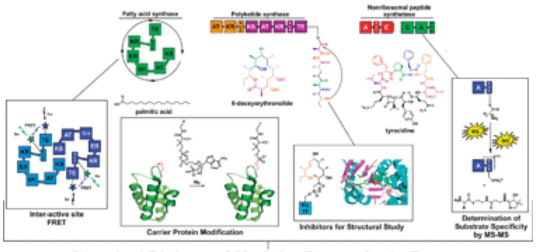
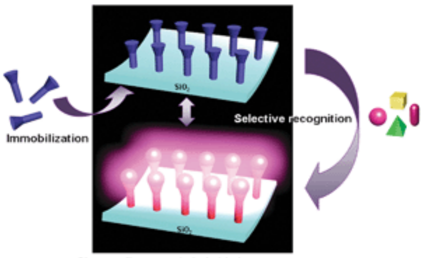
- The chemical biology of modular biosynthetic enzymes
  Meier, J. L.; Burkart, M. D. *Chem. Soc. Rev.* **2009**, *38*, 2012 – 2045.
  Abstract:



Chemical Biology of Modular Biosynthetic Enzymes

Fatty acid synthase (FAS), polyketide synthase (PKS), and nonribosomal peptide synthetase (NRPS) modular biosynthetic enzymes are responsible for the production of a multitude of structurally diverse and biologically important small molecule natural products. Traditional biochemical and genetic studies of these enzymes have contributed substantially to the understanding of their underlying biosynthetic mechanisms. More recently these investigations have been aided by the skillful application of a combination of chemical and biological techniques to aid in overcoming the unique challenges associated with the enzymology of these large multifunctional enzymes. This *critical review* provides a historical context and details studies (through July 2008) which aim to identify and characterize these enzymes using synthetically and/or chemoenzymatically generated small molecule probes (233 references).

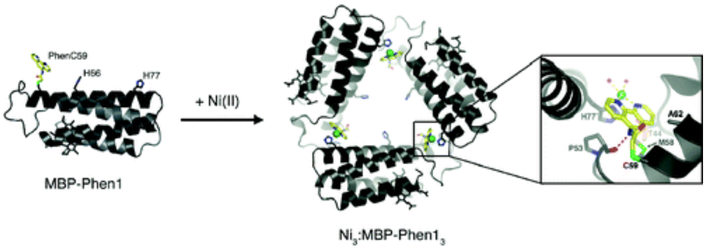
- Silica-based chromogenic and fluorogenic hybrid chemosensor materials
  Han, W. S.; Lee, H. Y.; Jung, S. H.; Lee, S. J.; Jung, S. H. *Chem. Soc. Rev.* **2009**, *38*, 1904 – 1915.
  Abstract:



Chromo-fluorogenic hybrid chemosensor

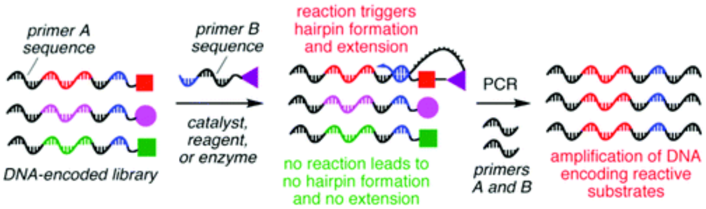
This *tutorial review* focuses on the recent development of silica-based organic–inorganic hybrid nanomaterials for use in biological and environmental applications, in which these chromogenic and fluorogenic chemosensors can selectively detect and separate specific anions and neutral organic guests as well as toxic metal ions.

