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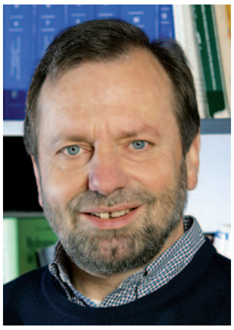
25 Years Full of Chemical Discovery

*François Diederich**



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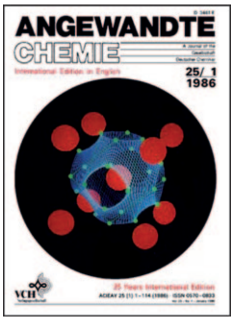

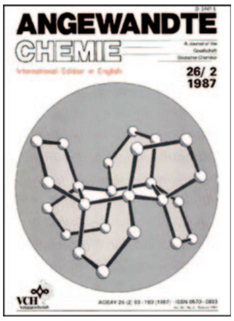

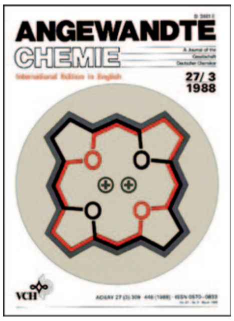

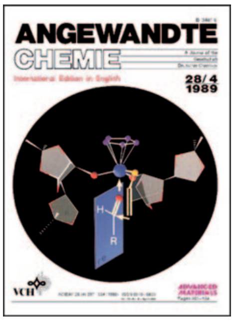

50 years of *Angewandte Chemie International Edition* give me the opportunity to reflect on some of the highlights of chemical sciences over the past 25 years. I was greatly aided in this task by the rich diversity of high-quality reviews published in this journal during this period. Many of the developments summarized briefly in the following have been recognized by Nobel Prizes.

Chemistry clearly has become a broader discipline, and its practitioners increasingly engage in interdisciplinary collaborations. While this trend has led to bold research contributions at the interfaces of biology, physics, and material sciences, chemistry has also seen refreshingly innovative developments in its core research. It has gained further stature and recognition as the central, enabling science which fertilizes the scientific progress in neighboring disciplines.

Take the developments in NMR spectroscopy. Sophisticated two-, three-, and four-dimensional NMR pulse sequences have been developed, which have made NMR spectroscopy available for the elucidation of biological structures such as nucleic acids and proteins. In 1989 only two NMR structures were submitted to the Protein Data Bank (PDB); up until October 2010 there were more than 8600. NMR spectroscopy nicely complements X-ray crystallographic techniques, but is even closer to the real systems, as the structures are obtained in solution. Magnetic resonance imaging (MRI) of tumors and in vivo metabolic investigations have become essential tools in the diagnostics of human diseases. In drug discovery research, various NMR techniques, such as HSQC (heteronuclear single quantum coherence), are used to screen compound libraries for protein–ligand binding potency and for identifying binding epitopes. These methods are particularly valuable in the screening of fragment libraries. Solid-state NMR spectroscopy has started to complement the solution studies, and first applications in the elucidation of biological structures, such as membrane proteins and amyloid fibrils, have been reported.

X-ray crystallography remains of eminent importance in biostructure elucidation, as is readily apparent from the PDB in which the total number of submitted X-ray structures has increased from less than 200 in 1985 to 11400 in 2000 and approaching 60000 in 2010. Prominent examples are the crystal structures of RNA polymerases, the ribosome, fatty acid synthase, and the nucleosome. After the first X-ray structure of a membrane protein, the photosynthetic reaction center, had been solved in 1982, an increasing number of membrane protein structures have been reported. Thus, an atomic-level understanding of the mechanism of selective ion and water transport across biological membranes became available when the structures of the potassium ion channel and the water channels, the aquaporins, were solved. The X-ray structure of the first G-protein coupled receptor (GPCR), bacteriorhodopsin, was reported in 1990 but recently, several other structures of GPCRs have been published. The increasing structural information on this class of membrane proteins promises to substantially aid the development of new medicines, as GPCRs are preferred targets for the development of pharmaceuticals for the treatment of various diseases.

Nevertheless, the past two-and-a-half decades are clearly identifiable as the age of mass spectrometry (MS). Ion trap, electrospray ionization (ESI), and matrix-assisted laser desorption ionization (MALDI) MS techniques have enabled bold advances in many directions, from the screening of homogenous catalysts, to polymer and materials characterization, and protein identification and characterization. The fields of proteomics, that is, the mapping of the proteome, and, in a broader sense, systems biology would not have developed without these techniques.

