



UNIVERSITATEA DIN
BUCUREȘTI
VIRTUTE ET SAPIENTIA



UNIVERSITATEA DIN BUCUREȘTI

Doctor Honoris Causa
Jean-Marie Lehn

JEAN-MARIE PIERRE LEHN
DOCTOR HONORIS CAUSA

Laudatio

Domini Jean-Marie Pierre Lehn

Senatul Universității din București a hotărât să acorde Profesorului Jean-Marie Lehn titlul de *Doctor Honoris Causa*. Este un mare privilegiu și o mare onoare pentru Universitatea din București să recunoască rolul important jucat de Profesorul Jean-Marie Lehn în știința modernă.

Domnul Profesor Jean-Marie Lehn este, fără îndoială, unul din cei mai mari chimiști ai tuturor timpurilor. Prin lucrările sale privind criptanzii, pentru care a primit Premiul Nobel, în anul 1987, împreună cu Donald Cram și Charles Pedersen, a creat Chimia supramoleculară, ale cărei concepte au schimbat profund modul de gândire al oamenilor de știință. Recunoașterea moleculară, informația înscrisă în molecule, descrierea și înțelegerea fenomenelor de auto-asamblare și auto-organizare reprezintă momente cruciale în dezvoltarea chimiei contemporane.

Puțini chimiști au influențat atât de puternic toate ramurile chimiei: recunoașterea moleculară și transportul selectiv al ionilor metalici au contribuit la dezvoltarea spectaculoasă a Biochimiei; fenomenele de auto-asamblare dirijate de ioni metalici, respectiv sintezele de grile, helicați și scări moleculare au inițiat chimia metalosupramoleculară; chimia macromoleculelor și chimia analitică au beneficiat, și ele, de ideile chimiei supramoleculare, dezvoltându-se pe noi direcții; reactivitatea și cataliza supramoleculară își au originile în lucrările Profesorului Lehn.

Dacă luăm ca punct de reper anul 1987, când a primit Premiul Nobel, vom constata că lucrările publicate după acest an au avut un impact la fel de puternic. Profesorul Lehn revoluționează Știința, din nou, prin dezvoltarea chimiei constituționale dinamice, care deschide drumul spre chimia adaptativă și evolutivă, cea din urmă cu un rol hotărâtor în înțelegerea mecanismelor complexe ale vieții. Aceștia li se adaugă cercetările privind sinteza de noi materiale foto-și electroactive, polimeri supramoleculari, cristale lichide. O atenție specială este acordată proceselor fotochimice (stocarea și conversia energiei solare, activarea

fotochimică a moleculelor mici, fotoliza apei, fotoreducerea bioxidului de carbon). Contribuțiile în chimia bioorganică și în biochimie sunt, de asemenea, cruciale (modele pentru receptori biologici, pentru enzime și procese de transport, agenți de marcare imunologici etc.).

Profesorul Jean-Marie Lehn s-a născut pe 30 septembrie 1939 la Rosheim, Franța. A studiat la Universitatea din Strasbourg, unde obține și titlul de doctor cu o teză privind triterpenele, sub îndrumarea Profesorului Guy Ourisson (1963). Efectuează apoi un stagiul post-doctoral la Universitatea Harvard, cu Profesorul Robert B. Woodward, unul de corifeii Chimiei organice, laureat al Premiului Nobel (1965). Din 1970 este Profesor la Universitatea din Strasbourg și, în perioada 1979–2010, la *Collège de France*, ca titular al Catedrei de interacțiuni moleculare. A înființat la Strasbourg *Institut de Science et d'Ingénierie Supramoléculaires*, al cărui Director a fost între 1997 și 2004.

Producția științifică a Profesorului Lehn este impresionantă, fiind reprezentată de aproximativ 1000 de articole științifice și 3 cărți. În egală măsură, Profesorul Lehn a creat și o școală de cercetare extrem de puternică, elevii săi fiind nume importante în Chimia contemporană. Jean-Pierre Sauvage, laureat al Premiului Nobel pentru Chimie în anul 2016, a fost doctorand al Profesorului Lehn. În laboratoarele sale s-au format câțiva cercetători români, care își desfășoară acum activitatea fie în țară, fie în străinătate. Doi dintre ei provin de la Universitatea din București iar unul, Augustin Mădălan, este acum conferențiar la Departamentul de Chimie Anorganică.

A fost profesor invitat la universități de pe toate continentele. Legăturile Profesorului Lehn cu știința românească sunt vechi. A venit pentru prima dată în România la sfârșitul anilor '60 ai secolului trecut. A revenit în repetate rânduri, ținând conferințe la Academia Română, la universități din București și Cluj-Napoca, la *Institut Français* (București). În anul 1994 a fost ales membru de onoare al Academiei Române.

