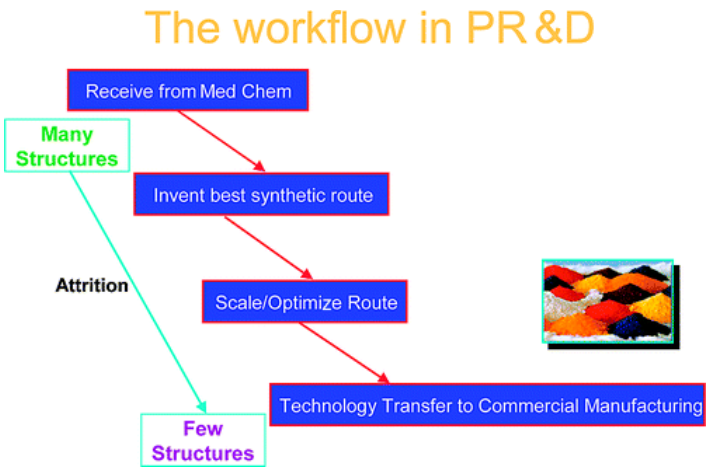
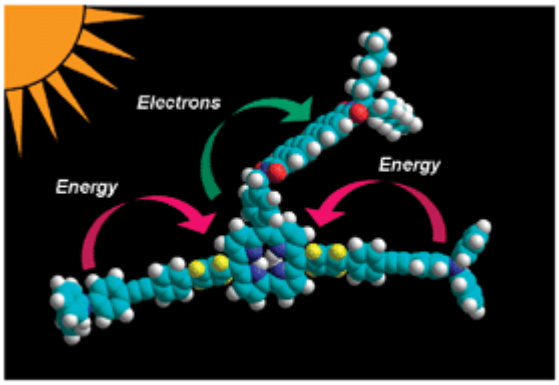
- Chemical Process Research and Development in the 21st Century: Challenges, Strategies, and Solutions from a Pharmaceutical Industry Perspective
  Federsel, H.-J. *Acc. Chem. Res.* **2009**, *42*, 671–680.
  Abstract:




In process research and development (PR&D), the generation and manipulation of small-molecule drugs ranges from bench-scale (laboratory) chemistry to pilot plant manufacture to commercial production. A broad range of disciplines, including process chemistry (organic synthesis), analytical chemistry, process engineering (mass and heat transfer, unit operations), process safety (chemical risk assessment), regulatory compliance, and plant operation, must be effectively applied. In the critical handover between medicinal chemistry and PR&D, compound production is typically scaled up from a few hundred grams to several kilograms. Can the methodologies applied to the former also satisfy the technical, safety, and scalability aspects that come into play in the latter? Occasionally, the transition might occur smoothly, but more often the situation is the opposite: much work and resources must be invested to design a process that is feasible for manufacturing on pilot scale and, eventually, for commercial production.

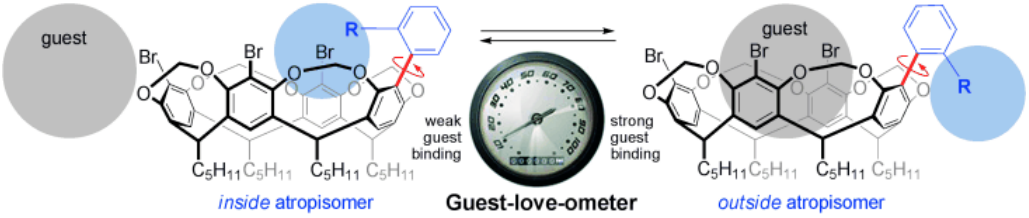
Authentic examples provide enlightening illustrations of dos and don’ts for developing syntheses designed for round-flask operation into production-scale processes. Factors that are easily underestimated or even neglected in the laboratory, such as method robustness, chemical hazards, safety concerns, environmental impact, availability of starting materials and building blocks in bulk quantities, intellectual property (IP) issues, and the final cost of the product, will come into play and need to be addressed appropriately. The decision on which route will be the best for further development is a crucial event and should come into focus early on the R&D timeline. In addition to scientific and technical concerns, the parameter of speed has come to the forefront in the pharmaceutical arena. Although historically the drug industry has tolerated a total time investment of far more than 10 years from idea to market, the current worldwide paradigm requires a reduction to under 10 years for the specific segment covering preclinical development through launch. This change puts enormous pressure on the entire organization, and the implication for PR&D is that the time allowed for conducting route design and scale-up has shrunk accordingly. Furthermore, molecular complexity has become extremely challenging in many instances, and demand steadily grows for process understanding and knowledge generation about low-level byproduct, which often must be controlled even at trace concentrations to meet regulatory specifications (especially in the case of potentially genotoxic impurities). In this Account, we paint a broad picture of the technical challenges the PR&D community is grappling with today, focusing on what measures have been taken over the years to create more efficiency and effectiveness.

