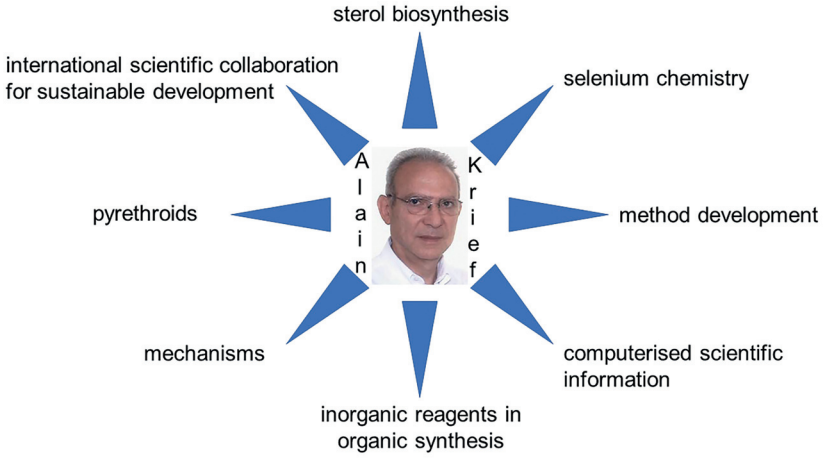
Synthesis H. Hopf et al. Preface

Professor Alain Krief: Advancing Chemistry; From Innovative Synthesis to Promoting Sustainable Development

Henning Hopf[*a]
Goverdhan Mehta[b]
Stephen A. Matlin[c]

[a] Institute of Organic Chemistry, Technische Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany
h.hopf@tu-braunschweig.de
[b] School of Chemistry, University of Hyderabad, Prof. CR Rao Road, Gachibowli, Hyderabad 500046, India
gmehta43@gmail.com
[c] Institute of Global Health Innovation, Imperial College London, Faculty Building, South Kensington, London SW7 2AZ, UK
s.matlin@imperial.ac.uk

Dedicated to our dear friend, colleague and inspiration, Alain Krief, on his 80th birthday.



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Abstract Over more than five decades, Alain Krief's career has encompassed many contributions to chemistry, notably in his innovative work in the areas of organic synthesis and the use of inorganic and organic reagents, as well as his work on bioorganic chemistry and applications of information technology in chemistry. His research on the synthesis of cyclopropanes, including chrysanthemic acid and other pyrethroids, and the uses of selenium compounds in organic synthesis, have been of particular importance and have found widespread applications. In addition, his roles in international collaborations in research and his leadership of the International Organization for Chemical Sciences in Development from 2009 to 2020 have marked his strong commitment to the importance of chemistry as a science for the benefit of society and a contributor to the goal of sustainable development.

Key words synthetic methods, selenium compounds, pyrethroids, chemistry and information technology, International Organization for Chemical Sciences in Development, sustainable development

Henning Hopf studied chemistry in Göttingen and Madison, Wisconsin, where he got his Ph.D. in 1967. After his return to Germany he worked at Marburg, Bochum and Karlsruhe where he got his habilitation in 1972. After a stay at Würzburg University he received a call to Braunschweig where he stayed until his retirement in 2005. He has received numerous national and international awards and served as the President of the German Chemical Society. His main field of study was the chemistry of hydrocarbons (aromatics, polyolefins, cumulenes, acetylenes, polycyclics).

Goverdhan Mehta was Director of the Indian Institute of Science in Bangalore and Vice-Chancellor of the University of Hyderabad, where he is now University Distinguished Professor in the School of Chemistry. He was President of the Indian National Science Academy and of the International Council for Science (ICSU).

Stephen Matlin was Professor in Biological Chemistry in City University, London, and Warwick University, UK and Executive Director of the Global Forum for Health Research, Geneva. He is Visiting Professor in the Institute of Global Health Innovation, Imperial College London. All co-authors are members of the International Organization for Chemical Sciences in Development, Belgium.

1 Introduction

Alain Krief's professional career as a scientist, spanning more than half a century, has been distinguished by many awards and achievements in his outstanding work as an organic chemist and also by his leadership of an international organization dedicated to the role of chemistry in sustainable development. In both areas, his intellectual insights, innovation, attention to detail, drive and commitment to the pursuit of excellence and impacts have been the hallmarks of his approaches. Across all aspects, Alain emerges as a creative scientist with broad interests driven by curios-

ity, effectiveness in networking and developing alliances, having a somewhat sarcastic sense of humor and exuding friendliness.