- A Superprotein Triangle Driven by Nickel(II) Coordination: Exploiting Non-Natural Metal Ligands in Protein Self-Assembly
  Radford, R. J.; Tezcan, F. A. *J. Am. Chem. Soc.* **2009**, *131*, 9136–9137.
  Abstract:



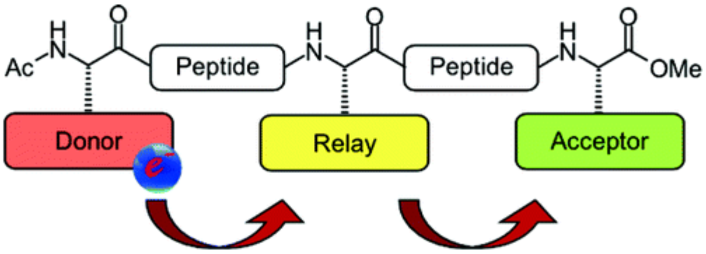
We previously devised a strategy (metal-directed protein self-assembly, MDPSA) that utilizes the simultaneous stability, lability, and directionality of metal−ligand bonds to drive protein−protein interactions. Here we show that both the structural and functional scopes of MDPSA can be broadened by incorporation of non-natural metal-chelating ligands onto protein surfaces. A cytochrome cb562 variant, MBP-Phen1, which features a covalently attached phenanthroline (Phen) group on its surface, self-assembles into an unusual triangular architecture (Ni3:MBP-Phen13) upon binding Ni as a result of specific Phen−protein interactions. The crystal structure of Ni3:MBP-Phen13 reveals that the Phen group is buried in a small pocket on the protein surface, which results in an unsaturated Ni coordination environment.

- Reactivity-Dependent PCR: Direct, Solution-Phase in Vitro Selection for Bond Formation
  Gorin, D. J.; Kamlet, A. S.; Liu, D. R. *J. Am. Chem. Soc.* **2009**, *131*, 9189–9191.
  <u>Abstract:</u>



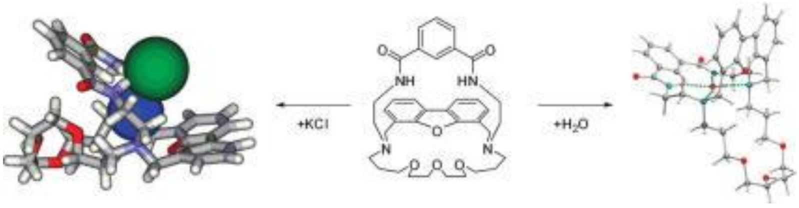
In vitro selection is a key component of efforts to discover functional nucleic acids and small molecules from libraries of DNA, RNA, and DNA-encoded small molecules. Such selections have been widely used to evolve RNA and DNA catalysts and, more recently, to discover new reactions from DNA-encoded libraries of potential substrates. While effective, current strategies for selections of bond-forming and bond-cleaving reactivity are generally indirect, require the synthesis of biotin-linked substrates, and involve multiple solution-phase and solid-phase manipulations. In this work we report the successful development and validation of reactivity-dependent PCR (RDPCR), a new method that more directly links bond formation or bond cleavage with the amplification of desired sequences and that obviates the need for solid-phase capture, washing, and elution steps. We show that RDPCR can be used to select for bond formation in the context of reaction discovery and for bond cleavage in the context of protease activity profiling.

- Electron Relay Race in Peptides
  Giese, B.; Wang, M.; Gao, J.; Stoltz, M.; Muller, P.; Graber, M. *J. Org. Chem.*, **2009**, *74*, 3621–3625.
  <u>Abstract:</u>



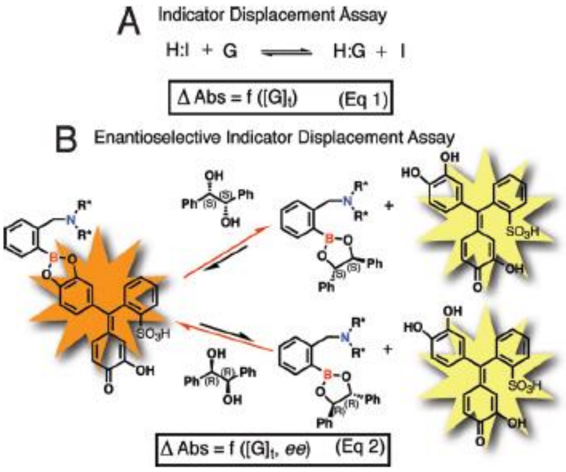
A peptide assay was developed that allows the measurement of electron-transfer (ET) efficiencies in peptides. It turns out that two-step ET processes are faster than single-step reactions. This requires relay amino acids with appropriate redox potentials. Not only arom. but also sulfur-contg. aliph. amino acids can act as stepping stones for the charge. With tryptophan, histidine, and cysteine the reaction is a more complex proton-coupled ET.

