F. Diederich

*François Diederich has published more than **35 articles** since 2000 in Angewandte Chemie, most recently:* "Quinone-Based, Redox-Active Resorcin[4]arene Cavitands": I. Pochorovski, C. Boudon, J.-P. Gisselbrecht, M.-O. Ebert, W. B. Schweizer, F. Diederich, *Angew. Chem.* **2012**, *124*, 269–273; *Angew. Chem. Int. Ed.* **2012**, *51*, 262–266.

François Diederich

Date of birth:	July 9, 1952
Position:	Professor of Organic Chemistry, ETH Zurich, (Switzerland)
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Education:	1977 Diploma, University of Heidelberg (Germany) 1979 PhD with Prof. Heinz A. Staab, University of Heidelberg 1979–1981 Postdoctoral position with Prof. Orville L. Chapman, University of California Los Angeles (USA)
Awards:	**2000** Janssen Prize for Creativity in Organic Synthesis; **2006** GDCh August Wilhelm von Hofmann Medal; **2007** ACS Ronald Breslow Award for Achievement in Biomimetic Chemistry; **2011** GDCh Adolf von Baeyer Medal
Current research interests:	Weak intermolecular interactions in studies with biological receptors, synthetic host–guest systems, and unimolecular model systems; medicinal chemistry: structure-based design of leads for new targets against malaria, african sleeping sickness, and shigellosis; optoelectronic and chiroptical molecular materials based on acetylene and cumulene chemistry; π chromophores; switchable containers with portals and supramolecular chemistry on surfaces
Hobbies:	Reading (novels, history books), movies, walking, watching soccer games

My favorite food is … Japanese cuisine.

The most important thing I learned from my parents is … a love for dedicated and reliable craftsmanship.

The best stage in a scientist's career is … being a postdoctoral fellow in a high-caliber international research group.

My favorite author is … Isaac Bashevis Singer.

My top three films of all time are … "Annie Hall" by Woody Allen, "The Big Lebowski" by Ethan and Joel Coen, and "Stolen Kisses" ("Baisers Volés") by François Truffaut.

Guaranteed to make me laugh are … movies with Louis de Funès.

If I would not have become a scientist, … I would have attempted to make a living as a fiction writer.

The downside of my job is … that it leaves only very little time for my other interests.

What is the best way to, or how do you make young people enthusiastic for studying science?

The best way is clearly the problem-solving approach. Start by discussing the challenges that society faces today: renewable and sustainable energy sources, climate change, decent housing conditions, food and clean water for all, transportation, new medicines against cancer and infectious diseases, to name just a few. Show examples of how scientific research and technology development have provided beneficial solutions for society in the past, leading to an enormous increase in the average life expectancy since the mid-1800s, and make a convincing argument that scientific progress will also be the only way to address and solve contemporary and future challenges on the planet. Discuss specific examples, openly addressing concerns that exist, and certainly do not come across as knowing the solution for everything. In particular in chemistry, we teach too often in a way that makes the field look overly mature, as if everything has been understood. Generate the confidence that advances in basic research in chemistry in most cases can be fully translated into sustainable industrial technology. Students also appreciate a broader historic picture, such as how modern chemical industry evolved since the beginning of the dyestuff industry, or how eminent chemists such as Emil Fischer pursued their academic training and career. They are also interested in the economic role of chemistry as an innovation driver.

Chemistry has become fully interdisciplinary and the leap from education to forefront scientific research could become more and more difficult to bridge for young people. How should we deal with this dilemma from an education perspective?

Again, teaching how to address and solve important problems is the solution. We clearly cannot teach everything. Substituting too much in our teaching of the fundamentals in the core chemical disciplines, such as synthesis and reactivity, physical analysis and analytics, structure and stereochemistry, by trendy new interdisciplinary developments would indeed bring some danger. Of course, examples from new interdisciplinary developments

are always most welcome and chemists need to understand the language and basics of neighboring scientific and emerging disciplines. But chemists will only continue to be in high demand and make exceptional contributions to the progress at the various scientific interfaces if they profoundly master their own core disciplines and have learned, through research projects, and in particular their doctoral dissertation, how to solve an ambitious, worthwhile problem. On a positive note, the classical lab courses have mostly been replaced by research projects, which involve problem solving. Necessary curriculum and teaching adjustments to respond to the flood of new knowledge, however, are unfortunately frequently hampered by the time constraints imposed on academic scientists through endless grant writing and administrative duties.

Which subject (apart from chemistry of course) and where would you study, assuming you would be a high-school graduate this year?