- Photoactive corrole-based arrays
  Flamigni, L.; Gryko, D. T. *Chem. Soc. Rev.* **2009**, *38*, 1635 – 1646.
  Abstract:



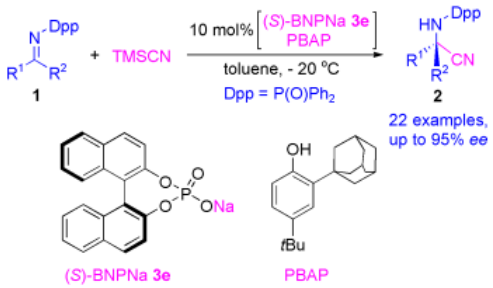

The collection and conversion of light energy into chemical energy is based on the use of molecular structures of various complexity, where the absorbed light energy is first converted into an excited state able to undergo energy or electron transfer processes and finally it is stored in a charge separated state as chemical (electrochemical) potential. A bio-mimetic approach has seen tetrapyrroles number among the most common components of these arrays. This *tutorial review* reports on the use of relatively new tetrapyrroles, corroles, in this field. A brief presentation of the electrochemical and photophysical properties of the corrole units relevant to the application is presented together with a discussion on the photo- and thermal stability issues, followed by an overview of the activity and improvements in the preparation of photo-active molecular arrays containing corroles.

- Guest Binding Drives Reversible Atropisomerism in Cavitand Hosts
  Nguyen, T. V.; Sinclair, D. J.; Willis, A. C.; Sherburn, M. S. *Chem. Eur. J.* **2009**, *24*, 5892-5895.
  Abstract:




**Guest-love-ometer**: The equilibrium *inside-outside* atropisomeric ratio of *ortho*-substituted phenyl cavitands shows a strong solvent dependence. The competition between the *ortho*-substituent and the solvent guest for the bowl cavity leads to a sensitive system for the measurement of relative guest binding affinities.

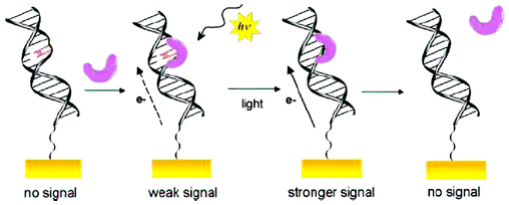
- Facile and Efficient Enantioselective Strecker Reaction of Ketimines by Chiral Sodium Phosphate
  Shen, K.; Liu, X.; Cai, Y.; Lin, L.; Feng, X. *Chem. Eur. J.* **2009**, *24*, 6008-6014.
  Abstract:




**Asymmetric catalysis**: A facile enantioselective Strecker reaction of ketimines with trimethylsilyl cyanide (TMSCN) was realized by employing chiral (*S*)-BNPNa **3 e** and PBAP as an additive (see image). A wide substrate scope and good-to-excellent enantioselectivities were achieved.

A facile and efficient enantioselective Strecker reaction of ketimines catalyzed by a chiral alkali-metal salt has been developed. When 10 mol % BNPNa (BNP=1,1′-binaphthyl-2,2′-diylphosphate) prepared in situ and 10 mol % *para*-*tert*-butyl-*ortho*-adamantylphenol (PBAP) were introduced into the reaction, up to 96 % yield and up to 95 % *ee* (*ee*=enantiomeric excess) were obtained. Both aliphatic and aromatic ketimines, especially sterically bulky cyclic ketimines derived from β-acetonaphthone, α-indanone, and α-tetralone were found suitable for this reaction. On the basis of the experimental results and previous reports, trimethylsilyl cyanide (TMSCN) was indicated to be the real reactive nucleophile despite the existence of PBAP, and a possible working model was proposed to explain the origin of the asymmetric induction. The facile availability of 1,1′-binaphthyl-2,2′-diylphosphoric acid (BNPH) and the simplicity of the procedure are beneficial for practical applications.