- Anion Recognition by a Macrobicycle Based on a Tetraoxadiaza-Macrocycle and an Isophthalamide Head Unit
  Bernier, N.; Carvalho, S.; Li, F.; Delgado, R.; Félix, V. *J. Org. Chem.* **2009**, *74*, 4819–4827.
  Abstract:



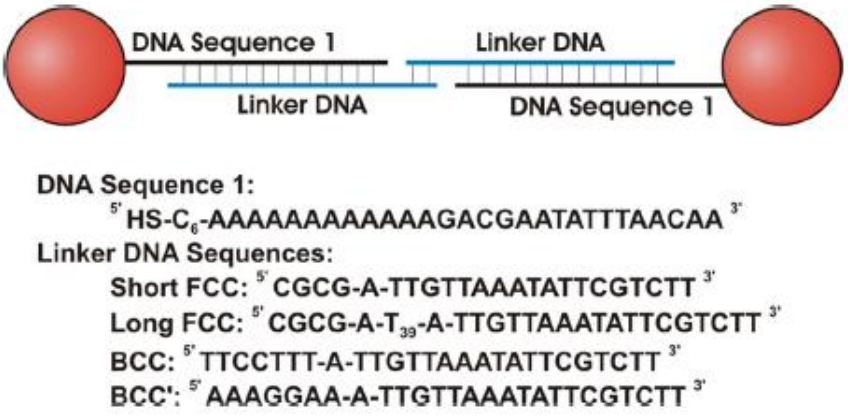
A macrobicycle formed by a tetraoxadiaza macrocycle containing a dibenzofuran (DBF) spacer and an isophthalamide head unit, named DBF-bz, was used as receptor for anion recognition. The molecular structure of DBF-bz was established in solution by NMR and ESI-MS spectroscopies and in single crystal by X-ray diffraction analysis. The X-ray structure showed a water molecule encapsulated into the macrobicyclic cavity by four hydrogen bonds, two of them involving the two N−H amide binding sites and the oxygen of the water molecule (N−H···O hydrogen bonds) and the other two (O−H···N) involving the amine groups as hydrogen bonding acceptors. ^{1}H NMR temperature dependence studies demonstrated that the same structure exists in solution. The ability of this ditopic receptor to recognize alkali halide salts was evaluated by extraction studies followed by ^{1}H NMR and ESI-MS spectroscopies. The macrobicycle showed a capacity to extract halide salts from aqueous solutions into organic phases. The binding ability of this macrobicycle for halides was also quantitatively investigated using ^{1}H NMR titrations in $CDCl_3$ (and DMSO-d_6) solution, and in acidic D_2O solution. The largest binding association constant was found for the chloride anion and the completely protonated receptor. The results suggest that the diammonium-diamide unit of the receptor strongly bind the anionic substrate via multiple N−H···Cl^- hydrogen bonds and electrostatic interactions. The binding trend follows the order $Cl^- > Br^- > I^- \approx F^-$ established from the best fit between the size of the anion and the cavity size of the protonated macrobicycle. Molecular dynamics (MD) simulations of the DBF-bz in $CHCl_3$ solution allowed a detailed insight into the structural and binding properties of the receptor.

- A general protocol for creating high-throughput screening assays for reaction yield and enantiomeric excess applied to hydrobenzoin
  Shabbir, S. H.; Regan, C. J.; Anslyn, E. V. *Proc. Nat. Acad. Sci.* **2009,** *106*, 10487–10492.
  Abstract:



A general approach to high-throughput screening of enantiomeric excess (*ee*) and concentration was developed by using indicator displacement assays (IDAs), and the protocol was then applied to the vicinal diol hydrobenzoin. The method involves the sequential utilization of what we define herein as screening, training, and analysis plates. Several enantioselective boronic acid-based receptors were screened by using 96-well plates, both for their ability to discriminate the enantiomers of hydrobenzoin and to find their optimal pairing with indicators resulting in the largest optical responses. The best receptor/indicator combination was then used to train an artificial neural network to determine concentration and *ee*. To prove the practicality of the developed protocol, analysis plates were created containing true unknown samples of hydrobenzoin generated by established Sharpless asymmetric dihydroxylation reactions, and the best ligand was correctly identified.