Personalitate covârșitoare a științei, Profesorul Jean-Marie Lehn a fost distins cu cele mai importante premii științifice naționale și internaționale:

Medalia de bronz CNRS, 1963; Premiul Adrian al Societății Franceze de Chimie, 1968; Medalia de argint CNRS, 1972; Premiul Raymond Berr al Societății Franceze de Chimie, 1978; Medalia de aur a Academiei Pontificale de Științe, 1981; Medalia de aur CNRS, 1981; Medalia Pierre Bruylants, Louvain, 1981; Premiul Paracelsus al Societății Elvețiene de Chimie, 1982; Premiul Alexander von Humboldt, 1982; Premiul Rolf-Sammet, Universitatea din Frankfurt, 1985; Premiul Fundației Alsace, 1986; Premiul George Kenner, University of Liverpool, 1987; *Sigillum Magnum*, Universitatea din Bologna, 1988; Premiul Minnie Rosen, 1989; Premiul

Karl-Ziegler, *Gesellschaft Deutscher Chemiker*, Medalia de aur a *Société Académique Arts-Sciences-Lettres*, 1995; Medalia de aur, Universitatea Comenius, Bratislava, 1995; Medalia de aur a Facultății de Științe, Universitatea Carolina, Praga, 1995; Medalia Institutului de Chimie Fizică al Academiei Poloneze de Științe, Varșovia, 1996; Medalia Davy a *Royal Society*, 1997; Medalia Lavoisier a Societății Franceze de Chimie, 1997; *Top 75 Award*, C&N, *American Chemical Society*, 1998; Premiul Allan R. Day al *Philadelphia Organic Chemists' Club*, 1998; Medalia Messel, *Society of Chemical Industry*, Londra, 1998; Medalia de aur "Giulio Natta" a Societății Italiene de Chimie, 2003; JSPS Award (*Japan Society for the Promotion of Science*), 2003; Medalia de aur la a 70-a aniversare a *Fondation de la Maison de la Chimie*, 2004; Medalia de aur a Universității Paul Sabatier Toulouse III, 2005; Premiul Johannes Gutenberg Mainz, 2006; Premiul Burckhardt-Helferich Leipzig, 2007; Medalia Costin Nenițescu a Societății de Chimie din România, 2008; Medalia Societății Cehe de Chimie, 2008; Sigilli d'Oro, Universitatea din Bari, 2008; *Sigillum* Conferința Avogadro, *Società Chimica Italiana*, Universitatea din Salento, 2011; Medalia Chandler, Columbia University, 2011; Medalia MacDiarmid, University of Pennsylvania, 2011; ERC *Advanced Grant*, 2011; Sir Derek Barton Gold Medal, *Royal Society of Chemistry*, 2012; Eucor Medal, 2013; Medalia de aur a Societății Slovac de Chimie, Bratislava, 2015; Medalia de Merit a Universității Adam Mickiewicz, Poznan, 2015; *China Friendship Award*, 2015; *Distinguished KIT-Professor*, Karlsruhe, 2016.

Profesorul Lehn a primit un număr impresionant de titluri *Doctor Honoris Causa*:

Universitatea Hebrew Ierusalim, 1984; Universidad Autonoma, Madrid, 1985; Universitatea Georg-August Göttingen, 1987; Université Libre din Bruxelles, 1987; Universitatea Iraklion, 1989; Università degli Studi di Bologna, 1989; Universitatea Carolina, Praga, 1990; University of Sheffield, 1991; University of Twente, 1991; Universitatea din Atena, 1992; Universitatea Politehnică din Atena, 1992; Universitatea Politehnică București, 1994; Illinois Wesleyan University, 1995; Université de Montréal, 1995; Universitatea din Bielefeld, 1998; Weizmann Institute of Science, Rehovot, 1998; Faculté des Sciences Appliquées, Université Libre de Bruxelles, 1999; Universitatea din Nagoya, 2000; Université de Sherbrooke, 2000; Università di Trieste, 2001; Royal Institute of Technology, Stockholm, 2003; University of St. Andrews, 2004; Heriot Watt University, Edinburgh, 2005; Universitatea Tehnică, St Petersburg, 2005; Universitatea Mazaryk, Brno, 2005; Universitatea Kyushu, 2005; Universitatea M. V. Lomonosov Moscova, 2006; Aristotle University of Thessaloniki, 2006; Universitatea de Stat din Kazan, 2006; Universitatea de Stat din Novosibirsk, 2006; Universitatea din Patras, 2008; Universitatea Babeș-Bolyai, Cluj-Napoca, 2008; Università della Basilicata, Potenza, 2008; Universitatea Taras

Shevchenko, Kiev, 2009; Technion, Israel, 2009; Universitatea din Ljubljana, 2009; City University Hong Kong, 2010; Queen's University, Belfast, 2012; University of Oxford (Dr. Sci.), 2014; Macau University of Science and Technology (MUST), 2015; Universitatea din Malaga, 2015; Institute of Chemical Technology, Mumbai, 2017; New York University, 2017; University of Cambridge, 2017.

