• The economies of synthesis
Abstract:

In this tutorial review the economies of synthesis are analysed from both detailed and macroscopic perspectives, using case-studies from complex molecule synthesis. Atom, step, and redox economy are more than philosophical constructs, but rather guidelines, which enable the synthetic chemist to design and execute an efficient synthesis. Students entering the field of synthesis might find this tutorial helpful for understanding the subtle differences between these economic principles and also see real-world situations where such principles are put into practice.

• Molecular Behavior in Small Spaces
Abstract:

The study of physical organic chemistry in solution is a mature science, over a century old, but over the last 10 years or so, reversible encapsulation has changed the way researchers view molecular interactions. It is now clear that the behavior of molecules in dilute solution is really quite different from their behavior in capsules. Molecules isolated from bulk media in spaces barely large enough to accommodate them and a few neighbors show new phenomena: their activities resemble those of molecules inside biochemical structures—pockets of enzymes, interiors of chaperones, or the inner space of the ribosome—rather than conventional behavior in solution.

In this Account, we recount the behavior of molecules in these small spaces with emphasis on structures and reactivities that have not been, and perhaps cannot be, seen in conventional solution chemistry. The capsules self-assemble through a variety of forces, including hydrogen bonds, metal–ligand interactions, and hydrophobic effects. Their lifetimes range from milliseconds to hours, long enough for NMR spectroscopy to reveal what is going on inside. We describe one particular capsule, the elongated shape of which gives rise to many of the effects and unique phenomena. Molecular guests that are congruent to the space of the host can be tightly packed inside and show reduced mobilities such as rotation and translation within the capsule. These mobilities depend strongly on what else is encapsulated with them. We also relate how asymmetric spaces can be created inside the capsule by using a chiral guest. In contrast to the situation in dilute solution,
where rapid exchange of solute partners and free molecular motion average out the steric and magnetic effects of chirality, the long lifetimes of the encounters in the capsules magnify the effects of an asymmetric environment. The capsule remains achiral, but the remaining space is chiral, and coencapsulated molecules respond in an amplified way.

We probe the various regions of the capsule with guests of different shape. Primary acetylenes, the narrowest of functional groups, can access the tapered ends of the capsule that exclude functions as small as methyl groups. The shape of the capsule also has consequences for aromatic guests, gently bending some and straightening out others. Flexible structures such as normal alkanes can be compressed to fit within the capsule and conform to its shape. We obtain a measure of the internal pressure caused by the compressed guests by determining its effect on the motion of the capsule’s components. These forces can also drive a spring-loaded device under the control of external acids and bases. We show that spacer elements can be added to give self-assembled capsules of increased complexity, with 15 or more molecules spontaneously coming together in the assembly. In addition, we analyze the behavior of gases, including the breakdown of ideal gas behavior, inside these capsules.

The versatility of these capsule structures points to possible applications as nanoscale reaction chambers. The exploration of these confined spaces and of the molecules within them continues to open new frontiers.

- The Use of Calixarenes in Metal-Based Catalysis
  Abstract:

  ![Calixarene Structure]

  The condensation of formaldehyde with \( p \)-alkylphenols under alkaline conditions, a reaction dating back to the days of Baeyer and Zinke, affords initially linear polyphenols, which, once a certain temperature is achieved, yield cyclic oligomeric phenolic compounds. One-step, multigram synthetic procedures have now been developed, which by varying either the temperature or amount of base used in the preparation, readily afford the tetrameric, hexameric, and octameric phenolic ring systems, bridged by methylene (−CH\(_2\)−) spacers. Ring systems with up to 20 phenolic residues are now known, although methods of preparation for these higher members, and for those with an odd number of phenolic residues, are usually low yielding. The smaller members of the family adopt a cone-shaped structure, hence the name calix[n]arene coined by Gutsche, from the Greek “calix” meaning vase, where \( n \) denotes the number of phenolic residues. Such a bowl shape results in the formation of a hydrophobic, electron-rich cavity, which is well-suited to the formation of inclusion complexes, particularly cations. The synthetic methodology has also been adapted to allow for the incorporation of bridging groups other than methylene, such as dimethyleneoxa (−CH\(_2\)OCH\(_2\)−), thia (−S−), and aza [−CH\(_3\)N(R)CH\(_2\)−] bridged calixarenes, and these additional donors can provide extra binding sites.