- Assembly and organization processes in DNA-directed colloidal crystallization
  Macfarlane, R. J.; Lee, B.; Hill, H. D.; Senesi, A. J.; Seifert, S.; Mirkin, C. A. *Proc. Nat. Acad. Sci.* **2009,** *106*, 10493–10498.
  Abstract:



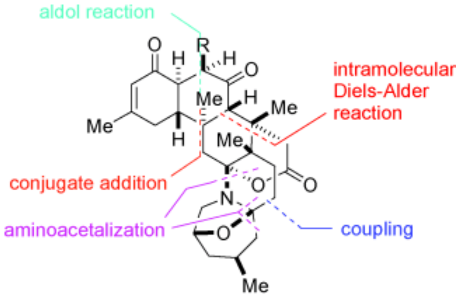
We present an analysis of the key steps involved in the DNA directed assembly of nanoparticles into crystallites and polycrystalline aggregates. Additionally, the rate of crystal growth as a function of increased DNA linker length, solution temperature, and self-complementary versus non-self-complementary DNA linker strands (1- versus 2-component systems) has been studied. The data show that the crystals grow via a 3-step process: an initial ‘‘random binding’’ phase resulting in disordered DNA-AuNP aggregates, followed by localized reorganization and subsequent growth of crystalline domain size, where the resulting crystals are well-ordered at all subsequent stages of growth.

- Supramolecular Alternating Block Copolymers via Metal Coordination
  Yang, S. K.; Ambade, A. V.; Weck, M. *Chem. Eur. J.* **2009**, *15*, 6605-6611.
  Abstract:

Suprapolymers: The synthesis of symmetrically end-functionalized polymers in a single step has been developed by means of ring-opening metathesis polymerization by using a bimetallic ruthenium initiator and functional chain terminators. Self-assembly of the resulting polymers allows for the formation of supramolecular alternating block copolymers (see figure).

A bimetallic ruthenium olefin metathesis initiator was synthesized and used to polymerize functionalized norbornenes, affording polymers that are living at both polymer chain-ends. Using this bis-ruthenium initiator strategy and combining it with functional chain-terminators, highly-efficient syntheses of either SCS-Pd^{II} pincer- or pyridine-functionalized symmetrical telechelic polymers were developed. The terminal functional group incorporation was confirmed by ^{1}H NMR spectroscopy analyses. The telechelic polymers were self-assembled into block copolymers by means of metal coordination between corresponding terminal recognition units. The self-assembly process was monitored by ^{1}H NMR spectroscopy revealing nearly quantitative functionalization. The resulting supramolecular block copolymers were further characterized by viscometry and dynamic light scattering.

- Synthetic Studies of the Zoanthamine Alkaloids: The Total Syntheses of Norzoanthamine and Zoanthamine
  Yoshimura, F.; Sasaki, M.; Hattori, I.; Komatsu, K.; Sakai, M.; Tanino, K.; Miyashita, M. *Chem. Eur. J.* **2009**, *15*, 6626-6644.
  Abstract:

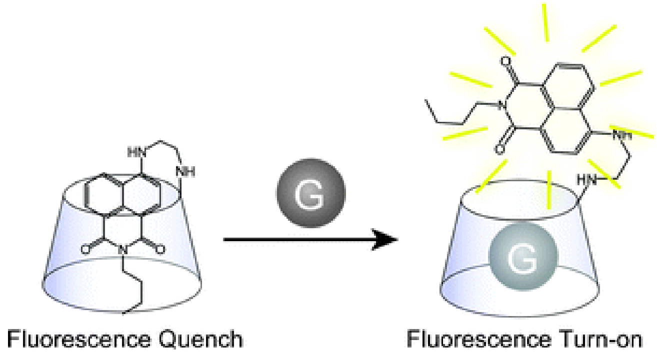


norzoanthamine (R = H)
zoanthamine (R = CH_3)

Highly effective: We report herein the first and highly efficient total syntheses of norzoanthamine and zoanthamine in full detail, which involves stereoselective synthesis of the requisite triene for an intramolecular Diels-Alder reaction via three-component coupling reactions, the intramolecular Diels-Alder reaction, and subsequent crucial bis-aminoacetalization as the key steps.