Ultrafast vibrational spectroscopy has been applied to the investigation of the hydration of nucleic acids, and Raman optical activity (ROA) is explored in the conformational analysis of biomolecules. Optical tweezers already find application in cell sorting. Vibrational and optical spectroscopic techniques, in partic-

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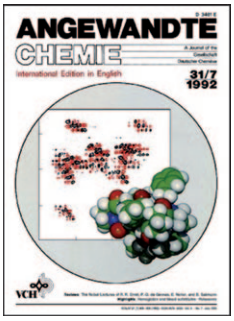
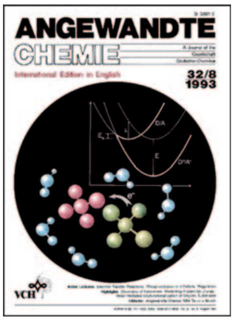
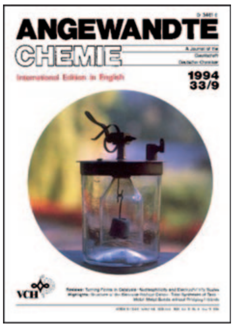
ular time-resolved methods, benefit from the continuing advances in ultrafast laser technologies. As in many other research directions, in particular in chemical dynamics, spectroscopic techniques also thrive on the continuing increase in computing speed, power, and data-storage capacity. Computer simulations and theoretical calculations based on quantum mechanics and density functional theory are now broadly used in chemistry thanks to the availability of excellent software packages. With increasing computing capacity, the elucidation of the mechanisms of protein folding by using molecular dynamics simulations comes in reach. Computing capacity is also directly connected to progress in the emerging field of de novo protein design, which targets new enzyme catalysts and other proteins, such as novel chaperones, by a combination of in silico design and experimental selection and evolution methods.

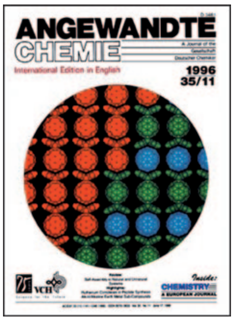
Chemical biology research has adopted the polymerase chain reaction (PCR) as a rapid method to multiply DNA in mutagenesis, genetic fingerprinting, and the cloning of genes, to name only a few applications. Decades after the structure of DNA had been revealed, chemists have indeed claimed back the genetic material for diverse study. Synthetic analogues, such as peptide nucleic acids (PNA) and nucleic acids incorporating different nucleobases and backbone scaffolds, have been prepared for antisense gene transfection, as well as for comparative study of the special features that made nature select DNA and RNA as genetic material. Yet the transfection process, that is, the introduction of nucleic acids into cells, remains problematic and this currently hampers efforts to use interference RNA (RNAi) for the control of gene activity in therapeutic applications. RNA cleavage by ribozymes was discovered. Selection methods have enabled the preparation of RNA aptamers with strong, selective ligand-binding properties. The molecular recognition properties of the major and minor groove of double-stranded DNA have been investigated in detail, which has aided the elucidation of the mechanism of transcription regulation by nuclear factors. Electron transfer across DNA has been studied as a mechanism for DNA cleavage and repair. Finally, the materials properties of tailor-made DNA fragments have been recognized and applied to the formation of nanostructures.

Chemists have also addressed the other biopolymers and their assemblies. Synthetic bilayer membranes and model systems have been designed and their structural, transport, and recognition properties explored. Complex saccharides, glycopeptides, and glycolipids have been prepared with the aim, among others, of developing glyco-vaccines. β-Peptides show much higher biological stability than α-peptides as well as a distinct preference for adopting helical secondary structures. Research on catalytic antibodies has provided strong support to the Pauling proposal from the 1940s that transition-state stabilization is a major mechanism of enzymatic catalysis. From a technological perspective, a more important development has been the modification and stabilization of enzymes for use in the industrial-scale production of useful achiral and chiral chemical intermediates ("white biotechnology"). Other highlights strongly affecting chemical biology are the elucidation of the mechanisms of protein degradation in vertebrates by ubiquitination and subsequent disposal by the proteasome, of cell communication by NO, and of cellular signal transduction pathways.