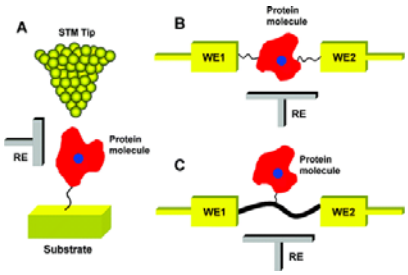
- Electron Transfer in DNA and in DNA-Related Biological Processes. Electrochemical Insights
  Boussicault, F.; Robert, M. *Chem. Rev.* **2008***, 108,* 2622-2645.
  <u>Abstract:</u>




Since the pioneering work of Berg, Paleček, and Elving, many studies have been devoted to the electrochemical investigation of the electrical properties of nucleic acids and DNA strands. Based on polarographic methods, these early works involved mercury electrodes, with which nucleic acids strongly interact, thus complicating analysis of the experimental signals. With the development of molecular electrochemistry, solid electrodes (metals, carbon-based electrodes, and semiconductors, for example, indium tin oxide) were later introduced. Interactions of these materials with biological molecules are therefore lessened or to some extent controlled, opening the door toward assembly-controlled nanometric architectures at the interface between electrode and solution. It has been demonstrated that both holes and electrons can migrate through the DNA helix over distances. Consequently, electrochemistry of nucleic acids and DNA constituents at electrodes may provide valuable insights into the mechanisms involved in these processes, complementary to photochemical methods, product studies, quantum calculations, and modeling. Such electrochemical studies may further improve the understanding of biological reactions such as aging, DNA oxidative lesion formation, and DNA repair. Charge transfer through DNA could also be exploited in the design of electrochemical DNA-based biosensors. For example, sensitive and selective sensors based on a

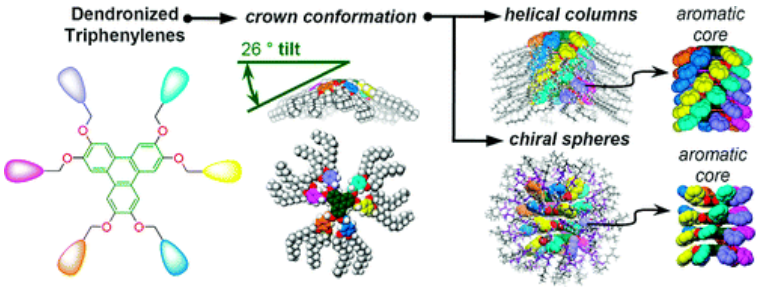
single-strand DNA recognition interface to a sample containing a sequence target and a redox-active intercalator probe have been proposed. Description of this type of sensors stands beyond the scope of this review.

- Single-Molecule Electron Transfer in Electrochemical Environments
  Zhang, J.; Kuznetsov, A. M.; Medvedev, I. G.; Chi, Q.; Albrecht, T.; Jensen, P. S.; Ulstrup, J. *Chem. Rev.* **2008***, 108,* 2737-2791.
  Abstract:



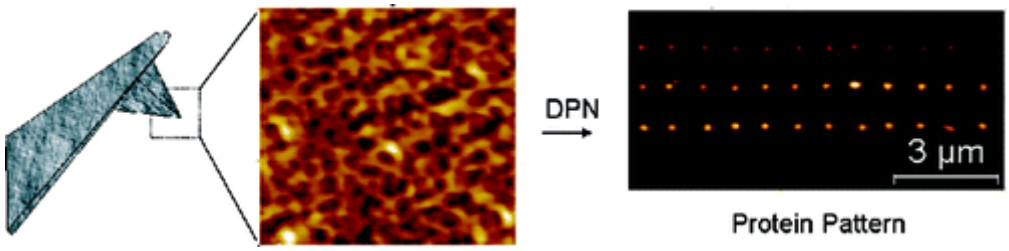

Interfacial molecular electrochemistry is presently moving toward new levels of structural and functional resolution, approaching even that of the single molecules. This evolution extends, notably to fragile biological molecules and macromolecules such as redox metalloproteins and metalloenzymes. Underlying fundamentals of electron and proton transfer of redox molecules and biomolecules in homogeneous solution are broadly understood, with increasing detail and theoretical sophistication currently added. Fundamentals of interfacial electrochemical electron transfer (ET) are also well understood, but the composite inhomogeneous and anisotropic interfacial solid-electrolyte environment is in current need of new concepts, and rationalization of even new ET phenomena. The latter applies for example to new working configurations such as electrochemical scanning tunneling microscopy (in situ STM) or electrochemically controlled nanoscale electrodes where interfacial electrochemical ET of the single (bio)molecule can now be addressed.
Nanoparticles with single-electron charging features (Coulomb blockade) and nanoparticles as catalysts in bioelectrochemistry of redox metalloproteins are particularly addressed and some perspectives noted. Section offers a few suggestions regarding new scientific information and electrochemical and bioelectrochemical “device-like” constructions rooted in the nanoscale and single-molecule nature of the core systems.

- Self-Assembly of Dendronized Triphenylenes into Helical Pyramidal Columns and Chiral Spheres
  Percec, V.; Imam, M. R.; Peterca, M.; Wilson, D. A.; Graf, R.; Spiess, H. W.; Balagurusamy, V. S. K.; Heiney, P. A. *J. Am. Chem. Soc.* **2009**, *131*, 7662–7677.
  Abstract:



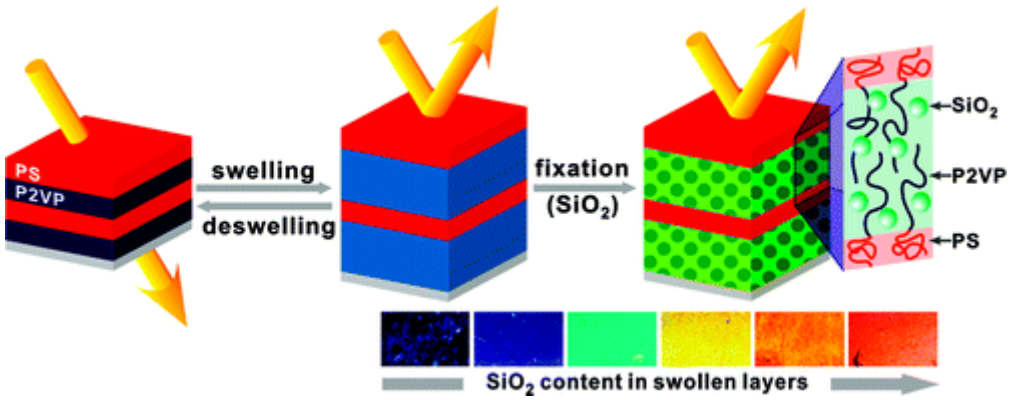
The synthesis and structural and retrostructural analyses of a library containing 10 triphenylenes functionalized with self-assembling benzyl ether and phenyl propyl ether dendrons are reported. These dendronized triphenylenes adopt a crown rather than discotic conformation. Their crown conformation mediates the self-assembly of the discotic triphenylene unit in helical pyramidal columns and in chiral spheres. The chiral spheres are generated from short segments of helical pyramidal columns that are spherically distorted. Therefore, the chirality of the sphere is determined by a short helical pyramidal column that represents the inner part of the supramolecular sphere. Both the helical pyramidal columns and the chiral spheres represent supramolecular architectures that were self-assembled for the first time from discotic molecules. The helical pyramidal columns self-organize in various hexagonal and rectangular lattices, while the chiral spheres self-organize into cubic and tetragonal periodic arrays and into a quasiperiodic 12-fold liquid quasicrystal. The helical sense of the helical pyramidal columns and of helical spheres is selected by a stereocenter that can be incorporated either in the alkyl groups of the dendron or in the triphenylene part of the dendritic crown via donor−acceptor interactions. The self-assembly process of the dendronized triphenylene donor can be programmed by a new supramolecular “polymer effect” generated by donor−acceptor interactions.