A citizen of France and Tunisia, born in Tunis on 13 December 1942, Alain Krief[1] received his advanced education in chemistry at the University 'Pierre et Marie Curie' in Paris, where he completed a Ph.D. in 1970 under the supervision of Jacqueline Ficini on cycloaddition of ynamines with α,β-unsaturated carbonyl compounds, while holding a CNRS Research Associate position (1968–1972). Securing a US National Science Foundation Fellowship in 1970, he made a 10-month postdoctoral visit to the laboratory of Elias Corey in Harvard University, working on sterol biosynthesis. Returning to Paris in 1971, he conducted studies of the cycloaddition of ynamines and the reactivity of sulfur ylides. In 1972, he was appointed associate professor in the new Laboratory of Organic Chemistry in Notre-Dame de la Paix University in Namur, Belgium, and was to remain there throughout his career, becoming a full professor in 1975 and serving as Director of the Laboratory of Organic Chemistry (1972–1997) and Director of the Laboratoire de Chimie Organique de Synthèse (1997–2008).

Alain has focused his attention on a number of themes, ranging from an abiding interest in bioorganic chemistry and the mechanism of sterol biosynthesis to synthetic reagents and their mechanisms, as well as methodologies, with a prolific output of research that has led to more than 350 papers. The theoretical and practical significance of his work has been recognized by a number of academic awards, including the Prize of the French 'Académie des Sciences' in 1985 and the International Wernaers Prize for Research and Broadcasting of Knowledge in 1999, as well as prestigious appointments including Presidencies of the Janssen Prize for Creativity in Organic Synthesis (2002–2008) and the Société Royale de Chimie Belge (1993–1995).

From an early stage in his career, Alain cultivated close relationships with industry, developing collaborations with Roussel Uclaf, France (1972–1985), ICI Plant Protection Division, UK (1980: sabbatical leave), ACROS Company, Belgium (1993–1996: as Head of the Namur R&D Unit), Janssen Pharmaceutical Company, Belgium (1998–2002) and Unimark Remedies Ltd, India (since 2012). He has also worked as an expert for a number of prominent associations, such as the CNRS in France, the European Community, the World Academy of Sciences (TWAS) and the Petroleum Fund of the American Chemical Society. His service to chemistry has included membership of the editorial boards of many international journals, examples being *Synlett*, the *Russian Journal of Organic Chemistry*, *Sulfur Reports* and *Mini-Reviews in Organic Chemistry*.

Committed to working internationally, Alain has been invited as a visiting professor to more than 14 universities worldwide and has given hundreds of lectures at congresses and symposia and in universities and industries. He has organized and been chairman of several congresses, including the Belgian Organic Synthesis Symposium (BOSS) and the 40th Bürgenstock Conference (Switzerland, 2005). He has had a long-standing association with the HEJ Research Institute for Chemical Sciences at the University of Karachi, Pakistan, where he is an Adjunct Professor, and is a Fellow of the Chemical Society of Pakistan (2014 to present), as well as being a Senior Associate to the UNESCO UNISA Africa Chair in Nanosciences and Nanotechnology, South Africa (2017 to present). His major role in the International Organization for Chemical Sciences for Development is discussed in Section 3 below.

Beyond organic chemistry, Alain has also pursued a deep interest in information technology (IT), including developing a computerized scientific information system, seeking a new way to transfer knowledge. This has involved international collaborations, including with France and India, aiming at ontology building, the use and implementation of communication tools for collaboration, work towards creating an online dictionary, the development of semantic-rich descriptions of chemical structures, modelling of a search engine and the description of protocols of communications.[2]