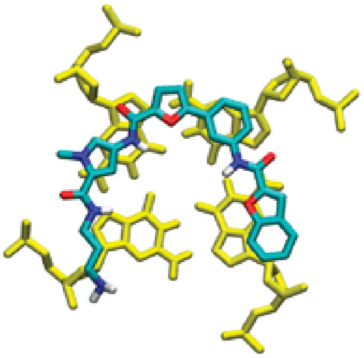
The zoanthamine alkaloids, a type of heptacyclic marine alkaloid isolated from colonial zoanthids of the genus *Zoanthus* sp., have distinctive biological and pharmacological properties in addition to their unique chemical structures with stereochemical complexity. Namely, norzoanthamine (**1**) can suppress the loss of bone weight and strength in ovariectomized mice and has been expected as a promising candidate for a new type of antiosteoporotic drug, while zoanthamine (**2**) has exhibited potent inhibitory activity toward phorbol myristate-induced inflammation in addition to powerful analgesic effects. Recently, norzoanthamine derivatives were demonstrated to inhibit strongly the growth of P-388 murine leukemia cell lines, in addition to their potent antiplatelet activities on human platelet aggregation. Their distinctive biological properties, combined with novel chemical structures, make this family of alkaloids extremely attractive targets for chemical synthesis. However, the chemical synthesis of the zoanthamine alkaloids has been impeded owing to their densely functionalized complex stereostructures. In this paper, we report the first and highly efficient total syntheses of norzoanthamine (**1**) and zoanthamine (**2**) in full detail, which involve stereoselective synthesis of the requisite triene (**18**) for an intramolecular Diels-Alder reaction via the sequential three-component coupling reactions, the key intramolecular Diels-Alder reaction, and subsequent crucial bis-aminoacetalization as the key steps. Ultimately, we achieved the total synthesis of norzoanthamine (**1**) in 41 steps with an overall yield of 3.5 % (an average of 92 % yield each step) and that of zoanthamine (**2**) in 43 steps with an overall yield of 2.2 % (an average of 91 % yield each step) starting from (*R*)-5-methylcyclohexenone (**3**), respectively.

- Unexpected fluorescent behavior of a 4-amino-1,8-naphthalimide derived -cyclodextrin: conformation analysis and sensing properties.
  Zhong, C.; Mu, T.; Wang, L.; Fu, L.; Qin, J. *Chem. Commun*. **2009**, 4091 – 4093.
  <u>Abstract :</u>



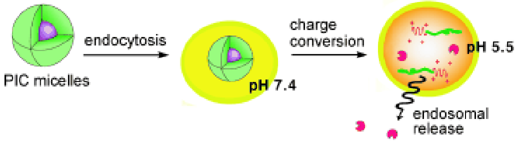
A new fluorescent cyclodextrin shows unexpected and strong fluorescence enhancement upon binding of organic molecules, and the enhancing mechanism is found to be different from those reported in the literature.

- Biaryl polyamides as a new class of DNA quadruplex-binding ligands.
  Rahman, K. M.; Reszka, A. P.; Gunaratnam, M.; Haider, S. M.; Howard, P. W.; Fox, K. R.; Neidle, S.; Thursto, D. E. *Chem. Commun.* **2009**, 4097 – 4099.
  <u>Abstract :</u>



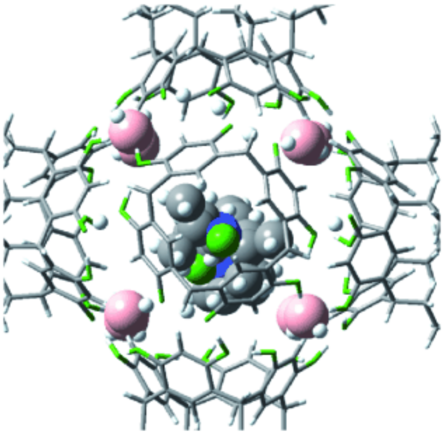
We report a novel class of biaryl polyamides highly selective for G-quadruplex DNA, and with significant cytotoxicity in several cancer cell lines; they form planar U-shaped structures that match the surface area dimensions of a terminal G-quartet in quadruplex structures rather than the grooves of duplex DNA.