Domnia Sa este membru de onoare al unor academii, din care menționăm:

National Academy of Sciences of the USA, 1980; American Academy of Arts and Sciences, 1980; Royal Netherlands Academy of Arts and Sciences, 1983; Académie des Sciences, Institut de France, 1985; Deutsche Akademie der Naturforscher Leopoldina, 1985; Accademia Nazionale dei Lincei, 1985; American Philosophical Society, 1987; Académie Européenne des Sciences, des Arts et des Lettres, 1987; Academia Europaea, 1988; Académie d'Alsace, 1989; Akademie der Wissenschaften und der Literatur-Mainz, 1989; Akademie der Wissenschaften of Göttingen, 1990; Koninklijke Vlaamse Academie van België voor Wetenschappen en Kunsten, 1990; Indian Academy of Sciences, 1991; Academia Poloneză de Științe, 1991; Academy of Arts and Sciences of Puerto Rico, 1991; Academia de Științe din Ucraina, 1992; Institut Grand Ducal, Luxembourg, 1992; Royal Society, 1993; Academia Română, 1993; Korean Academy of Science and Technology (KAST), 1995; Academia Pontificală de Științe, 1996; Royal Irish Academy, Section Science, 1999; Academia Rusă de Științe, 1999; Académie des Technologies, Institut de France, 2001; Academia de Științe din China, 2004; Real Academia Sevillana de Ciencias, 2005; Académie Royale des Sciences, des lettres et des beaux-arts de Belgique, 2009; Academia de Științe Hong Kong, 2015; Real Academia de Ciencias de Espana, 2017.

Acordarea titlului *Doctor Honoris Causa* Domnului Profesor Jean-Marie Lehn este un semn de recunoaștere din partea Universității din București a prestigioasei sale activități științifice, pentru prodigioasa sa activitate de promovare a științei și cunoașterii, pentru întreaga sa carieră.

Laudatio

Domini Jean-Marie Pierre Lehn

“The essence of chemistry is not only to discover but to invent, and, above all, *to create*.” (J.-M. Lehn)

The University of Bucharest decided to embrace the proposal of the Faculty of Chemistry and award the title of *Doctor Honoris Causa* to Professor Jean-Marie Lehn.

For the University of Bucharest it is both a privilege and an honour that you, Professor Lehn, accepted this title and now became a member of our academic community. Beyond any particular achievement worth mentioning, you have changed the way that we see chemistry: you built the chemical and conceptual toolbox that allowed chemists to expand the horizon of research from the (complicated enough) study of molecules to the understanding of their subtle, yet crucially important, symphony of interactions, equating to a genuine “molecular sociology”. One is not too generous to your achievements by stating that the way we see chemistry is not the same before and after your contribution.

In an over-standardized society that increasingly feels the need to put numbers on any aspect of life – starting with the number of “likes” on Facebook and ending with all sorts of “scientometric” evaluations of one’s academic achievements – Professor Jean-Marie Lehn stands in his own league. His achievements in chemistry are beyond the meaning of any objective evaluation: while we, chemists, read scientific articles in order to know “what is the chemistry of today”, we grew accustomed to read professor Lehn’s articles because we want to know “what is the chemistry of tomorrow”.

Just as the first notes of a symphony allow the trained ear to detect the greatness of the opus that will unravel, Professor Lehn’s first steps in the scientific world were an early indication of his capacity to be at the forefront of science. The 22 year old scientist’s first publication was in the field of the (then) brand new NMR studies of the structure of steroids. It was, indeed, the prelude of a career on steroids. Sharper and sharper, just as the NMR signals were to become.

Fundamental studies were soon to follow: Professor Lehn studied through the mid-sixties nitrogen inversion phenomena, both theoretically, through ab-initio methods and experimentally using NMR. Notably, some of the pioneering results of his independent career, such as the finding of a second-order transition of quinolein in the liquid phase at 158°C, were only confirmed and published some 20 years later.

He published the first results on cryptands as early as 1969 and led to an entire field of research recognised by the 1987 chemistry Nobel Prize along with Donald J. Cram and Charles J. Pedersen. This research field – supramolecular chemistry– now matured into a science in its own right: we now often talk about supramolecular science. It operates with concepts such as molecular recognition, encoding information in the structure of molecules, defining and understanding self-assembly and self-organization phenomena which taken together represent crucial moments in the development of contemporary chemistry and have profoundly changed the mindset of scientists.

Renowned for the depth in which he studies each subject, the scientific community recognises Professor Lehn even more for the breadth of his interests. Indeed, few chemists have so strongly influenced all branches of chemistry: inorganic, organic, physical chemistry, biochemistry and even the most recently recognized area of chemistry, namely cellular biology. The metal ion directed self-assembly phenomena, respectively the synthesis of grids, helices, and molecular ladders initiated the field of metallosupramolecular chemistry; the great synthetic prowess demonstrated with every new studied molecule, the diverse physical chemistry methods used for the characterisation of events linked to molecular recognition and selective transport of metal ions, supramolecular reactivity and catalysis as well as advances in macromolecular chemistry and analytical chemistry are witnesses of the breadth of subjects embraced during your ongoing career.

No description of Professor Lehn's contribution is complete without mentioning a unique feature that distinguishes him from other great scientists. In truth, for the vast majority of Nobel laureates the Nobel Prize represents the crowning of a brilliant career. For Professor Lehn on the other hand, it appears today as if the award of the Nobel Prize was a mere recognition of his debut in chemistry! Taking 1987, the year of the Nobel Prize, as landmark, one finds that the work developed subsequently had the same or even stronger impact on the development of modern chemistry.