2 A Spectrum of Research

Alain's research career has been notable for effective forays into many diverse fields of contemporary interest in organic chemistry. A scan of the research areas that have drawn him is formidable in range, testifying to his versatility as a creative practitioner in organic chemistry and its diverse interfaces. Some of these areas include the development of novel synthetic methods such as the use of selenium as an activating group, the applications of α-heterosubstituted carbanions in synthesis and the exploration of their reactivity, the synthesis of small-ring carbocycles and their varied applications, the total synthesis of small bioactive natural products (pyrethroid insecticides), the antioxidant selenomethionine, anti-viral compounds, the use of antibodies in organic synthesis and the study of the intimate mechanism of steroid biosynthesis. Another field of interest involved the use of classical inorganic reagents in organic synthesis, such as bromoazide, diphosphorus tetraiodide, samarium diiodide, osmium tetraoxide and others, underlining his holistic view of chemistry in which a distinction between organic and inorganic chemistry might be useful as an organizing principle but limits the view on general reactivity patterns. Many of Alain's original contributions have generated intellectual property and have been commercialized by leading pharma companies. Among his many outstanding contributions in the broad area of organic synthesis, we particularly highlight two here, concerned with cyclopropane/pyrethroid synthesis and selenium chemistry.

2.1 Cyclopropane Chemistry/Pyrethroids

In the last two decades of the 20th century, as serious concerns about the harmful environmental impact of synthetic insecticides began to surface, Alain recognized the importance and potential of plant-based, eco-friendly agrochemicals like pyrethroids. He pioneered novel syntheses of chrysanthemic acid and its analogs through short synthetic strategies. Some of these approaches were quite robust and scalable and have found their way to commercial exploitation. Following Alain's early, elegant but classical syntheses of chrysanthemic acid, his group devised a novel cascade process involving cyclopropane formation and fragmentation from readily accessed precursors with elements of regio- stereo- and enantioselectivity and scalability embedded.[3] This evolving methodology was extended to many new synthetic pyrethroids, most notably to the potent synthetic analogue deltamethrin,[4] a pyrethroid-derived ester with very low mammalian toxicity. The cornerstone of Alain's syntheses of pyrethroids is the built-in flexibility of the approach and therefore potential adaptability to expand the chemical space around their basic scaffold.

2.2 Selenium Chemistry

In the field of method development, Alain was one of the pioneers of organoselenium chemistry[5] and has remained one of the leaders in the field.[6] Selenium is an element that practically played no role in synthetic chemistry for a long time. Due to the ground-breaking studies of the Krief group, this has changed fundamentally.

Alain's entry into the selenium field occurred more or less serendipitously. Working on the chemical behavior of sulfur ylides, he simply thought of replacing the sulfur with selenium, thus hoping to increase the reactivity. He therefore prepared selenium ylides from selenonium salts – and soon found that he had hit a gold mine. It was shown that selenium-based reagents such as β-hydroxyselenides or selenoxides were able to perform specific transformations not only under milder conditions than their sulfur counterparts but often also with higher selectivity. Many of these conversions were later summarized in a monograph on organoselenium chemistry that became a widely cited text in the field.[7] Moreover, selenides can also be employed as precursors for the preparation of organolithium reagents,[8] making the former of even wider significance in metal–organic chemistry.

3 Leadership of the International Organization for Chemical Sciences in Development (IOCD)

During the period 2009 to 2020, Alain Krief served as Executive Director of the IOCD. This international, non-governmental organization was launched at UNESCO in Paris in 1981, with the Nobel Laureate Glenn Seaborg[9] and organic chemist Pierre Crabbé as its founding President and Executive Director, respectively. Working through research programs, provision of services and the improvement of education in the chemical sciences,[10] it was the first organization devoted to the role of the chemical sciences in global development, and at the outset gave special attention to helping chemists in low- and middle-income countries (LMICs) to engage with projects of relevance to the development of their countries and regions.[11] Following Crabbé's untimely death in 1987, Robert Maybury was appointed Executive Director. Seaborg was succeeded as President by the Nobel Laureate Jean-Marie Lehn in 1992. When Maybury retired in 2009, Alain Krief was selected to follow him and his eleven years at the helm were marked by a number of notable achievements, both in the internal reorganization and reform of the IOCD and in its external activities and impact.

Krief took over at a time when the IOCD had passed a peak of success and was in need of rejuvenation. In the early years, a number of grants from international organizations and private foundations had enabled the IOCD to expand, establish a range of working groups and projects in areas such as agricultural and medicinal chemistry, natural products, biotic exploration and environmental analytical chemistry, and to provide a range of analytical services and help stock chemistry libraries in LMICs. By 2009, not only had funding for such development activities become much harder to find, but the focus of attention in international development work had shifted towards national capacity-building and self-sufficiency and a new conceptualization of the IOCD's role was required. Krief found that the IOCD was rapidly spending its reserves, but was not receiving significant new income – an unsustainable recipe that would have forced closure within a few years. The fact that the IOCD survived to celebrate its 40th anniversary[12] in 2021 was, in no small measure, due to his dedication, tenacity and ability to recruit and work with people.