- Charge-Conversional Polyionic Complex Micelles - Efficient Nanocarriers for Protein Delivery into Cytoplasm
  Lee, Y.; Ishii, T.; Cabral, H.; Kim, H. J.; Seo, J.-H.; Nishiyama, N.; Oshima, H.; Osada, K.; Kataoka, K. *Angew. Chem. Int. Ed.* **2009,** *48*, 5309 –5312.
  Abstract:



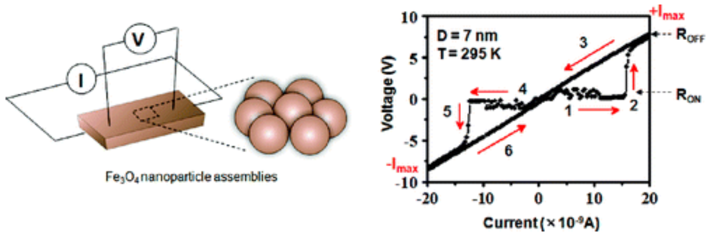
Special delivery! Polyionic complex (PIC) micelles that contain the charge-conversional moieties citaconic amide or *cis*-aconitic amide were developed for cytoplasmic protein delivery. The increase of the charge density on the protein cargo helped the stability of the PIC micelles without cross-linking, and the charge-conversion in endosomes induced the dissociation of the PIC micelles to result in efficient endosomal release (see picture).

- Probing the Inner Space of Resorcinarene Molecular Capsules with Nitroxide Guests
  Mileo, E.; Yi, S.; Bhattacharya, P.; Kaifer, A. E. *Angew. Chem. Int. Ed*. **2009**, *48*, 5337 –5340.
  Abstract:



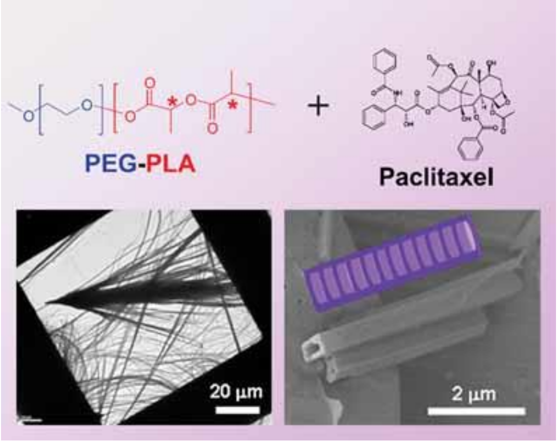
In quarantine: Nitroxide spin probes are encapsulated by hexameric resorcinarene molecular capsules in dichloromethane solutions (see picture). A substantial reduction in the tumbling rates occurs upon encapsulation of two cationic probes and one neutral probe. As the molecular volume of the probe increases, the tumbling rate of the probe reflects the overall tumbling rate of the entire supramolecular assembly.

- Nanoparticle Assemblies as Memristors
  Kim, T. H.; Jang, E. Y.; Lee, N. J.; Choi, D. J.; Lee, K.-J.; Jang, J.; Choi, J.; Moon, S. H.; Cheon, J. *Nano Lett.* **2009**, *9*, 2229–2233.
  Abstract:



Recently a memristor (Chua, L. O. *IEEE Trans. Circuit Theory* 1971, *18*, 507), the fourth fundamental passive circuit element, has been demonstrated as thin film device operations (Strukov, D. B.; Snider, G. S.; Stewart, D. R.; Williams, R. S. *Nature (London)* 2008, *453*, 80; Yang, J. J.; Pickett. M. D.; Li, X.; Ohlberg, D. A. A.; Stewart, D. R.; Williams, R. S. *Nat. Nanotechnol.* 2008, *3*, 429). A new addition to the memristor family can be nanoparticle assemblies consisting of an infinite number of monodispersed, crystalline magnetite (Fe_3O_4) particles. Assembly of nanoparticles that have sizes below 10 nm, exhibits at room temperature a voltage–current hysteresis with an abrupt and large bipolar resistance switching ($R_{OFF}/R_{ON} \approx 20$). Interestingly, observed behavior could be interpreted by adopting an extended memristor model that combines both a time-dependent resistance and a time-dependent capacitance. We also observed that such behavior is not restricted to magnetites; it is a general property of nanoparticle assemblies as it was consistently observed in different types of spinel structured nanoparticles with different sizes and compositions. Further investigation into this new nanoassembly system will be of importance to the realization of the next generation nanodevices with potential advantages of simpler and inexpensive device fabrications**.**