- Chemistry of Polyvalent Iodine
Starting from the early 1990s, the chemistry of polyvalent iodine organic compounds has experienced an explosive development. This surging interest in iodine compounds is mainly due to the very useful oxidizing properties of polyvalent organic iodine reagents, combined with their benign environmental character and commercial availability. Iodine(III) and iodine(V) derivatives are now routinely used in organic synthesis as reagents for various selective oxidative transformations of complex organic molecules. Several areas of hypervalent organoiodine chemistry have recently attracted especially active interest and research activity. These areas, in particular, include the synthetic applications of 2-iodoxybenzoic acid (IBX) and similar oxidizing reagents based on the iodine(V) derivatives, the development and synthetic use of polymer-supported and recyclable polyvalent iodine reagents, the catalytic applications of organoiodine compounds, and structural studies of complexes and supramolecular assemblies of polyvalent iodine compounds. The main purpose of the present review is to summarize the data that appeared in the literature following publication of our previous reviews in 1996 and 2002. In addition, a brief introductory discussion of the most important earlier works is provided in each section. The review is organized according to the classes of organic polyvalent iodine compounds, with emphasis on their synthetic application. Literature coverage is through July 2008.

- Rapid Synthesis, Screening, and Identification of Xanthone- and Xanthene-Based Fluorophores Using Click Chemistry

  **Abstract:**
  A panel of new fluorophores with emission wavelengths from blue to yellow regions using the Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction of alkyne-functionalized xanthones and xanthenes with various azides have been synthesized. Screening of the “click” products led to the identification of “hit” fluorophores which showed a fluorescence increase upon triazole formation. These novel “click” fluorophores could potentially be used for bioconjugation and bioimaging purposes.

- Microcapsules with Three Orthogonal Reactive Sites
Polymeric microcapsules containing reactive sites on the shell surface and two orthogonally reactive polymers encapsulated within the interior are selectively labeled. The capsules provide three spatially separate and differentially reactive sites. Confocal fluorescence microscopy is used to characterize the distribution of labels. Polymers encapsulated are distributed homogeneously within the core and do not interact with the shell even when oppositely charged.

- **Dibenzo[f,h]thieno[3,4-b] quinoxaline-Based Small Molecules for Efficient Bulk-Heterojunction Solar Cells**
  Abstract:

Two isomeric compounds (1 and 2) containing a dibenzo[f,h]thieno[3,4-b]quinoxaline core and two peripheral arylamines were synthesized. Solution-processed bulk heterojunction (BHJ) solar cells based on these sensitizers and [6,6]-phenyl-C61-butyric acid methyl ester (PCBM) are reported. The cell fabricated from 1/67 wt % of PCBM exhibited a high power conversion efficiency of 1.70% and an external quantum yield of 55%. The film of the cell was found to have balanced electron and hole mobility and good film morphology.

- **Carbohydrate sensing using a fluorescent molecular tweezer.**
  Abstract:
A fluorescent molecular tweezer for carbohydrates has been prepared which utilises two boronic acid receptor groups.


  Abstract:

  We describe the formation of a complex [2]rotaxane both in solution and in the solid state. The rotaxane ring is composed of a cyclic trinuclear gold complex and the Au(PMe$_3$)$_2$ rod is held in place by three aurophilic interactions to the ring Au atoms. The existence of the [2]rotaxane in solution is confirmed by VT-NMR and MS analysis.

- Tunable Hybrid Photodetectors with Superhigh Responsivity

  Abstract:

  A responsivity as high as five orders of magnitude is achieved for hybrid photodetectors fabricated by the surface functionalization of single-walled carbon nanotubes with ZnO nanoparticles as antennas for UV detection. Due to the photoinduced adsorption and desorption of oxygen from the nanoparticle surface (see picture), the devices show photoswitching effects with good reversibility and reproducibility.

- Low Temperature Synthesis of Vertically Aligned Carbon Nanotubes with Electrical Contact to Metallic Substrates Enabled by Thermal Decomposition of the Carbon Feedstock
Abstract:

Growth of vertically aligned carbon nanotube (CNT) carpets on metallic substrates at low temperatures was achieved by controlled thermal treatment of ethylene and hydrogen at a temperature higher than the substrate temperature. High-resolution transmission electron microscopy showed that nanotubes were crystalline for a preheating temperature of 770 °C and a substrate temperature of 500 °C. Conductive atomic force microscopy measurements indicated electrical contact through the CNT carpet to the metallic substrate with an approximate resistance of 35 kΩ for multiwall carpets taller than two micrometers. An analysis of the activation energies indicated that thermal decomposition of the hydrocarbon/hydrogen gas mixture was the rate-limiting step for low-temperature chemical vapor deposition growth of CNTs. These results represent a significant advance toward the goal of replacing copper interconnects with nanotubes using CMOS-compatible processes.