The restructuring of the IOCD to improve its viability was a challenging process requiring a multi-year effort. It involved gradually closing down activities that were becoming increasingly less viable and unproductive, while searching for impactful new projects; controlling and drastically reducing expenditure; reforming the Statutes of the IOCD to create a more streamlined and efficient Secretariat and General Assembly (IOCD's governing body); and redefining the strategy of the IOCD to modernize it as a contemporary organization with a mission relevant to 21st Century problems. Krief energetically took up all these challenges, acquiring new skills and processes in organizational management as needed along the way. He found support from a long-time member of the IOCD, Stephen Matlin, a chemist who worked in academia before moving into international

development and had experience at a senior level in non-governmental, governmental and international organizations.

One of Krief's talents has been to identify and bring on board people who share his passion for promoting the role of the chemical sciences and to assemble a core group of individuals who have supported him and helped to take forward the essential reforms. This has been demonstrated not only in the changed composition of the IOCD General Assembly, but also in the activities and functions that enabled the IOCD to resurface as a visible organization in the world of chemistry. Krief's personal stature and reputation as an internationally prominent synthetic organic chemist enabled him to use his contacts and alliances across the world to benefit the IOCD. At the local level, his collaboration with Davide Bonifazi at the University of Namur led to the establishment of a series of Symposia jointly sponsored by the IOCD and the Namur Research College (NARC). These attracted participation by leading chemists including the Nobel Laureates Ryoji Noyori and Ada Yonath, as well as Jean-Marie Lehn.

Federico Rosei was invited as the lead speaker at the 2012 joint IOCD-NARC Symposium, and in 2013 was recruited to establish a new IOCD Working Group—the first in many years—on Materials for Energy Conversion, Saving and Storage (MATECSS), which he co-led with his colleague Mohamed Chaker based at the Institut National de la Recherche Scientifique (INRS), Montreal. Krief did not hesitate to lend support to Rosei's successful bid for a UNESCO Chair in MATECSS and also to successfully nominate him for the World Cultural Council's 2014 José Vasconcelos World Award of Education. In a closing of the historic circle, it was Rosei who was chosen to succeed Krief as the IOCD's next Executive Director in 2021.

Krief was able to attract interest and collaboration from highly respected scientists globally. One result was that the composition and character of the General Assembly was transformed. While it was reduced in size, it was expanded in diversity with the inclusion of prominent chemists from Africa and Asia as well as Europe and the Americas.

Of particular significance, in terms of increasing the IOCD's visibility and impact, was Krief's recruitment of chemists committed to advancing the roles of chemistry, both as the 'central science' and as the engine of a sustainable future. Together with Krief, three of these (Henning Hopf, Stephen Matlin and Goverdhan Mehta) began discussions and preliminary drafting of essays in 2014, and the work later crystallized into a formal IOCD action group, 'Chemists for Sustainability' (C4S), which flexibly expands by co-opting others with expertise in particular topics. Since 2015, C4S has published more than 30 peer-reviewed papers, including in leading journals such as *Nature*, *Science*, *Royal Society Open Science* and *Angewandte Chemie*, as well as many other articles online and in news media.[13] Very importantly for its own sustainability, C4S has attracted financial support, including from the German and UK Chemical Societies. C4S has addressed a number of themes that cast light on the status, roles and potentials of the chemical sciences in the context of science, society and the challenges of the 21st Century.

A pair of early papers[14] by the C4S group highlighted the important contributions that the chemical sciences must make to achieving the UN Sustainable Development Goals and stressed the need for chemistry to repurpose itself as 'one-world' chemistry for optimum effect. This involved re-orienting chemistry's role as a science for the benefit of society and embracing cross-disciplinary working. The need was emphasized for chemistry to adopt systems thinking and this attracted considerable attention, leading to two successive projects[15] of the International Union of Pure and Applied Chemistry (IUPAC), supported by the IOCD, on the inclusion of systems thinking in chemistry through education. The far-reaching impact of this work[16] will be a major legacy of the C4S group, which Krief helped establish and of which he has been an enthusiastic member.

Conflict of Interest

The authors declare no conflict of interest.

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