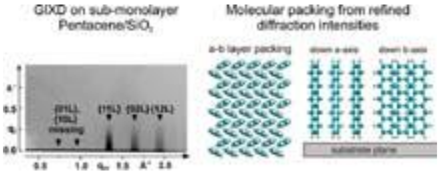
- Hierarchical Supermolecular Structures for Sustained Drug Release
  Tan, J. P. K.; Kim, S. H.; Nederberg, F.; Appel, E. A.; Waymouth, R. M.; Zhang, Y.; Hedrick, J. L.; Yang, Y. Y. *Small* **2009**, *5*, 1504-1507.
  Abstract:



Fiber-like supermolecular structures having hierarchical order are formed from the coassembly of stereoregular poly(ethylene glycol)-*block*-polylactide (PEG-*b*-PLA) block copolymers with paclitaxel, a well-known anticancer drug (see image). Importantly, these paclitaxel- loaded block copolymer complexes possess a PEG shell, show stable sustained release of the drug under simulated physiological conditions, and have great potential in clinical applications for localized drug delivery.

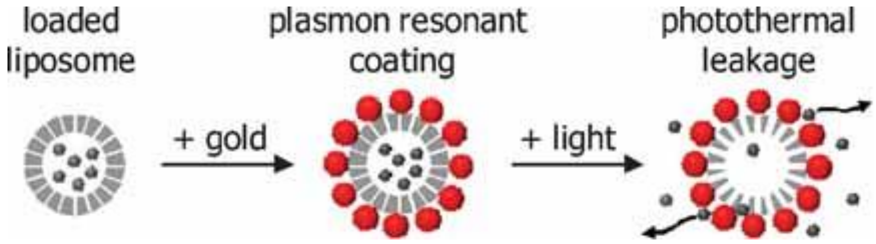
- Precise Structure of Pentacene Monolayers on Amorphous Silicon Oxide and Relation to Charge Transport

Mannsfeld, S. C. B.; Virkar, A.; Reese, C.; Toney, M. F.; Bao, Z. *Adv. Mater.* **2009**, *21*, 2294-2298.
Abstract:



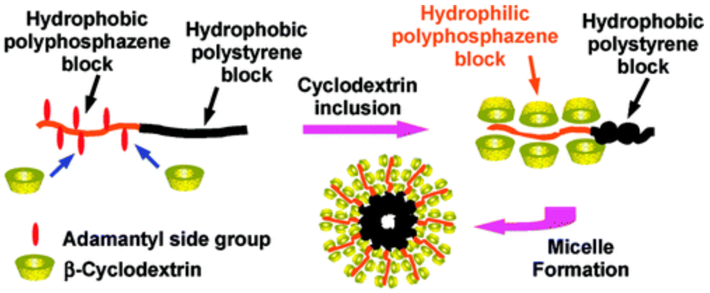
The precise molecular packing in pentacene monolayers on silicon oxide is determined for the first time using a combination of grazing incidence X-ray diffraction (GIXD) and crystallographic refinement calculations. The pentacene molecules are found to adopt a completely tilt-free herringbone motif, the charge-transport properties of which are discussed on the basis of density functional theory calculations.