- Porous Multilayer-Coated AFM Tips for Dip-Pen Nanolithography of Proteins
  Wu, C.-C.; Xu, H.; Otto, C.; Reinhoudt, D. N.; Lammertink, R. G. B.; Huskens, J.; Subramaniam, V.; Velders, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7526–7527.
  Abstract:



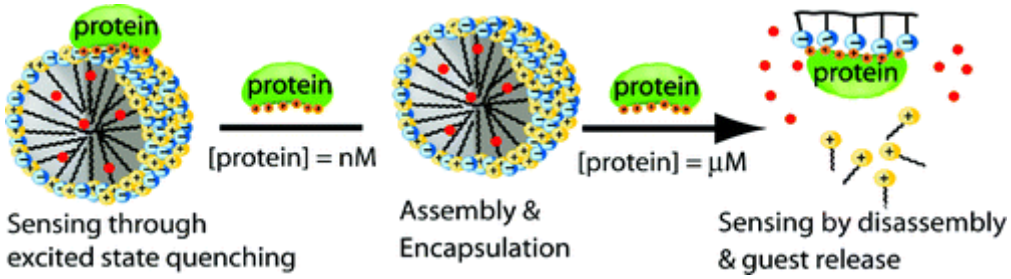

A simple and novel method for fabricating nanoporous-structure-coated silicon nitride tips for dip-pen nanolithography (DPN) by using the layer-by-layer (LbL) technique has been developed. The pore sizes can be adjusted by treating the LbL films coated onto the amino-terminated self-assembled monolayer ($NH_2$−SAM)-functionalized AFM tip surface with a base solution for different periods of time. This hydrophilic porous material can absorb biomolecules easily and also provides a larger-volume ink reservoir compared with a bare silicon nitride tip. Proof-of-concept of the porous AFM tip is demonstrated by using fluorescent proteins as ink molecules to fabricate protein patterns at the micrometer and submicrometer length scales.

- Full Color Stop Bands in Hybrid Organic/Inorganic Block Copolymer Photonic Gels by Swelling−Freezing
  Kang, C.; Kim, E.; Baek, H.; Hwang, K.; Kwak, D.; Kang, Y.; Thomas, E. L. *J. Am. Chem. Soc.* **2009**, *131*, 7538–7539.
  Abstract:



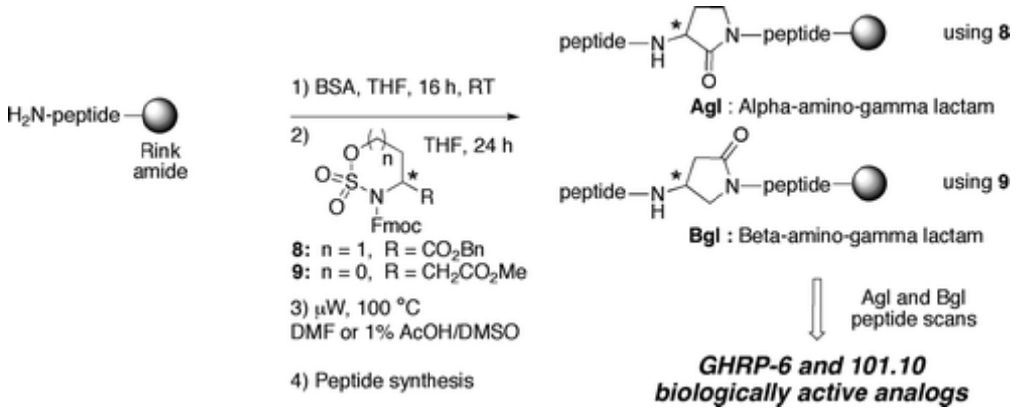

We report a facile way of fabricating hybrid organic/inorganic photonic gels by selective swelling and subsequent infiltration of $SiO_2$ into one type of lamellar microdomain previously self-assembled from modest-molecular-weight block copolymers. Transparent, in-plane lamellar films were first prepared by assembly of polystyrene-*block*-poly(2-vinylpyridine) (PS-*b*-P2VP), and subsequently the P2VP domains were swollen with a selective solvent, methanol. The swollen structures were then fixated by synthesizing $SiO_2$ nanoparticles within P2VP domains. The resulting frozen photonic gels (*f*-photonic gels) exhibited strong reflective colors with stop bands across the visible region of wavelengths.