- Single-Site, Catalytic Water Oxidation on Oxide Surfaces
  Abstract:

Electrocatalytic water oxidation occurs through the use of the phosphonate-derivatized single-site catalyst [Ru(Mebimpy)(4,4′-((HO)2OPCH2)bpy)(OH2)]2+ [Mebimpy = 2,6-bis(1-methylbenzimidazol-2-yl)pyridine; bpy = 2,2′-bipyridine] at pH 1 and 5 on fluorine-doped SnO2 or Sn(IV)-doped In2O3 electrodes or on nanocrystalline TiO2. The surface-bound catalyst appears to retain the water oxidation mechanism found for [Ru(tpy)(bpm)(OH2)]2+ and [Ru(tpy)(bpz)(OH2)]2+ (tpy = 2,2′:6′,2″-
terpyridine; bpm = 2,2′-bipyrimidine; bpz = 2,2′-bipyrazine) in solution and acts as a surface electrocatalyst for sustained water oxidation.

• Highly Efficient Reversible Z–E Photoisomerization of a Bridged Azobenzene with Visible Light through Resolved S1(nπ*) Absorption Bands
  Abstract:
  The reversible Z–E photoswitching properties of the (Z) and (E) isomers of the severely constrained bridged azobenzene derivative 5,6-dihydrodibenzo[c,g][1,2]diazocine (1) were investigated quantitatively by UV/vis absorption spectroscopy in solution in n-hexane. In contrast to normal azobenzene (AB), 1 has well separated S1(nπ*) absorption bands, peaking at λZ = 404 nm and λE = 490 nm. Using light at λ = 385 nm, it was found that 1Z can be switched to 1E with very high efficiency, Γ = 92 ± 3%. Conversely, 1E can be switched back to 1Z using light at λ = 520 nm with ~100% yield. The measured quantum yields are ΦZ→E = 72 ± 4% and ΦE→Z = 50 ± 10%. The thermal lifetime of the (E) isomer is 4.5 ± 0.1 h at 28.5 °C. The observed photochromic and photoswitching properties of 1 are much more favorable than those for normal AB, making our title compound a promising candidate for interesting applications as a molecular photoswitch especially at low temperatures. The severe constraints by the ethylenic bridge apparently do not hinder but favor the Z–E photoisomerization reactions.

• Active Metal Template Synthesis of [2]Catenanes
  Abstract:
  The synthesis of [2]catenanes by single macrocyclization and double macrocyclization strategies using Cu(I) ions to catalyze covalent bond formation while simultaneously acting as the template for the mechanically interlocked structure is reported. These “active metal template” strategies employ appropriately functionalized pyridine ether or bipyridine ligands and either the CuAAC “click” reaction of azides with terminal alkynes or the Cu(I)-mediated Cadiot–Chodkiewicz heterocoupling of
an alkyne halide with a terminal alkyne. Using one macrocyclic and one acyclic building block, heterocircuit (the rings are constitutionally different) [2]catenanes are produced via the single macrocyclization route in up to 53% yield by optimizing the reaction conditions and relative stoichiometry of the starting materials. Alternatively, with the active template CuAAC reaction, a single acyclic unit can be used to form a homocircuit (two identical rings) [2]catenane in 46% yield through a one-pot, double macrocyclization, procedure. Remarkably, <7% of the corresponding noninterlocked macrocycle is isolated from this reaction, indicating the efficacy of Cu(I) as both a template for the catenane and a catalyst for covalent bond formation in the reaction.

- **RDC Enhanced NMR Spectroscopy in Organic Solvent Media: The Importance for the Experimental Determination of Periodic Hydrogen Bonded Secondary Structures**
  Abstract: Precise NMR structural determination of distinct hydrogen-bonded secondary folds in unnatural peptides is demonstrated by using residual dipolar couplings (RDCs), measured in organic solvent media. The results show that the conventional constraints, $\text{J}_{HH}$ and NOE-derived distances alone do not allow the accurate structural elucidation even for rigid foldamers and emphasize the need of RDC-based structure validation and refinement for unnatural peptides in particular and small organic molecules in general.

- **Zn–Zn Porphyrin Dimer-Sensitized Solar Cells: Toward 3-D Light Harvesting**
  Abstract:
Zn–Zn porphyrin dimers have been incorporated into thin dye-sensitized solar cells (DSSCs) to boost their light harvesting efficiency. The photoexcited dimers show efficient and fast electron injection into TiO2 indicating that both photoexcited chromophores contribute to current generation. The improved light harvesting ability coupled to enhanced DSSC performance demonstrates the potential of 3-D light harvesting arrays as next generation light harvesters for artificial solar energy conversion systems.