- Light-Induced Content Release from Plasmon-Resonant Liposomes
  Troutman, T. S.; Leung, S. J.; Romanowski, M. *Adv. Mater.* **2009**, *21*, 2334-2338.
  Abstract:



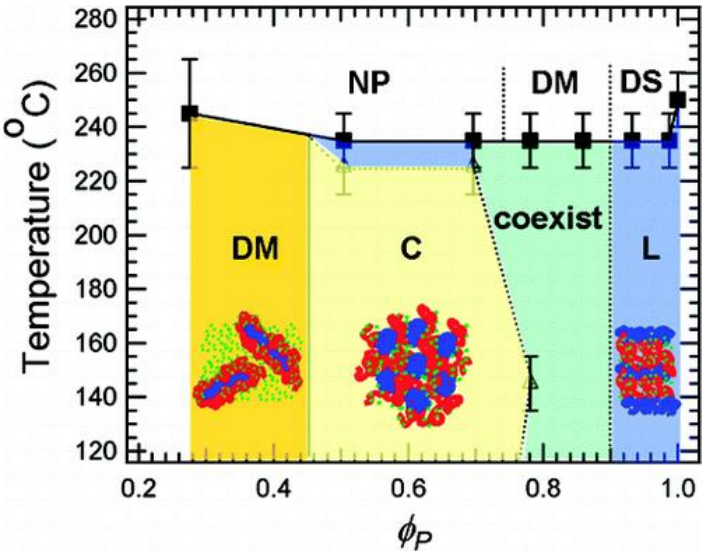
Thermosenstive liposomes coated with gold form plasmon-resonant shells with optical resonances tunable in the near-infrared range. When exposed to laser light, these liposomes release their content in a spectrally-dependent manner. Spectrally addressable release may find applications in the delivery of diagnostic and therapeutic agents, or more broadly, in developing a technological basis of nanomedicine.

- Synthesis of Adamantyl Polyphosphazene-Polystyrene Block Copolymers, and β-Cyclodextrin-Adamantyl Side Group Complexation.
  Cho, S. Y.; Allcock, H. R. *Macromolecules* **2009**, *42*, 4484–4490.
  Abstract:



Hydrophobic block copolymers with adamantyl polyphosphazene and polystyrene blocks were synthesized via the controlled cationic living polymerization of a phosphoranimine at ambient temperature. β-Cyclodextrins (β-CDs) were then complexed with the adamantyl side groups in aqueous media to generate amphiphilic block copolymers. These underwent micelle formation in an aqueous environment. The micellar behavior of these complexes was monitored using fluorescence techniques, transmission electron microscopy (TEM), and dynamic light scattering. The critical micelle concentration of the adamantyl polyphosphazene-polystyrene block copolymer complexes was 0.925 mg/L. TEM imaging revealed spherically shaped micelles.Amean diameter of 193nmwas measured by dynamic light scattering. It was possible to control micelle formation by changing the amount of β-CD in the aqueous medium at constant block copolymer concentration.

- Phase Behavior of Polystyrene-block-poly(2-vinylpyridine) Copolymers in a Selective Ionic Liquid Solvent.
  Virgili, J. M.; Hexemer, A.; Pople, J. A.; Balsara, N. P.; Segalman, R. A. *Macromolecules* **2009**, *42*, 4604–4613.
  Abstract:



The phase behavior of poly(styrene-block-2-vinylpyridine) copolymer solutions in an imidazolium bis(trifluoromethane)sulfonamide ([Im][TFSI]) ionic liquid has been studied using small-angle X-ray scattering (SAXS) and optical transmission characterization. Through scaling analysis of SAXS data, we demonstrate that the [Im][TFSI] ionic liquid behaves as a selective solvent toward one of the blocks. We observe lyotropic and thermotropic phase transitions that correspond qualitatively to the phase behaviour observed in block copolymer melts and block copolymer solutions in molecular solvents. In addition, we have studied the thermal properties of block copolymer solutions in the ionic liquid using differential scanning calorimetry and wide-angle X-ray scattering. We observe distinct composition regimes corresponding to the change in the block copolymer's glass transition temperature, Tg, with respect to the concentration of polymer in ionic liquid. At high block copolymer concentrations, a "salt-like" regime corresponding to an increase in the block copolymer Tg is observed, while at intermediate block copolymer concentrations, a "solvent-like" regime corresponding to a decrease in the block copolymer Tg is observed. An unusual thermal transition consisting of crystallization and subsequent melting of the ionic liquid is observed at the lowest block copolymer concentration characterized.