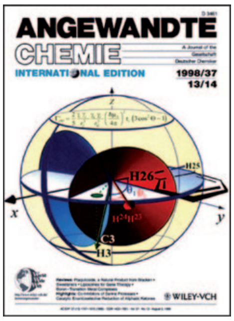


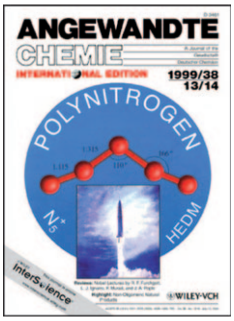


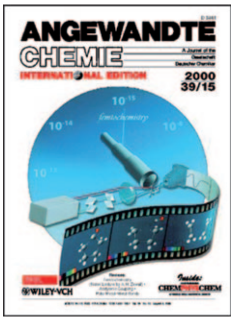
The invention of effective and safe medical drugs has greatly benefited from the insight gained into the regulation of signal transduction pathways by protein kinase mediated phosphorylation and protein phosphatase mediated dephosphorylation. There are more than 500 human kinases, as revealed by the completed human genome project. Creative chemical synthesis has succeeded in the preparation of highly selective protein kinase inhibitors, some of which are already on the market as effective antitumor drugs. This tremendous selectivity for one or a few kinases over all others deserves much appreciation, as it is achieved by molecules docking into the ATP–adenine binding pocket, which is common to all kinases. The attrition rate in modern preclinical drug development is currently being lowered through application of a multidimensional lead optimization approach. Target binding affinity and selectivity are optimized through judicious filling of chemical space, for which new chemical building blocks are invented, and this is increasingly guided by structure-based design strategies. At the same time, chemists optimize early on in lead generation important physicochemical properties such as bioavailability, pharmacokinetics, and metabolic stability, and prevent undesirable effects such as off-target binding, such as to cytochrome P450 enzymes, and hERG ion channel binding which causes cardiac side effects. This multidimensional approach to lead optimization is increasingly aided by computer-based predictive tools. Frequently, organofluorine groups are introduced to improve properties, and fluorine chemistry has seen an explosive growth in view of its many applications in the optimization of medical drugs and crop protection agents. One timely issue in drug discovery research is the energetically beneficial replacement of crystallographically observed water molecules at receptor active sites by ligand parts. Another major topic is the disruption of protein–protein interactions with small-molecule drugs, a possibility yet poorly developed. While nonpeptidic small-molecule drugs encounter strong competition by biologics such as therapeutic antibodies and peptides, their future remains bright, in particular since the problem of oral bioavailability of peptide drugs has not been generally solved. Surface plasmon resonance (SPR) should be mentioned as one of the enabling techniques for the high-throughput screening of the immense libraries that the pharmaceutical companies have assembled to find hits against new targets.

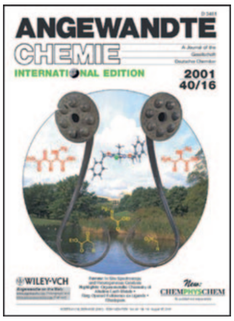
DNA-chip and microarray technologies have profoundly changed gene identification and analysis. The development of chemical and biological probes for in vitro and in vivo analytics is at the forefront of current chemical biology research. They extend from green fluorescence protein (GFP) to molecules used as fluorescent or PET (positron emission tomography) biomarkers to detect deposited amyloid plaques, and fluorophores to monitor kinase activity. Amyloid plaque formation accompanies major diseases, such as Alzheimer's disease, which increasingly affect the aging society. It is somewhat surprising that the number of academic chemistry research groups involved in creative brain research has remained quite small. This certainly will change in the coming decades. Similary, epigenetic gene regulation, such as by histone modification or DNA methylation, is easily predicted as an area of vigorous future chemical research.

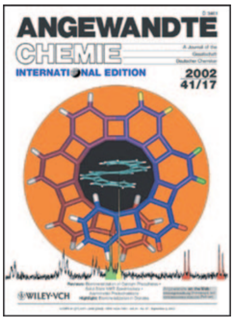
Supramolecular chemistry has been tremendously fueled by the Nobel Prizes awarded in 1987. Approximately one-third of all papers published in the premier chemical journals deal with supramolecular systems that link chemistry more than anything else to biology and materials sciences. Intermolecular interactions, such as cation–π interactions, anion–arene recognition, halogen bonding, and dipolar interactions, have been recognized and quantified in chemical and increasingly in biological systems. Although addressed, the impact of water as a solvent on supramolecular association remains to be fully understood. Fascinating novel host structures have emerged, such as covalent and self-assembled molecular container and capsules, featuring distinct inner-phase properties. The appealing structural motifs of molecular knots and Borromean rings have been realized in chemical systems. Unidirectional motion in molecular propellors, rotaxanes, and catenanes has been controlled in first examples but the realization of practical chemical motors is still a long way off. Much of this research is stimulated by biological examples, such as the ATPase and the muscle-moving actin–myosin system. The use of templates has greatly facilitated the synthesis of supramolecular systems. A particularly promising class of self-assembled systems are the metal–organic frameworks (MOFs)—crystalline porous lattices assembled by the judicious use of organic linkers connecting metal centers, with pores for gas storage, catalysis, and other applications. As an extension of combinatorial chemistry, which emerged vigorously at the beginning of the 1990s, dynamic combinatorial chemistry has been introduced as another original approach to the assembly of supramolecular systems.











