR used (prone or not prone to suffer hydrogen abstraction), the type of radical produced from the initiator (charged or uncharged, oxygen centered or carbon centered), the phase where the radicals are produced (aqueous or oil phase) and the type of monomer (hydrophobic like styrene or more hydrophilic like methyl methacrylate).

- A new crosslinkable system based on thermal Huisgen reaction to enhance the stability of electro-optic polymers.
  Abstract:

The thermal Huisgen cycloaddition reaction is a new and efficient process to crosslink electro-optic polymers, since it leads to an effective increase of the thermal alignment stability of the NLO chromophores.

- DNA-based routes to semiconducting nanomaterials
  Abstract:
The controlled preparation and assembly of opto-electronic nanoscale materials is being tackled by top-down and bottom-up approaches. The latter draws inspiration from biology, where complex hierarchical systems are assembled from simpler building blocks. One of these, DNA, is proving especially useful: its size, stability, topology; the assorted chemical functional groups; plus its capacity for self-assembly provide a powerful nanoscale toolbox for materials preparation. Here we review recent research that shows the roles DNA can play in the preparation and organisation of semiconductor nanomaterials. Studies show that both hard inorganic and soft polymer materials can be directed to grow at nanoscale lengths using DNA and its constituents. In some cases the resulting materials have been used as components in simple electrical devices and the methodology has been extended to analytical tools. Intriguingly, these DNA–semiconductor hybrid materials have been found to self-assemble themselves, forming highly regular rope-like assemblies and conducting network structures.

- Optical Detection of Glucose by Means of Metal Nanoparticles or Semiconductor Quantum Dots
  **Abstract:**

  The glucose dehydrogenase biocatalyzed generation of NADH by the oxidation of glucose enables the fluorescence detection of glucose by methylene-blue-functionalized CdSe/ZnS quantum dots and the colorimetric determination of glucose by the NADH-mediated growth of Au nanoparticles

- Self-Assembly of Giant Peptide Nanobelts
  **Abstract:**
Many alkylated peptide amphiphiles have been reported to self-assemble into cylindrical nanofibers with diameters on the order of a few nanometers and micrometer scale lengths; these nanostructures can be highly bioactive and are of great interest in many biomedical applications. We have discovered the sequences for these molecules that can eliminate all curvature from the nanostructures they form in water and generate completely flat nanobelts with giant dimensions relative to previously reported systems. The nanobelts have fairly monodisperse widths on the order of 150 nm and lengths of up to 0.1 mm. The sequences have an alternating sequence with hydrophobic and hydrophilic side chains and variations in monomer concentration generate a “broom” morphology with twisted ribbons that reveals the mechanism through which giant nanobelts form. Interestingly, a variation in pH generates reversibly periodic 2 nm grooves on the surfaces of the nanobelts. With proper functionalization, these nanostructures offer a novel architecture to present epitopes to cells for therapeutic applications.

- Chemistry, Biology, and Medicinal Potential of Narciclasine and its Congener

**Abstract:**

Ornamental flower growers know that placing a cut daffodil (aka narcissus) in a vase with other flowers has a negative effect on the quality of those flowers and significantly shortens their vase life. Furthermore, a common horticultural practice for the cultivation of narcissus flowers involves the introduction of cuts on the bulbs before immersing them into water. The mucilage that leaches out from the cuts is constantly removed by frequent changing of the water, and this leads to sprouting. These observations raise speculation that specific components in the mucilage of the narcissus bulbs may have powerful growth-inhibitory effects. Historical use of narcissus flowers, as well as at least 30 other plants of the Amaryllidaceae family, in folk medicine for the management of cancer speaks volumes to validate this conjecture.

On the basis of the present scientific evidence, it is likely that isocarbostyril constituents of the Amaryllidaceae, such as narciclasine, pancratistatin, and their congeners, are the most important metabolites responsible for the therapeutic benefits of these plants in the folk medical treatment of cancer. Notably, *N. poeticus* L. used by the ancient Greek physicians, as was eluded before, is now known to contain some 0.12 g of narciclasine per kg of fresh bulbs. Continuing along this intriguing path, the focus of the present review is a comprehensive literature survey and discussion of the chemistry and biology of these compounds as specifically relevant to their potential use in medicine. The examination of the synthetic organic chemistry, more specifically the total synthesis efforts inspired by the challenging chemical structures of narciclasine, pancratistatin, and their congeners,
will be reduced to a minimum in view of the two very recent excellent reviews published on this subject.

- Ionic Liquids in Heterocyclic Synthesis
  Abstract:

  Heterocycles form by far the largest of the classical divisions of organic chemistry. Moreover, they are of immense importance not only both biologically and industrially but to the functioning of any developed human society as well. Their participation in a wide range of areas can not be underestimated. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles. Most of the significant advances against disease have been made by designing and testing new structures, which are often heteroaromatic derivatives. In addition, a number of pesticides, antibiotics, alkaloids, and cardiac glycosides are heterocyclic natural products of significance for human and animal health. Therefore, researchers are on a continuous pursuit to design and produce better pharmaceuticals, pesticides, insecticides, rodenticides, and weed killers by following natural models. A significant part of such biologically active compounds is composed of heterocycles. These compounds play a major part in biochemical processes and the side groups of the most typical and essential constituents of living cells. Other important practical applications of heterocycles can also be cited, for instance, additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators.