- Vesicular perylene dye nanocapsules as supramolecular fluorescent pH sensor systems

  **Abstract:**

Water-soluble, self-assembled nanocapsules composed of a functional bilayer membrane and enclosed guest molecules can provide smart (that is, condition responsive) sensors for a variety of purposes. Owing to their outstanding optical and redox properties, perylene bisimide chromophores are interesting building blocks for a functional bilayer membrane in a water environment. Here, we report water-soluble perylene bisimide vesicles loaded with bispyrene-based energy donors in their
aqueous interior. These loaded vesicles are stabilized by in situ photopolymerization to give nanocapsules that are stable over the entire aqueous pH range. On the basis of pH-tunable spectral overlap of donors and acceptors, the donor-loaded polymerized vesicles display pH-dependent fluorescence resonance energy transfer from the encapsulated donors to the bilayer dye membrane, providing ultrasensitive pH information on their aqueous environment with fluorescence colour changes covering the whole visible light range. At pH 9.0, quite exceptional white fluorescence could be observed for such water-soluble donor-loaded perylene vesicles.

- Mechanically induced luminescence changes in molecular assemblies
  Abstract:

  Altering the shape and properties of a material through external factors such as heat, light, pressure, pH, electric or magnetic fields, or the introduction of a guest molecule, is an attractive prospect. In this Perspective, piezochromic luminescent materials — which change the colour of their luminescence in response to mechanical stimuli — are described. Such piezochromism has been observed for a few molecular materials that contain luminescent cores in liquid-crystalline and crystalline solid states, as well as for polymeric materials doped with dyes. These changes in photoluminescent colour can be activated by various types of mechanical pressure such as shearing, grinding or elongation, which can trigger different mechanisms of producing the colour. Such stimuli-responsive materials have potential for various applications, including sensors, memory and displays.

- Di- and Dodeca-Mitsunobu Reactions on C₆₀ Derivatives: Post-Functionalization of Fullerene Mono- and Hexakis-Adducts
  Abstract:
**Fullerene derivatives:** The Mitsunobu reaction was applied to the post-functionalization of mono- and hexakis-methanofullerenes (see figure). This novel approach can be used in combination with other fullerene derivatizations and thus allows easy access to new structures.


  **Abstract:**

  We have investigated how doubly selective synthetic mimics of antimicrobial peptides (SMAMPs), which can differentiate not only between bacteria and mammalian cells, but also between Gram-negative and Gram-positive bacteria, make the latter distinction. By dye-leakage experiments on model vesicles and complementary experiments on bacteria, we were able to relate the Gram selectivity to structural differences of these bacteria types. We showed that the double membrane of *E. coli* rather than the difference in lipid composition between *E. coli* and *S. aureus* was responsible for Gram selectivity. The molecular weight-dependent antimicrobial activity of the SMAMPs was shown to be a sieving effect: while the 3000 g·mol$^{-1}$ SMAMP was able to penetrate the peptidoglycan layer of the Gram-positive *S. aureus* bacteria, the 50000 g·mol$^{-1}$ SMAMP got stuck and consequently did not have antimicrobial activity.

- Facile One-Step Fabrication of Ordered Organic Nanowire Films

  **Abstract:**

  Squaraine nanowires self-organize into a well-ordered film through a simple solvent-evaporation process at the dichloromethane/water interface. The film can be transferred onto various substrates
or stacked layer-by-layer into a multilayered structure. This one-step approach offers a low-cost method for producing scalable films of aligned organic nanowires suitable for large-scale applications.

- **Dynamic, 3D-Pattern Formation Within Enzyme-Responsive Hydrogels**
  Abstract: Dynamic, 3D hydrogel patterns emerge over time in response to cell-secreted enzymes (see image). Composite hydrogels fabricated from engineered proteins exhibit customized half-lives ranging across two orders of magnitude due to slight changes in the primary amino acid sequence. The evolution of internal 3D void structures within these polymeric materials is used to release multiple payload molecules with distinct spatial and temporal delivery profiles.