When I was in this situation in 1971, I decided between studying mathematics, physics, and chemistry on the basis that I equally enjoyed working with my brain and with my hands. I decided on chemistry as I enjoyed and admired the craftsmanship that this discipline involves. At that time, modern molecular biology and biostructure were still in their infancy. Today, I would again enroll in chemistry but in a program that has also a strong molecular-biology side, as I am most fascinated by recent developments such as in epigenetics. I would enroll in a competitive program such as at the ETH Zurich or at the top German universities.

Multiple intermolecular interactions have been discovered and evaluated in the (recent) past. Are we at the end or will we discover or develop new types of intermolecular interactions?

Indeed, the past years have been particularly fruitful in the deciphering and quantification of new types or hitherto overlooked intermolecular interactions, in particular involving dipoles. Examples are orthogonal dipolar interactions, such as those between carbonyl groups or involving fluorine in organic compounds, and of course halogen bonding. Honestly, I would never have predicted that halogen bonding is of a similar strength to strong hydrogen bonding when contributing to protein–ligand interactions. Much remains to be investigated and quantified: intermolecular interactions involving sulfur atoms, substituent effects on aromatic–aromatic interactions, cooperative effects in multiple interactions such as in hydrogen-bonding networks, anion–π interactions between electron-deficient rings of nucleobases and related heterocycles, and the impact of water as a solvent on supramolecular association. The origins of the enthalpic and entropic quantities measured for binding processes in water are poorly understood and require new research and model development.

What are the main drug-discovery problems to address in an academic research group?

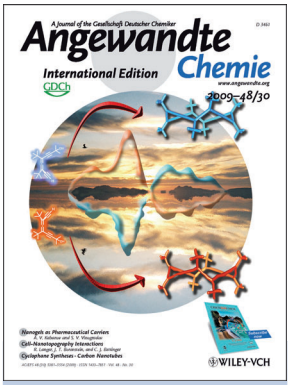
The development of new enabling tools and methods should have priority over the development of leads in areas that are heavily pursued in the major pharmaceutical industry. As this industry neglects infectious and in particular third-world diseases, lead generation against new targets in these areas is a worthwhile effort. Examples for methodological targets are: development of agents for cellular uptake, such as of siRNA; rendering peptide drugs stable and membrane-permeable; optimizing methods for rational ligand design; searching for phosphate replacements; developing new strategies for disrupting protein–protein interactions; and on the more biological side, developing new efficient target-fishing strategies.

Studying model systems generates insights into "isolated" chemical processes. Systems approaches aim to provide insights into large complex networks. Which route should be taken, or how can the two approaches be integrated?

Both approaches are important, and it will depend on the individual personality as to which route to take. Being a physical-organic chemist, I am of course a close admirer of the concept formulated by Marcelin Berthelot, "la chimie crée son objet". I am convinced that we only fully understand a process in biology, such as recognition, transport, and catalysis, if we are able to reproduce it with similar efficiency in an artificial chemical system. Similar to the transition from biology to molecular biology over the past decades, which expresses the desire and need for a more detailed structural and mechanistic understanding down to the atomic level, I also foresee the transition from systems biology to molecular systems biology.

Which polymers would you like to see developed by scientists in the next generation?

It is amazing how innovative processing of the existing polymers, such as polyamides, polyurethanes, or polycarbonates, has provided solutions to problems in the chemical and other industries, such as transportation, construction, and electronics. In fact, new polymers based on new monomers have not been introduced for more than two decades. Regulations (such as REACH) make the introduction of new monomers and polymers more costly. Biodegradable polymers will see increasing interest, and good ideas for supramolecular, self-healing polymers will be in demand, as well as



The work of François Diederich has been featured on the cover of Angewandte Chemie:
"An Enantiomerically Pure Alleno-Acetylenic Macrocycle: Synthesis and Rationalization of Outstanding Chiroptical Response": J. L. Alonso-Gomez, P. Rivera-Fuentes, N. Harada, N. Berova, F. Diederich, *Angew. Chem.* **2009**, *121*, 5653 – 5656; *Angew. Chem. Int. Ed.* **2009**, *48*, 5545 – 5548.

biocompatible polymers for biomedical applications, such as tissue replacement.

Technological developments (e.g., mass spectrometry, molecular imaging, miniaturization) have had a huge impact. What will the (organic) chemical lab of the future look like?

A revolution in asymmetric synthesis and catalysis, paired with increasing facility to separate enantiomers by HPLC on a chiral stationary phase, ensures that all chiral molecules can be prepared in enantiomerically pure forms in the future. We shall still rely in analysis on the pillars of mass spectrometry, X-ray analysis, NMR, vibrational, and optical spectroscopy. Miniaturization will be further advanced but I warn, for reasons of safety, against exclusive micro- and small-scale experiments in the training of chemists. They would never learn about heat evolution in exothermic reactions, and this can present a safety risk later on in academic and industrial labs.