One such example is that Professor Lehn built on the understanding and control of subtle molecular interactions in order to put forward the concept of “instructed mixtures”, namely complex mixtures of interacting molecules so designed as each

molecule to be able to distinguish and bind a specific partner among a collection of (very) similar other substances. If binding within these mixtures occurs simultaneously with reversible preferential chemical reactions among defined components “le tour est joué” and yet another field of chemistry comes out of the seemingly magical hat full of ideas of Jean-Marie Lehn. Experts have by now recognized in this brief description the field of dynamic combinatorial chemistry, that expands the chemical space that we are now able to explore to a new dimension: the dimension of molecular evolution under selection pressure, not foreign to the fundamental question of biological evolution! Dynamic constitutional chemistry, that stems from the concepts of dynamic combinatorial chemistry paves the way for adaptive and evolutionary chemistry, as we mentioned earlier, with a significant role in understanding the complex mechanisms of life. Other, not less important research results, include also the synthesis of new photo- and electro-active materials, supramolecular polymers, and liquid crystals. Particular attention was paid to photochemical processes (storage and conversion of solar energy, photochemical activation of small molecules, photolysis of water, photoreduction of carbon dioxide). Contributions in bio-organic chemistry and biochemistry are also crucial: models for biological receptors, enzymes and transport processes, immunological markers and a great many other diversity of subjects.

Professor Jean-Marie Lehn was born on 30 September 1939 in Rosheim, France. He studied at the University of Strasbourg, where he obtained his Ph.D. with a thesis on the triterpenes, under the guidance of Professor Guy Ourisson (1963). He carried out a post-doctoral research stage at Harvard University with Professor Robert B. Woodward, Nobel Prize laureate (1965). Since 1970, he has been Professor at the University of Strasbourg and from 1979 to 2010 at the Collège de France (Department of Molecular Interaction). Professor Lehn has founded in Strasbourg the *Institut de Science et d'Ingénierie Supramoléculaires*, whose director was from 1997 to 2004. He was visiting professor at universities on all continents.

Usually under such circumstance, one lists the scientific awards of the distinguished personality under consideration. Considerably too long for such an event, I will refrain from reading the complete list. However, there is a truth widely accepted by those that know Professor Lehn and that must be enounced: it is not Professor Lehn's profile that was elevated by any of the received awards, rather it is the prestige of the awards themselves that was elevated by having Professor Lehn among the recipients.

There is, however, an achievement that Professor Lehn has not succeeded: he still did not transform any material into gold. But in order to compensate for this shortcoming, he transformed a very large number of doctoral and postdoctoral students into accomplished scientists, which, according to those that value of

thoughts and ideas higher than the value of gold, is a far greater achievement. Among those that learned their trade at his research school, one can cite Jean-Pierre Sauvage, Nobel Prize laureate of Chemistry in 2016, and if bets are to be made I strongly suggest that you put your money on the fact that there are many more to come. Several Romanian researchers worked together with Professor Lehn: Daniel Funeriu, Silviu Balaban, Mihai Barboiu, Augustin Madalan and Mihail Stadler. They were some of the strings, we would like to say important ones, that under the experts hands of the master allows the chemical symphony of Professor Lehn to continue enchanting the chemical audience with many more discoveries to come. These outstanding Romanian researchers are clear witnesses of Professor Lehn's long relation with Romania: he first came to Romania in the late 1960s, and has returned many times invited to speak at the Romanian Academy, at universities in Bucharest and Cluj-Napoca, at the *Institut Français* (Bucharest). In 1994 he was elected honorary member of the Romanian Academy.

Jean-Marie Pierre Lehn
Speech on the occasion of receiving the honorary
Title of Dr. Honoris Causa

I wish to thank very warmly the Senate of the University of Bucharest for conferring upon me a Doctorate Honoris Causa. I would like to salute here the high level of teaching and research activities pursued at this renowned Institution.

I would also like to mention, at the outset, that I have had several highly gifted Romanian co-workers. They made very significant contributions to our work and one of them even occupied a high position in the running of your country.

Through this Honorary Degree, this Institution also recognizes the role of Science and in particular the vitality of a specific field, my field of activity, Chemistry.

Indeed, chemistry plays a *central role* both by its place in the natural sciences and in knowledge, and by its economic importance and omnipresence in our everyday lives. Being present everywhere, it tends to be forgotten and to go unnoticed. It does not advertise itself but, without it, those achievements we consider spectacular would not see the light of day: therapeutic exploits, feats in space, marvels of technology, and so forth. It contributes to meeting humanity's needs in food and medication, in clothing and shelter, in energy and raw materials, in transport and communications. It supplies materials for physics and industry, models and substrates for biology and pharmacology, properties and processes for technology and industry.

Chemistry is the *science of matter and of its transformations*. It plays a primordial role in our understanding of the processes of matter, in our capability to act upon them, to modify them, to control them and to invent new expressions of them.

Chemistry is also a *science of transfers*, a communication knot and a relay between the simple and the complex, between the law of physics and the rules of life, between the basic and the applied.

In its *method*, chemistry is a *science of structures of interactions and of transformations*.

In its *object*, the molecule and the material, chemistry expresses its *creativity*. Chemical synthesis has the power to produce new molecules and new materials with new properties. New indeed, because they did not exist before being created by the recomposition of atomic arrangements into novel and infinitely varied combinations and structures.

Chemistry has been evolving over the years towards an increase in complexity and in diversity in both structural and functional features, from simple molecules to molecular populations, from small molecular structures to large supramolecular architectures, from molecular properties to supramolecular functions. Thus, one witnesses the emergence of a chemistry of systems and of functions on the basis of a chemistry of species and reactions.