Since self-association modulates and generates new physical properties, the principles of supramolecular chemistry have particularly impacted functional materials research. For example, magnetism is a three-dimensional property and relies on the communication between molecular or ionic components. Self-association and controlled dimensionality are equally important for the formation of organic light-emitting diodes (OLEDs), field-effect transistors, photovoltaic devices, and solar cells, to name some of the major subjects of study. Materials research, driven by chemistry, has developed with admirable vigor and success over the past 25 years. Following the introduction of the first metallic polymers, electroluminescent conjugated polymers have attracted much interest. Oligomers have been intensively investigated as models for infinite polymers and for their intrinsic properties, such as for use in photovoltaic devices. But no new monomer has been introduced into the realm of bulk industrial polymers over the past 25 years; rather it is amazing how the properties of known polymers, such as polyurethanes and polyamides, have been enhanced and diversified through proper processing. Hyperbranched polymers and dendrimers have attracted much interest as new soft-matter materials, and ionic liquids promise new solutions in catalysis.

Soft lithography has been established as an alternative to photolithographic processes to generate patterning and structuring on the micro- and even the nanoscale. The visualization of self-assembled molecules on surfaces has become possible by the introduction of scanning tunneling microscopy (STM) and atomic force microscopy (AFM), which also allow the study of single molecules. Heterogenous catalysis has greatly benefitted from the probe microscopy techniques including scanning near-field optical microscopy (SNOM), as they permit the monitoring of elementary steps in the catalytic processes. A plethora of new solid catalyst materials have been prepared, mainly originating from advances in inorganic solid-state chemistry. New methods for the preparation of ceramic materials have widened their range of application. Strong interest has also developed in biocompatible materials for applications in medical devices and in body-tissue replacement.

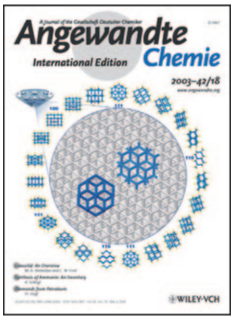
But the most original discoveries in materials research deal with the element carbon. The first observation and the subsequent practical synthesis of buckminsterfullerene C_{60} and higher fullerenes led to the frenzied development of the chemistry of these molecular carbon allotropes, which continues today with the introduction of soluble fullerenes as components in photovoltaic and solar-cell devices. The insoluble carbon nanotubes (CNTs) raised exceptional interest owing to their mechanical properties, such as special hardness, flexibility, and stability, and also their electronic properties. In parallel, metal oxide and metal sulfide based nanotubes have been discovered. All these developments are rivaled by the recent discovery of a method to prepare single layers of graphite, graphene, a material with fascinating properties and great promise for future technological applications.

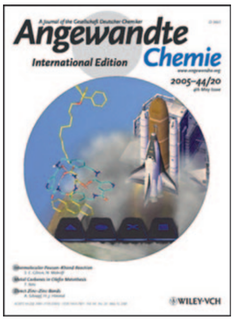
Many of the new materials have been produced as nanoparticles of defined size and shape, and a great variety of organic and/or inorganic matter that has been downsized to the nanometer scale displays special functions and properties. Other classes of compounds, such as the polyoxalates and other transition-metal complexes, have been expanded to defined clusters of multi-nanometer size. Nanoparticles are used not only as additives in composite materials, but they are also exploited as catalysts, in membranes and separation devices, as vehicles for gene transfection, in nanoelectronics, and in diverse biomedical applications. In addition to STM and AFM, transmission electron microscopy (TEM) is one of the preferred methods for their characterization. Concerns about the safety of nanoparticles are being properly addressed in ongoing studies.

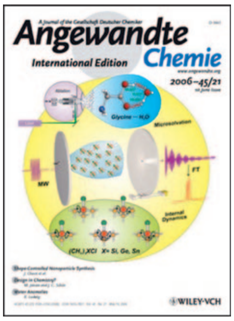
Advances in analytical separation techniques have strongly impacted synthetic organic chemistry. For enantiomer separations by HPLC, highly efficient chiral stationary phases are now available. The performance of chromatographic separations has been further extended by the application of very high pressure and supercritical fluids. Reaction workups have been facilitated by the introduction of fluorous phases and transformations miniaturized by using microfluidics and microdroplets.