  Ionic liquids are generally defined as liquid electrolytes composed entirely of ions, and occasionally a melting point criterion has been proposed to distinguish between molten salts and ionic liquids (mp < 100 °C). However, both molten salts and ionic liquids are better described as liquid compounds that display ionic–covalent crystalline structures. The purpose of this review is to show the application of ionic liquids in heterocyclic syntheses from cyclocondensation reactions. This denotes a great deal of material to be covered; thus it was necessary to make some limitations to the scope of this review: (i) heterocycles obtained from cycloaddition reactions were excluded; (ii) only papers using ionic liquids as a solvent, liquid support, or catalyst have been considered, but biocatalyst reactions have been excluded; (iii) papers in which the reactivity of ionic liquids was evaluated have also been excluded.

- Self-Assembly of Nanostructured Diatom Microshells into Patterned Arrays Assisted by Polyelectrolyte Multilayer Deposition and Inkjet Printing
Individual shells of the diatom *Coscinodiscus* were self-assembled into a rectangular array on a glass surface that possessed a polyelectrolyte multilayer patterned through inkjet printing. This patterned thin film possessed hierarchical order with nanostructure provided by the diatom biosilica. The process used two polyelectrolytes with opposite electric potentials to control the surface charge of the substrate. The fine features of the diatom frustules were perfectly preserved as a result of the mild conditions of the deposition process. This technique has the potential to enable large-scale device applications that harness the unique properties of functionalized diatom biosilica.

- **Self-Assembly of Bis(merocyanine) Tweezers into Discrete Bimolecular \( \pi \)-Stacks**

Abstract:

Dipolar aggregation: Examples of a novel class of tweezer molecules have been constructed through the tethering of two dipolar merocyanine chromophores. The electrostatic-interaction-directed self-assembly of these tweezers affords centrosymmetric bimolecular complexes with a unique aggregate geometry of four \( \pi \)-stacked chromophores (see picture) with an alternating arrangement of their dipole moments and very high dimerization constants, even in the good solvating solvent chloroform. Examples of a novel class of tweezer molecules have been constructed through the tethering of two dipolar merocyanine chromophores by a naphthalenedimethylene or dimethylenediphenylmethane spacer. The electrostatic-interaction-directed self-assembly of these bis(merocyanine) tweezers affords centrosymmetric bimolecular complexes with very high dimerization constants of up to \( >10^9 \text{M}^{-1} \), even in the good solvating solvent chloroform. This pronounced self-association of the bis(merocyanine) tweezers is attributed to the strongly dipolar nature of the merocyanine chromophores and a unique aggregate geometry of four \( \pi \)-stacked chromophores with an alternating arrangement of their dipole moments. The structural assignment of the tetrachromophoric \( \pi \)-stack has been accomplished by MALDI-TOF mass spectrometry and ROESY NMR spectroscopy. Furthermore, molecular modeling studies have accounted for the relationships between the dimerization constants and optical properties of the bimolecular complexes of the present bis(merocyanine) dyes and the structure of the spacer and the positions at which the merocyanine chromophores are attached.
• Solvent-Assisted Organized Structures Based on Amphiphilic Anion-Responsive $\pi$-$\pi$ Conjugated Systems
Abstract:

Just subtract water: Amphiphilic $\pi$-$\pi$-conjugated acyclic oligopyrroles form solvent-assisted H-aggregates that give rise to vesicular structures in aqueous solution (see figure). The H-aggregates are sensitive to the conditions and are transformed into J-aggregates by the removal of water. The synthesis of amphiphilic $\pi$-$\pi$-conjugated acyclic oligopyrroles and the formation of solvent-assisted aggregates are reported. We have prepared various types of BF$_2$ complexes of 1,3-dipyrrrolylpropane-1,3-diones bearing aryl rings substituted with hydrophilic polyethylene glycol (PEG) chains, both as acyclic anion receptors and as building subunits for organized architectures based on $\pi$-$\pi$ stacking. The formation of supramolecular H-type assemblies of these amphiphilic derivatives in aqueous solution was suggested by UV/Vis and fluorescence spectroscopy and further supported by $^1$H NMR and dynamic light scattering (DLS) analyses. Cryogenic transmission electron microscopy (cryo-TEM) analyses of the aqueous solutions suggest that the fabrication of nanoscale network structures and vesicles depends on the peripheral substituents. The H-aggregates in aqueous solution are sensitive to the conditions required for transformation into monomers through replacement with miscible solvents such as alcohols and into J-type aggregates by water evaporation and freeze-drying procedures. However, they are fairly stable and sustainable to anion binding, whereas on CH$_2$Cl$_2$ extraction they are transformed into other assembled modes but remain in the aqueous solution. The metastable states of affairs for distributions between two immiscible solvents are controlled by the orders of solution preparation; this also suggests that the formation of stable assemblies is assisted by water molecules. Furthermore, assemblies in which the stacking modes depend on the aliphatic side chains are also observed in a nonpolar hydrocarbon solvent.