Over the years our work led to the definition of a new field of chemistry, “*supramolecular chemistry*”, which lies beyond the molecule. It is the domain of intermolecular relationships, a sort of molecular sociology, where molecular interactions define the interspecific bond, the action and reaction – in short the behaviour of molecular populations. It deals with the complex entities formed by the association of two or more chemical species held together by intermolecular forces, whereas molecular chemistry studies the features of the entities constructed from atoms linked by covalent bonds. From the investigation of molecular recognition processes, the field broadened towards supramolecular reactivity and transport processes. It also extended to the elaboration of functional devices, for supramolecular photonics, electronics and ionics.

Supramolecular chemistry strives for an increasing control over the structures and functions of molecular assemblies, supramolecular entities and materials.

The main line of further development concerned the chemistry of “*self-organization*” based on the design of “programmed” systems that undergo spontaneous assembly of suitable components into well-defined functional supramolecular architectures, directed by the supramolecular processing of molecular information. Thus, chemistry is not only the *science of the structure and transformation of matter*. It is also an information science, the *science of informed matter*, where chemical information is stored at the molecular level and processed at the supramolecular level.

More recently, importing into molecular chemistry, the dynamic features characteristic of supramolecular chemistry, through the introduction of reversible covalent bonds, allowed the implementation of selection in self-organization processes. It led to the definition and development of “*constitutional dynamic chemistry*”, whose molecular or supramolecular entities are able to undergo reorganization in response to external stimuli. It points to the emergence of an

“*adaptive chemistry*”, that involves dynamic networks linking chemical entities, thus opening towards the chemistry of *complex systems*.

In addition to a great interest for the exploration of the interface with molecular biology, a definite emphasis lies in abiotic, nonnatural species, figments of the imagination of the chemist, possessing a desired chemical or physical property. It opens wide the door to the creative imagination of the chemist at the meeting point of chemistry with biology and physics.

Like the artist, the chemist engraves into matter the products of his or her creative imagination. The stone, the sounds and the words do not contain the works that the sculptor, the composer, the writer express from them. Similarly, the chemist creates original molecules, new materials and novel properties from the elements provided by nature.

The essence of chemistry is not only to discover but to invent and *above all to create*. The book of chemistry is not just to be read but it is to be written! The score of chemistry is not just to be played but it is to be composed!

Thus, chemistry is a science and an art. It is also an *industry*: each scientific component of the discipline has its industrial counterpart. It has for this reason a very marked impact on economic and social life. It is therefore not surprising that chemistry is called upon more and more often to face a number of new, or increasingly important, socio-economic imperatives associated with geopolitical phenomena.

The resolution of pressing *economic and social problems* cannot be envisaged without fundamental discoveries to open the way to new processes. It is thus a twofold challenge, intellectual and technical. To meet it becomes ever more fascinating. One must have the courage to match the dangers, the ambition to meet the challenges, whether they originate from the abyss of our ignorance or from the spectre of our crises.

Beyond the general progress of knowledge and the technological development, the most important impact science can and must have on society is the *spirit* that it implies, the scientific, rational approaches towards the world, life and society.

Science education in our schools, colleges and universities as well as for the general public must therefore be a major priority, so as to train the researchers and discoverers of tomorrow, – to lift irrational fears and rejections, – to develop the scientific spirit, the scientific attitude, in order to fight the obscure, the deceitful, the irrational.

A very actual issue concerns the situation of the scientist with respect to ethics

and society. It is my strong opinion that the scientist has first of all *general responsibility to the truth* and only then is there responsibility to the society and the world at the particular time in history. Ethics is a function of time, location and knowledge. Pursuit of knowledge and truth supersedes present considerations on what nature, life or the world are or should be, for our vision can only be a narrow one and we have no right to switch out the lights of the future.

These perspectives for the future of science, for *our* future, have already been expressed in most fitting terms by this quintessence of the artist-scientist-engineer, *Leonardo da Vinci* when he wrote:

«Where nature finishes to produce its own species, man begins, using natural things, in harmony with this very nature, to create an infinity of species.»

The development of science is an irreversible process. We cannot turn it back. Knowledge cannot be erased. We must walk the way from the quest for knowledge to the control of our destiny and institutions of higher learning and research are showing the way.

Jean-Marie Lehn
University of Strasbourg

Curriculum Vitae

Jean-Marie Pierre Lehn

Born on September 30, 1939 at Rosheim, Bas-Rhin

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Presently

- Professor at the University of Strasbourg Institute for Advanced Study (USIAS),
Chair of Chemistry of Complex Systems
- Honorary Professor at the Collège de France, Paris
- Emeritus Professor at the University of Strasbourg

Director

- Director of ISIS (Institut de Science et d'Ingénierie Supramoléculaires),
Strasbourg, **1997–2004**
- Director of the Laboratoire de Chimie Supramoléculaire, ISIS, Université de
Strasbourg
- Director at the Nanotechnology Institute of the Karlsruhe Institute of
Technology, **since 1998**
- Honorary Director, “Lehn Institute of Functional Materials”, Sun Yat Sen
University, Guangzhou, **since 2010**

Education

Undergraduate Studies, University of Strasbourg: Licence ès-Sciences (Bachelor of Sciences), Strasbourg, **1960**; Graduate work on “Conformational Studies of Triperpenes” with Professor Guy OURISSON, University of Strasbourg;

Doctorat-ès-Sciences (Ph.D.), University of Strasbourg, **1963**; Post-Doctoral Research Fellow at Harvard University, **1964**: work on Vitamin B12 total synthesis with Professor Robert B. WOODWARD.