- Fluorescence Patterns from Supramolecular Polymer Assembly and Disassembly for Sensing Metallo- and Nonmetalloproteins
  Gonzalez, D. C.; Savariar, E. N.; Thayumanavan, S. *J. Am. Chem. Soc.* **2009**, *131*, 7708–7716.
  Abstract:



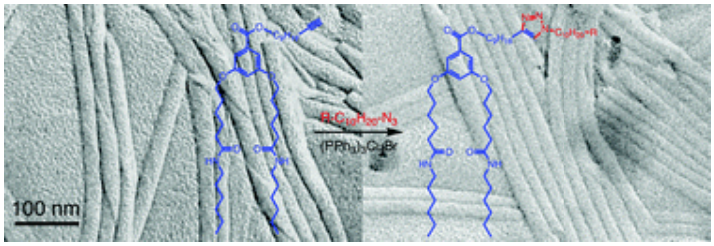

Critical aggregation concentration (CAC) of surfactants is lowered when polyelectrolytes act as counterions. At a concentration in between the CACs of the surfactant and the polymer−surfactant complex, protein-induced disassemblies can be achieved. This is because, when proteins competitively bind to the polyelectrolytes, the surfactants are not capable of sustaining a micelle-type assembly at this concentration. Since these amphiphilic aggregates are capable of noncovalently sequestering hydrophobic guest molecules, the protein binding induced disassembly process also results in a guest release from these assemblies. We show here that the change in fluorescence with different proteins is dependent not only on the nature of the polymer−surfactant complex, but also on the fluorescent transducer. Two processes can be responsible for the observed fluorescence change: fluorophore guest release from the hydrophobic interior of the assembly and excited state quenching due to complementary components in the analyte. The latter mechanism is especially possible with metalloproteins. We show here that an excited state quenching is possible at nanomolar concentrations of the proteins, while the disassembly based fluorescence reduction is the dominant pathway at micromolar concentrations.

- Positional Scanning for Peptide Secondary Structure by Systematic Solid-Phase Synthesis of Amino Lactam Peptides
  Jamieson, A. G.; Boutard, N.; Beauregard, K.; Bodas, M. S.; Ong, H.; Quiniou, C.; Chemtob, S.; Lubell, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 7917–7927.
  Abstract:




Incorporation of amino lactams into biologically active peptides has been commonly used to restrict conformational mobility, enhance selectivity, and increase potency. A solid-phase method using a Fmoc-protection strategy has been developed for the systematic synthesis of peptides containing configurationally defined α- and β-amino γ-lactams. N-Alkylation of N-silyl peptides with five- and six-member cyclic sulfamidates 9 and 8 minimized bis-alkylation and provided N-alkyl peptides, which underwent lactam annulation under microwave heating. Employing this solid-phase protocol on the growth hormone secretagogue GHRP-6, as well as on the allosteric modulator of the IL-1 receptor 101.10, has furnished 16 lactam derivatives and validated the effectiveness of this approach on peptides bearing aliphatic, aromatic, branched, charged, and heteroatomic side chains. The binding affinity IC50 values of the GHRP-6 lactam analogues on both the GHS-R1a and CD36 receptors are reported as well as inhibition of thymocyte proliferation measurements for the 101.10 lactam analogues. In these cases, lactam analogues were prepared exhibiting similar or improved properties compared with the parent peptide. Considering the potential for amino lactams to induce peptide turn conformations, the effective method described herein for their supported construction on growing peptides, and for the systematical amino lactam scan of peptides, has proven useful for the rapid identification of the secondary structure necessary for peptide biological activity.

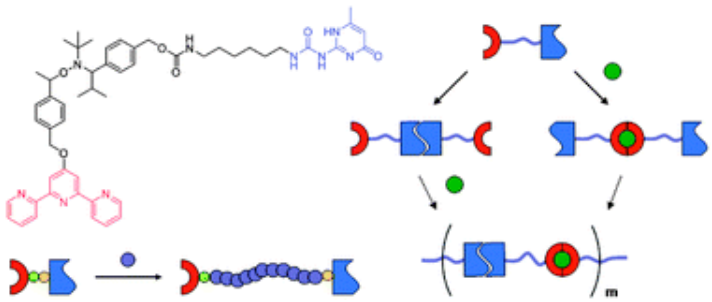
- Direct functionalization of self-assembled nanotubes overcomes unfavorable self-assembling processes.
  Nguyen, T. T. T.; Simon, F. X.; Schmutz, M.; Mésini, P. J. *Chem. Commun.* **2009**, 3457 – 3459.
  Abstract :