- **General Route for the Assembly of Functional Inorganic Capsules**
  Abstract: Semipermeable, hollow capsules are attractive materials for the encapsulation and delivery of active agents in food processing, pharmaceutical and agricultural industries, and biomedicine. These capsules can be produced by forming a solid shell of close packed colloidal particles, typically polymeric particles, at the surface of emulsion droplets. However, current methods to prepare such capsules may involve multistep chemical procedures to tailor the surface chemistry of particles or are limited to particles that exhibit inherently the right hydrophobic-hydrophilic balance to adsorb around emulsion droplets. In this work, we describe a general and simple method to fabricate semipermeable, inorganic capsules from emulsion droplets stabilized by a wide variety of colloidal metal oxide particles. The assembly of particles at the oil-water interface is induced by the in situ hydrophobization of the particle surface through the adsorption of short amphiphilic molecules. The adsorption of particles at the interface leads to stable capsules comprising a single layer of particles in the outer shell. Such capsules can be used in the wet state or can be further processed into dry capsules. The permeability of the capsules can be modified by filling the interstices between the shell particles with polymeric or inorganic species. Functional capsules with biocompatible, bioreabsorbable, heat-resistant, chemical-resistant, and magnetic properties were prepared using alumina, silica, iron oxide, or tricalcium phosphate as particles in the shell.
• Packing the Silica Colloidal Crystal Beads: A Facile Route to Superhydrophobic Surfaces

Abstract:

To mimic the structure of the lotus leaf, we present a facile route to prepare superhydrophobic surfaces by depositing nanoparticle clusters onto a solid surface. These clusters were fabricated via solidification of an emulsion droplet containing a nanoparticle in silicone oil. Thus, the microsized clusters and nanoparticles form dual-scale roughness structures. The surface is modified by fluoroalkylsilane and exhibits superhydrophobicity, with a contact angle greater than 165° as well as a sliding angle less than 1°. On the basis of size tuning of the nano/microstructures, various contact angles and sliding angles were investigated. Furthermore, the influence of micro/nanostructures on superhydrophobicity is discussed.

• Synthesis of Interlocked 56-Membered Rings by Dynamic Self-Templating

Abstract:

*A love of self*: Narcissistic macrocyclic rings self-assemble into highly ordered, chiral [2]-catenanes displaying high component diastereoselectivity. The picture shows one such structure. One ring is shown in a space-filling representation (C green, O red, N blue, H gray), while the other is shown as orange sticks.

• Syntheses and Biological Evaluation of Iriomoteolide 3a and Analogues

Abstract:
**Metathesis on stage**: A combined cross-metathesis (CM)/ring-closing metathesis (RCM) approach has led to the stereocontrolled synthesis of iriomoteolide 3a, a smaller but equally cytotoxic congener of amphidinolides. Chemical editing of the molecule has provided non-natural analogues which have comparable anticancer activity to that of the natural product, thereby allowing the iriomoteolides to be used as probe molecules in chemical biology.

- **Peptide/Protein-Synthetic Polymer Conjugates: Quo Vadis.**
  **Abstract:**

  Peptide/protein-synthetic polymer conjugates, which covalently combine one or more copies of a peptide sequence or protein with one or more synthetic polymer elements, offer unique possibilities to integrate the properties and functions of bio(macro)molecules and synthetic polymers in a single hybrid material. This article provides a status report of the field of peptide/protein-synthetic polymer conjugates. First, the main synthetic strategies for the preparation of peptide/protein-synthetic polymer conjugates will be discussed. In the last two sections, selected properties and applications of peptide-synthetic polymer conjugates and protein-synthetic polymer conjugates will be highlighted.

- **Synthesis of Maleimide-End-Functionalized Star Polymers and Multimeric Protein-Polymer Conjugates.**
  **Abstract:**

  Protein-polymer conjugates exhibit superior properties to unmodified proteins, generating a high demand for these materials in the fields of medicine, biotechnology, and nanotechnology.
Multimeric conjugates are predicted to surpass the activity of monomeric conjugates. Herein, we report a straightforward method to synthesize multimeric polymer conjugates. Four-armed poly(N-isopropylacrylamide) (pNIPAAm) was synthesized by reversible addition-fragmentation chain transfer (RAFT) polymerization in the presence of a tetrafunctionalized trithiocarbonate chain transfer agent (CTA). The polymer molecular weight, architecture, and polydispersity index (PDI) were verified by gel permeation chromatography (GPC), dynamic light scattering gel permeation chromatography (DLS-GPC), and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry. This approach afforded well-defined polymers (PDI’s < 1.06) and the ability to target various molecular weights. Maleimide functional groups were introduced at the chain ends by heating the polymers in the presence of a furan-protected azo-initiator. This allowed for site-specific conjugation of V131C T4 lysozyme to the polymers to generate multimeric protein-polymer conjugates. MALDI-TOF mass spectrometry, electrospray ionization gas-phase electrophoretic mobility macromolecule analysis (ESI-GEMMA), gel electrophoresis, and liquid chromatography tandem mass spectrometry (LC-MS/MS) of the trypsin digests demonstrated that multimeric protein-polymer conjugates had formed. This simple strategy provides ready access to star protein-polymer conjugates for application in the fields of drug discovery, drug delivery, and nanotechnology.