APPOINTMENTS

Member of the Centre National de la Recherche Scientifique (CNRS), **1960–1966**.
Maître de Conférences (Assistant Professor) at the University of Strasbourg, **1966–1969**.

Professeur sans chaire (Associate Professor) at the University Louis Pasteur of Strasbourg, **1970**.

Professor of Chemistry at the University Louis Pasteur of Strasbourg, **1970–1979**.

Professor at Collège de France, Paris, Chair of Chimie des Interactions Moléculaires **1979–2010**.

Visiting Professor of Chemistry at Harvard University, **1972 (Spring)**, **1974 (Spring)**, and on a part time basis **until 1980**.

Visiting Professor of Chemistry at the E.T.H. Zürich, **1977**.

Alexander Todd Visiting Professor of Chemistry, Cambridge University, **1984**.

Visiting Professor, University of Barcelona, **1985**.

Rolf-Sammet Gastprofessor, Frankfurt University, **1985–1986**.

Heinrich-Hertz Gastprofessor, Karlsruhe University, **Nov., Déc. 1989**.

Robert Burns Woodward Visiting Professor, Harvard University, **1997, 2000**.

Newton Abraham Professor, Lincoln College, Oxford University, **1999–2000**.

Adjunct Professor at the Asian Institute of Technology, Bangkok, **2005**.

Chair Professor-at-Large, City University of Hong Kong, **2008–2012**.

Honorary Director and Professor at Large, Lehn Institute for Functional Materials, Sun Yat Sen University, Guangzhou, **2010**.

Emeritus Professor, Université de Strasbourg, **2010–**

Professor, University of Strasbourg Institute of Advanced Study USIAS, Chair of Chemistry of Complex Systems, **2012–**

Visiting Distinguished Professor, City University of Hong Kong, **2013–2014**.

Visiting Chair Professor-at-Large, Macau University of Science and Technology, **2014**.

Honorary Degrees

Honoris Causa Doctorates: Hebrew University of Jerusalem, **1984**; Universidad Autonoma, Madrid, **1985**; Georg-August University of Göttingen, **1987**; Université Libre de Bruxelles, **1987**; Iraklion University, **1989**; Università degli Studi di Bologna, **1989**; Charles University of Prague, **1990**; University of Sheffield, **1991**; University of Twente, **1991**; University of Athens **1992**; Polytechnical University of Athens, **1992**; Polytechnic University of Bucarest,

1994; Illinois Wesleyan University, 1995; Université de Montréal, 1995; University of Bielefeld, 1998; Weizmann Institute of Science, Rehovot, 1998, Faculté des Sciences Appliquées, Université Libre de Bruxelles, 1999; Nagoya University, 2000; Université de Sherbrooke, 2000; Università di Trieste, 2001; Royal Institute of Technology, Stockholm, 2003; University of St. Andrews, 2004; Heriot Watt University, Edinburgh, 2005; Technical University, St Petersburg, 2005; Mazaryk University, Brno, 2005; Kyushu University, 2005; M.V. Lomonosov Moscow State University, 2006; Aristotle University of Thessaloniki, 2006; Kazan State University, 2006; Novosibirsk State University, 2006; University of Patras, 2008; Babeş-Bolyai University Cluj-Napoca, 2008; Università della Basilicata, Potenza, 2008; Taras Shevchenko University, Kiev, 2009; Technion, Israel, 2009; University of Ljubljana 2009; City University Hong Kong, 2010; Queen's University, Belfast, 2012; Lviv Polytechnic National University, 2012; University of Oxford (Dr. Sci.), 2014, Macau University of Science and Technology (MUST), 2015; University of Malaga, 2015; Institute of Chemical Technology, Mumbai, 2017; New York University, 2017; University of Cambridge, 2017.

Honorary Professorships: University of Science and Technology of China, Hefei, 1998; Honorary Professor, Southeast University, Nanjing, 1998; Peking University, 2001; Honorary Professor, Shanghai Jiao Tong University, 2003; Honorary Professor, Nanjing University, 2003; Beijing University, 2005; Zhejiang University, Hangzhou, 2007; Honorary Professor, Shaanxi Normal University, Xi'an, 2007; Special Honorary Professorship, Osaka Prefecture University, Sakai, 2008; Novosibirsk State University, 2012; Xiamen University, 2012; Jilin University, 2013; Shanxi University, 2013; Kyushu University, 2016; China Pharmaceutical University, 2016; Wuhan University of Technology, 2016.