Diamides containing alkyne and azido were self-assembled into nanotubes and were reacted under their self-assembled state with small molecules by click chemistry; the resulting compounds remain

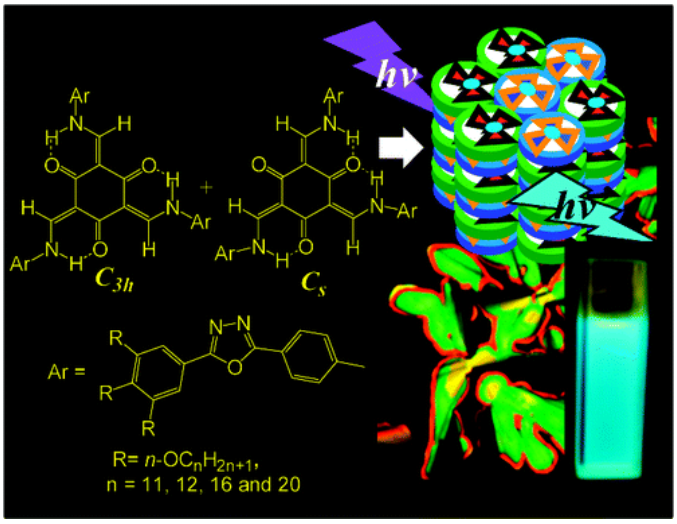
self-assembled into new nanotubes that cannot be formed by simple self-assembly of the constituting molecules.

- Advanced supramolecular initiator for nitroxide-mediated polymerizations containing both metal-ion coordination and hydrogen-bonding sites.
  Mansfeld, U.; Hager, M. D.; Hoogenboom, R.; Ott, C.; Winter, A.; Schubert, U. S. *Chem. Commun.* **2009**, 3386 – 3388.
  Abstract :



The synthesis of a new difunctional nitroxide initiator combining two orthogonal supramolecular entities is reported; controlled radical polymerization of styrene using this initiator is demonstrated to generate well-defined heterotelechelic polymers in a one-step procedure.

- Luminescent, Liquid Crystalline Tris(*N*-salicylideneaniline)s: Synthesis and Characterization, Yelamaggad, C. V.; Achalkumar, A. S.; Rao, D. S.; Prasad, S. K. *J. Org. Chem*. **2009**, *74*, 3168–3171.
  Abstract :

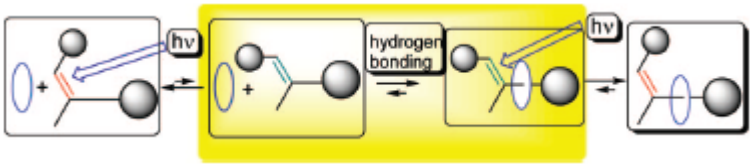



A new class of discotics derived from tris(*N*-salicylideneaniline)s have been synthesized and their thermal and photophysical properties are investigated. These systems with outer 1,3,4-oxadiazole wings exist in an inseparable mixture of two keto-enamine tautomeric forms with $C_{3h}$ and $C_s$ rotational symmetries, and self-assemble into fluid columnar phase over a wide thermal range as evidenced by several complementary studies. They possess emissive characteristics in both solution and columnar states; the blue light (λ = 474 nm) emission has been evidenced for the former state.

- Using Photoresponsive End-Closing and End-Opening Reactions for the Synthesis and Disassembly of [2]Rotaxanes: Implications for Dynamic Covalent Chemistry

Tokunaga, Y.; Akasaka, K.; Hashimoto, N.; Yamanaka, S.; Hisada, K.; Shimomura, Y.; Kakuchi, S. *J. Org. Chem.* **2009**, *74*, 2374–2379.