• Undulated Multicompartment Cylinders by the Controlled and Directed Stacking of Polymer Micelles with a Compartmentalized Corona
Abstract:

Like a bamboo rod: Long, bamboo-like undulated cylinders with distinct branch points and end groups (see picture) were obtained by the stacking of block terpolymer micelles that contain a fluorinated polybutadiene core and a compartmentalized corona of poly(4-tert-butoxystyrene) and
poly(tert-butyl methacrylate). Stacking of the polymer micelles, which can be reversed, occurred when the solvent was changed from dioxane to ethanol.

• Supramolecular ABC Triblock Copolymers
  Abstract:

  Just add it! Ruthenium initiators functionalized with hydrogen-bonding sites were utilized in ring-opening metathesis polymerization to prepare heterotelechelic polymers with hydrogen-bonding and metal-coordination units in a single step. Supramolecular ABC triblock copolymers were then self-assembled in one pot by simply adding complementary telechelic polymers to a solution of the heterotelechelic polymer (see picture).

• Minimal nucleotide duplex formation in water through enclathration in self-assembled hosts
  Abstract:

  Short nucleotide fragments such as mono- and dinucleotides are generally unable to form stable hydrogen-bonded base pairs or duplexes in water. Within the hydrophobic pockets of enzymes, however, even short fragments form stable duplexes to transmit genetic information. Here, we demonstrate the efficient formation of hydrogen-bonded base pairs from mononucleotides in water through enclathration in the hydrophobic cavities of self-assembled cages. Crystallographic studies and 1H- and 15N-NMR spectroscopy clearly reveals pair-selective recognition of mononucleotides and the selective formation of an anti-Hoogsteen-type base pair in the cage’s cavity. Within an analogous expanded cage, dinucleotides are also found to form a stable duplex in water. These results emphasize how hydrogen-bonded base pairing is amplified in a local hydrophobic area isolated from aqueous solution.

• Compressed alkanes in reversible encapsulation complexes
  Abstract:
Simple alkanes feature fully extended conformations as their lowest-energy shapes but can assume coiled, compressed conformations in small spaces. A series of normal alkanes, C_{16} to C_{19}, were encapsulated in self-assembled, hydrogen-bonded complexes. Coiling of the longer alkanes was observed by NMR spectroscopy. The coiling exerts pressure on the interior; the hydrogen bonding seams are loosened, and rotation of the capsule's components occurs on the NMR timescale. The rotation results in interconversion of mirror-image capsule assemblies (racemization). The racemization rates were determined and shown to increase with the length of the alkane, the longer alkanes exerting more pressure. Free energies of activation for racemization were determined at the coalescence temperatures, and were \( \Delta G^\ddagger = 15.7, 16.7 \) and 17.2 kcal mol\(^{-1} \) for C_{19}, C_{18} and C_{17}, respectively. The shorter C_{16} was encapsulated in its fully extended conformation, and does not seem to exert pressure inside the capsule.

  Abstract:

We have synthesized two [2]rotaxanes, each possessing a (Z)-\( \alpha \)-methylstilbene unit as one of its stoppers, in good yield through the photoisomerization of terminal (E)-\( \alpha \)-methylstilbene units of dialkylammonium salts in the presence of the crown ether dibenzo[24]crown-8 (DB24C8). The synthesis relies on the formation of pseudorotaxane intermediates through hydrogen bond-guided self-assembly and subsequent end-closing photoisomerization. An (E)-\( \alpha \)-methylstilbene unit is not sufficiently bulky to prevent dissociation of the DB24C8 unit, whereas a (Z)-\( \alpha \)-methylstilbene unit acts as a true stopper. We also synthesized these [2]rotaxanes from the (Z)-\( \alpha \)-methylstilbene-terminated axle-like salts though thermodynamic covalent chemistry by taking advantage of the reversibility of the photoisomerization. To dissociate the components of the [2]rotaxanes, we performed the reverse end-opening process under UV irradiation (i.e., Z-to-E isomerization of the \( \alpha \)-methylstilbene termini) in a polar solvent. These rotaxanes are stable at room temperature, but dissociate slowly to their two components at elevated temperatures.

- A Diastereoselective Unique Route to Cyclopropanes Functionalized at All Three Ring Carbon Atoms from Acyclic Vinyl Sulfone-Modified Carbohydrates
  Abstract:
In a departure from the current trend of using metal-catalyzed routes to cyclopropanation, pentosyl and hexosyl vinyl sulfone-modified carbohydrates having the terminal double bond and a suitably positioned leaving group are reacted in a stereoselective fashion with a series of nucleophiles to yield a myriad of cyclopropanes substituted at all three ring carbon atoms.