Awards

Bronze Medal of the CNRS, 1963; Adrian Prize of the Société Chimique de France, 1968; Silver Medal of the CNRS, 1972; Raymond Berr Prize of the Société Chimique de France, 1978; Gold Medal of the Académie Pontificale des Sciences, 1981; Gold Medal of the CNRS, 1981; Pierre Bruylants Medal, Louvain, 1981; Paracelsus Prize of the Swiss Chemical Society, 1982; Alexander von Humboldt Forschungspreis, 1982; Prize of the Commissariat à l'Énergie Atomique awarded by the Académie des Sciences, 1984; Rolf-Sammet Prize, Frankfurt University, 1985; Prize of the Fondation Alsace, 1986; George Kenner Prize, University of Liverpool, 1987; **Nobel Prize in Chemistry**, 1987; Sigillum Magnum, University of Bologna, 1988; Minnie Rosen Award, 1989; Vermeil Medal of the Ville de Paris, 1989; Gold Medal of

the Société d'Encouragement au Progrès, **1989**; Karl-Ziegler Prize, Gesellschaft Deutscher Chemiker, **1989**; Grand Bretzel d'Or, Institut des Arts et Traditions Populaires d'Alsace, **1992**; Bonner Chemiepreis, **1993**; "Ettore Majorana-Erice-Science for Peace" Prize, **1994**; Gold Medal of the Société Académique Arts-Sciences-Lettres, **1995**; Gold Medal of Comenius University, Bratislava, **1995**; Golden Memorial Medal of the Faculty of Sciences, Charles University, Prague, **1995**; Honorary Medal of the Institute of Physical Chemistry, Polish Academy of Sciences, Warszawa, **1996**; The Davy Medal of the Royal Society, **1997**; Lavoisier Medal **1997** of the Société Française de Chimie; Top 75 Award, C&N, American Chemical Society, **1998**; Allan R. Day Award of the Philadelphia Organic Chemists' Club, **1998**; Messel Medal, Society of Chemical Industry, London, **1998**; Gold Medal "Giulio Natta" of the Italian Chemical Society, **2003**; JSPS Award (Japan Society for the Promotion of Science), **2003**; Gold Medal of the 70th Anniversary of the Fondation de la Maison de la Chimie, **2004**; Gold Medal of the University Paul Sabatier Toulouse III, **2005**; Gold Medal, Scientific Partnership Foundation, Moscow, **2006**; Johannes Gutenberg Award, Mainz, **2006**; Burckhardt-Helferich Award, Leipzig, **2007**; Distinguished Schulich Lectureship Award Colloquium, Technion, Haifa, **2008**; Costin Nenitzescu Medal, **2008**; Medal of the Czech Chemical Society, **2008**; Sigilli d'Oro, Università degli Studi di Bari, **2008**; Sigillum for the Avogadro Lecture, Società Chimica Italiana, University of Salento, **2011**; Chandler Medal, Columbia University, **2011**; MacDiarmid Medal, University of Pennsylvania, **2011**; ERC Advanced Grant, **2011**; Sir Derek Barton Gold Medal, Royal Society of Chemistry, **2012**; Eucor Medal, **2013**; Distinguished Senior Member of the Société Chimique de France, **2013**; Chem Pub Soc Europe Honorary Fellow, **2015**; Gold Medal of the Slovak Chemical Society, Bratislava, **2015**; Dionyz Ilkovic SAS Medal of Honour of the Slovak Academy of Sciences, Bratislava, **2015**; Medal of Merit of the University Adam Mickiewicz, Poznan, **2015**; China Friendship Award, **2015**; Distinguished KIT-Professor, **2016**.

Academies

Foreign Associate of the National Academy of Sciences of the USA, **1980**.
 Foreign Honorary Member of the American Academy of Arts and Sciences, **1980**.
 Foreign Member of the Royal Netherlands Academy of Arts and Sciences, **1983**.
 Member of the Académie des Sciences, Institut de France, **1985**.
 Foreign Member of the Deutsche Akademie der Naturforscher Leopoldina, **1985**.
 Foreign Member of the Accademia Nazionale dei Lincei, **1985**.
 Foreign Member of the American Philosophical Society, **1987**.
 Honorary Member of the Académie Européenne des Sciences, des Arts et des Lettres, **1987**.

Honorary Member of the Royal Society of Chemistry (Belgium), **1987**.
 Member of the Academia Europaea, **1988**.
 Member of the Académie d'Alsace, **1989**.
 Foreign Associate of the Akademie der Wissenschaften und der Literatur-Mainz, **1989**.
 Honorary Member of the Yugoslav Academy of Sciences and Arts, **1990**.
 Member of the Akademie der Wissenschaften of Göttingen, **1990**.
 Associate Member of the Koninklijke Vlaamse Academie van België voor Wetenschappen en Kunsten, **1990**.
 Honorary Fellow of the Indian Academy of Sciences, **1991**.
 Foreign Member of the Polish Academy of Sciences, **1991**.
 Foreign Associate of the Academy of Arts and Sciences of Puerto Rico, **1991**.
 Foreign Member of the Ukrainian Academy of Sciences, **1992**.
 Honorary Member, Institut Grand Ducal, Luxembourg, **1992**.
 Foreign Member of the Royal Society, **1993**.
 Honorary Member of the Romanian Academy, **1993**.
 Honorary Foreign Member of the Korean Academy of Science and Technology (KAST), **1995**.
 Member of the Pontifical Academy of Sciences, **1996**.
 Foreign Member of the Third World Academy of Sciences, **1996**.
 Honorary Member of the Czech Learned Society, **1997**.
 Foreign Member of the Academy of Sciences of Turin, **1999**.
 Honorary Member of the Royal Irish Academy, Section Science, **1999**.
 Foreign Member of the Russian Academy of Sciences, **1999**.
 Member of the Académie des Technologies, Institut de France, **2001**.
 Honorary Member of the Hungarian Academy of Sciences, **2001**.
 Member of the International Academy of Humanism, **2001**.
 Corresponding Member of the Slovenian Academy of Sciences and Arts, **2003**.
 Foreign Member of the Chinese Academy of Sciences, **2004**.
 Honorary Member of the Académie des Sciences Inscriptions et Belles Lettres de Toulouse, **2005**.
 Honorary Member of the Real Academia Sevillana de Ciencias, **2005**.
 Associate Member of the Académie Royale des Sciences, des lettres et des beaux-arts de Belgique, **2009**.
 Charter Fellow, National Academy of Inventors, **2012**.
 The Academy of Sciences of Hong Kong, **2015**.
 Foreign Corresponding Member, Real Academia de Ciencias de Espana, **2017**.