The interview questions were provided by Luc Brunsveld (Eindhoven University of Technology, The Netherlands).

My 5 top papers:

1. "Strength of Molecular Complexation of Apolar Solutes in Water and in Organic Solvents is Predictable by Linear Free Energy Relationships: A General Model for Solvation Effects on Apolar Binding": D. B. Smithrud, F. Diederich, *J. Am. Chem. Soc.* **1990**, *112*, 339 – 343.
   This paper proposes that solvents with low molecular polarizabilities and high cohesive interactions, such as water, greatly benefit apolar complexation and association. It initiated subsequent microcalorimetric measurements that showed a strong enthalpic driving force for complexation in water and other polar protic solvents because of large gains in dispersion interactions and solvent cohesive interactions. This "enthalpic hydrophobic effect" is still the subject of intense investigations by our and other research groups as it affects all supramolecular association processes in the aqueous phase in chemistry and biology.
2. "Isolation of C_{76}: A Chiral (D_2) Allotrope of Carbon": R. Ettl, I. Chao, F. Diederich, R. L. Whetten, *Nature* **1991**, *353*, 149 – 153.
   When the Krätschmer – Huffman process for bulk fullerene production was invented, we immediately concentrated on the isolation and characterization of higher carbon spheres from the produced fullerene soot. These efforts were soon rewarded with the isolation and characterization of the first chiral molecular allotrope of carbon, (±)-D_2-C_{76}, which initiated a comprehensive experimental program to identify and demonstrate the various origins of chirality in chiral fullerenes and their adducts. Later, the Bingel cyclopropanation, introduction of optically active malonate addends, separation of the diastereoisomeric adducts, and subsequent electrochemical retro-Bingel reaction, enabled the preparation of the pure enantiomers of D_2-C_{76}.
3. "Dendritic Porphyrins: Modulating Redox Potentials of Electroactive Chromophores with Pendant Multifunctionality": P. J. Dandliker, F. Diederich, M. Gross, C. B. Knobler, A. Louati, E. M. Sanford, *Angew. Chem.* **1994**, *106*, 1821 – 1824; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1739 – 1742.
   This paper shows that dendritic branching creates a unique local microenvironment at the core, which profoundly changes and enhances properties such as the redox potentials of redox-active cores. In subsequent work, a water-soluble synthetic cytochrome c model was developed in which the potential of the Fe^{III}/Fe^{II} couple of the iron heme at the dendritic core was shifted by 420 mV to a more positive potential compared to a water-exposed iron heme. The investigations have profoundly influenced dendrimer chemistry, validating their mimicry of globular proteins.
4. "A Fluorine Scan of Thrombin Inhibitors to Map the Fluorophilicity/Fluorophobicity of an Enzyme Active Site: Evidence for C–F···C=O Interactions": J. A. Olsen, D. W. Banner, P. Seiler, U. Obst Sander, A. D'Arcy, M. Stihle, K. Müller, F. Diederich, *Angew. Chem.* **2003**, *115*, 2611 – 2615; *Angew. Chem. Int. Ed.* **2003**, *42*, 2507 – 2511.
   A fluorine scan of designed thrombin inhibitors revealed that orthogonal dipolar C–F···C=O interactions between a ligand fluorine and a peptide backbone carbonyl provide a substantial stabilization of the protein – ligand complex. In comprehensive database mining, orthogonal dipolar interactions were subsequently shown to be the preferred mode of interaction between any dipoles fixed at short distances, and these interactions were quantified by using molecular torsional balances. This result led to a systematic investigation of how interactions with organofluorine enhance stability and selectivity in protein – ligand binding.
5. "An Enantiomerically Pure Alleno-Acetylenic Macrocycle: Synthesis and Rationalization of Outstanding Chiroptical Response": J. L. Alonso-Gómez, P. Rivera-Fuentes, N. Harada, N. Berova, F. Diederich, *Angew. Chem.* **2009**, *121*, 5653 – 5656; *Angew. Chem. Int. Ed.* **2009**, *48*, 5545 – 5548.
   Shape-persistent optically active alleno-acetylenic macrocycles feature exceptionally intense chiroptical responses, and combined experimental – theoretical studies revealed that D_n symmetry leads to particularly high Cotton effects. Chiral amplification and unprecedentedly strong electronic circular dichroism were later also observed for alleno-acetylenic oligomers with a proposed helical secondary structure. It has become apparent that the chiroptical properties of alleno-acetylenic chromophores reach those of other benchmark chromophores and may even exceed them, thereby promising interesting fundamental and technological applications.

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