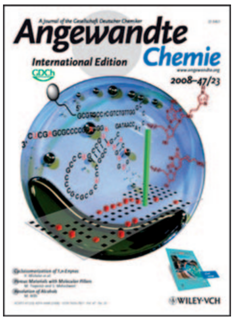
New synthetic protocols continue to be tested and applied to the total syntheses of challenging complex natural products with fascinating structures. The efficiency of the transformations has been enhanced by the introduction of rapid high-yielding, atom-economical click reactions. The number of steps in multistep syntheses has been reduced through the introduction of multicomponent reactions and cascade transformations and by eliminating the need for protecting groups. Environmental considerations increasingly come into play in what has been coined “green chemistry”, and an example is the replacement of toxic metal salts with hydrogen peroxide or dioxygen in oxidation reactions.

Transition-metal catalysis has profited from amazing advances in the development of new ligands such as N-heterocyclic carbenes (NHCs). Yet, a number of important transformations still await a solution, as exemplified by the selective C–H activation of alkanes. Also, efficient and economical activation of CO$_2$ could provide a new C$_1$ component in the chemical production chain. The tremendous success in developing efficient protocols for asymmetric catalysis testifies to the high creativity of synthetic chemists. Organocatalysis has emerged as another successful concept to selectively accelerate desired transformations.









Palladium-catalyzed cross-coupling reactions have moved rapidly from academic laboratories to industrial production. Increasingly, cross-couplings generate bonds not only between C(sp) and C(sp^2) but also at C(sp^3) centers, although there is still room for innovation in this direction. C–C bond formation by these transformations has been nicely complemented by similar protocols for efficient C–O and C–N bond formation.

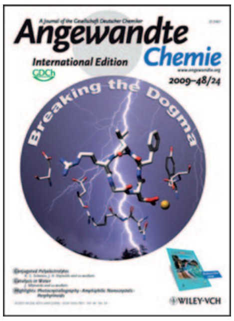
The discovery of the olefin metathesis reaction has had a tremendous impact. While this reaction was initially viewed predominantly as a new approach to polymers, the access to stable and versatile catalysts has fueled its broad application in organic synthesis. In particular ring-closing metathesis (RCM), starting from olefins and increasingly alkynes, has provided a new approach for the formation of small-, medium- and large-sized rings. For macrocyclizations, RCM is replacing most other transformations as the method of choice. Yet, a general solution for the selective formation of either *cis*- or *trans*-configured olefins has not yet been found.

The understanding of chemical bonding and its repertoire have greatly expanded, opening up new, often surprising structural opportunities, such as for silicon chemistry. Connecting transition metals and main-group elements by multiple bonds created a new interface between inorganic solid-state chemistry and organometallic chemistry. Also, the formation of multiple bonds between higher main-group elements has generated unprecedented complex and ligand structures. Such fundamental advances in chemistry open up new structural space full of surprises and opportunities. It is hoped that, in times of increasingly mission- and application-oriented funding programs, the support for excellent basis research will remain strong to enable true discovery. Basic research is vital for the healthy future of chemistry.

Chemistry has clearly signaled its commitment to contribute sustainable solutions for the major challenges related to the changes in global energy resources and to climate change. The mechanisms of atmospheric changes have been identified by chemists, and fluorocarbons, responsible for the depletion of the ozone layer, have been replaced.

Efficient homogenous and heterogenous catalysis is the best and most natural contribution of chemists to ecologically sustainable and economical chemical production. The desirable elimination of stoichiometric amounts of side products, in particular inorganic salts, rests on the development innovative new methods development.

Fuel cells, batteries and energy-storage systems, solar-energy-harvesting devices such as dye-sensitized solar cells, organic light-emitting diodes (OLEDs) with greatly reduced energy consumption, new insulating materials for construction, green biotechnology to meet the demands for food for our growing global population, sufficient clean water for everyone: these and many other goals will become reality through chemical research. Therefore, I am very optimistic that chemistry will remain the central enabling science in the future. This requires, however, that chemistry continues to strengthen its core research disciplines—synthesis, reactivity, stereochemistry, physical analysis, analytics—since chemists educated in these disciplines are the most valuable contributors to interfacial, interdisciplinary research and technology. I end with a few questions challenging our future teaching in the classroom and beyond: How can we continue to attract the best talent into chemistry? How will we communicate the enormous amount of knowledge that chemical research has generated so broadly? How do we manage to preserve the core strengths of chemistry in times of interdisciplinary research? I am of course optimistic that we will find good solutions to these crucial questions.



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