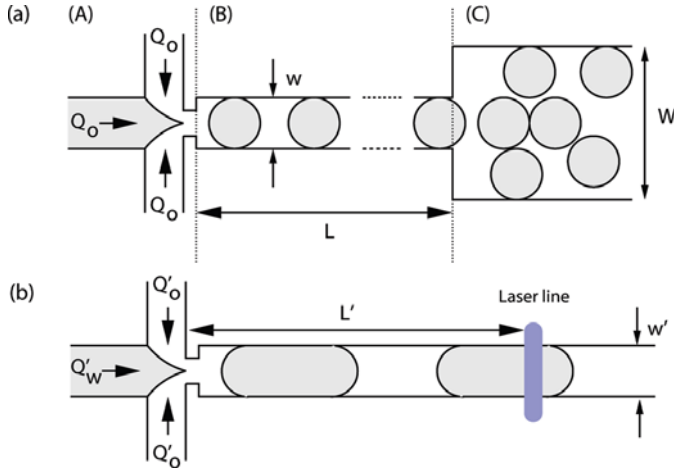
Abstract:




We have synthesized two [2]rotaxanes, each possessing a (*Z*)-R-methylstilbene unit as one of its stoppers, in good yield through the photoisomerization of terminal (*E*)-R-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*)-R-methylstilbene unit is not sufficiently bulky to prevent dissociation of the DB24C8 unit, whereas a (*Z*)-R-methylstilbene unit acts as a true stopper. We also synthesized these [2]rotaxanes from the (*Z*)-R-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 R-methylstilbene termini) in a polar solvent. These rotaxanes are stable at room temperature, but dissociate slowly to their two components at elevated temperatures.

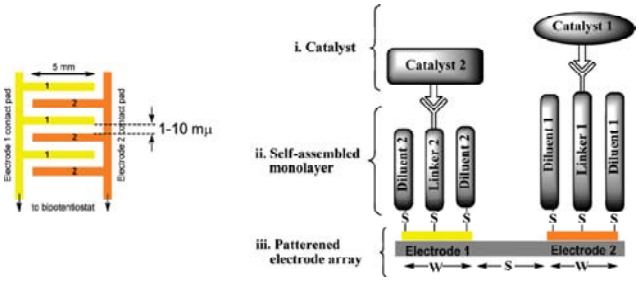
- Kinetic Aspects of Emulsion Stabilization by Surfactants: A Microfluidic Analysis
  Baret, J.-C.; Kleinschmidt, F.; El Harrak, A.; Griffiths, A. D. *Langmuir*, **2009**, *25*, 6088–6093.

Abstract:




In classical emulsification processes, surfactants play two roles: first, they reduce the interfacial tension, facilitating droplet deformation and rupture, and second, they reduce droplet coalescence. Here, we use a microfluidic emulsification system to completely uncouple these two processes, allowing stabilization againstcoalescence to be studied quantitatively and independently of droplet formation. We demonstrate that, in addition to the classical effect of stabilization by an increase of surfactant concentration, the dynamics of adsorption of surfactant at the water-oil interface is a key element for droplet stabilization. Microfluidic emulsification devices can therefore be tailored to improve emulsification while decreasing the concentration of surfactant by increasing the time before the droplets first come into contact.

- Selective Anodic Desorption for Assembly of Different Thiol Monolayers on the Individual Electrodes of an Array
  Collman, J. P.; Hosseini, A.; Eberspacher, T. A.; Chidsey, C. E. D. *Langmuir*, **2009**, *25*, 6517–6521.
  Abstract:




The close proximity of two individually addressable electrodes in an interdigitated array provides a unique platform for electrochemical study of multicatalytic processes. Here, we report a “plug-and-play” approach to control the underlying self-assembled monolayer and the electroactive species on each individually addressable electrode of an interdigitated array. The method presented here uses selective anodic desorption of a monolayer from one of the individually addressable electrodes and rapid formation of a different self-assembled monolayer on the freshly cleaned electrode. We illustrate this strategy by introducing variations in the length of the linker to the electroactive species in the self-assembled monolayer, which determines the rate of electron transfer. In order to separate the assembly of the monolayer from the choice of the electroactive species, we use CuI-catalyzed triazole formation (“click” chemistry) to covalently attach an acetylene-terminated electroactive species to an azide-terminated thiol monolayer selectively on each electrode. The resulting variations in the electron-transfer rate to surface-attached ferrocene and in the rate of catalytic oxidation of ascorbate by the ferrocenium/ferrocene couple demonstrate an application of this approach.