Honorary member of Learned Societies

Honorary Member of the Union des Physiciens, **1986**.

Honorary Fellow of the Royal Society of Chemistry (Great-Britain), **1987**.
 Honorary Fellow of Fondation de la Maison de la Chimie, **1989**.
 Honorary Member of the Gesellschaft Deutscher Chemiker, **1997**.
 Honorary Fellow of the Institute of Physics, **1999**.
 Honorary Fellow of the Singapore Institute of Chemistry, **2001**.
 Honorary Member of the Chemical Society of Japan (CSJ), **2002**.
 Honorary Fellow of the Chemical Research Society of India, **2002**.
 Honorary Member of the World Innovation Foundation, **2003**.
 AAAS Fellow, American Association for the Advancement of Science, **2003**.
 Honorary Fellowship of IChem^E Institution of Chemical Engineers, **2003**.
 President of the Academia Bibliotheca Alexandrinae, **2004**.
 Member of the Gesellschaft Österreichischer Chemiker, **2004**.
 Honorary Member of the Société Française de Chimie, **2005**.
 Honorary Membership of the Chemistry Society of Romania, **2008**.
 Honorary Member of the Société Philomathique de Paris, **2013**.

Decorations

Chevalier dans l'Ordre National du Mérite, **1976**; Chevalier dans l'ordre de la Légion d'Honneur, **1983**; Officier dans l'ordre de la Légion d'Honneur, **1988**; Chevalier dans l'Ordre des Palmes Académiques, **1989**; Member of the Order "Pour le Mérite" für Wissenschaften und Künste (RFA), **1990**; Officier dans l'Ordre National du Mérite, **1993**; Commandeur dans l'Ordre de la Légion d'Honneur, **1996**; Österreichisches Ehrenkreuz für Wissenschaft und Kunst, Erste Klasse, **2001**; High Officer in the Order of Cultural Merit in Romania, section Scientific Research, **2004**; Grosses Verdienstkreuz mit Stern der Bundesrepublik Deutschland, **2009**; Grand Officier de la Légion d'Honneur, **2014**; Officer of the Order of Merit of the Republic of Poland, **2015**.

Scientific Work

985 publications; 3 books

- 1) "*Chemia Supramolekularna*",
 Collection of publications by J.-M. LEHN, organised and translated into Polish under the direction of Janusz Lipkowski, Institute of Physical Chemistry, Polish Academy of Sciences, **1985**.
- 2) B. DIETRICH, P. VIOUT, J.-M. LEHN,
 "*Aspects de la chimie des composés macrocycliques*",
 InterEditions/Editions du CNRS, **1991**.
 – English Version: "*Macrocyclic Chemistry – Aspects of Organic and Inorganic Supramolecular Chemistry*", VCH, Weinheim, **1993**.

3) J.-M. LEHN,

“Supramolecular Chemistry – Concepts and Perspectives”,

VCH, **1995**.

– French Version : *“La chimie supramoléculaire : Concepts et perspectives”,*

Translated from the English original text by A. Pousse,

De Boeck Université, Bruxelles, **1997**.

– Portuguese Version, translated by M.J. Calhorda, R. Delgado, A.M. Martins, V. Gageiro Machado, N. Miranda, **2007**.

– Japanese Version, translated by Y. Takeuchi, Kagaku Dojin, Tokyo, **1997**.

– Russian Version, translated by E.V. Boldyreva; coeditors, V.V. Vlassov and A.A. Varnek; Nauka, Novosibirsk, **1998**.

– Chinese Version, translated by X. Shen, Peking University, Beijing, **2002**.

RELATIONSHIPS AND ACTIVITIES WITH THE PRIVATE SECTOR

MAJOR ACTIVITIES:

Member of the Board of Directors of:

- Ciba-Geigy (Verwaltungsrat) until the merger with Sandoz to form Novartis. Thereafter,
- Ciba Specialty Chemicals, until the merger with BASF in **2009**.
- Hoechst AG (Aufsichtsrat) until the merger with Rhône-Poulenc to form Aventis.
- Bruker France (Conseil de Surveillance, until **2010**).

Science Advisor/Advisory Boards:

- Rhône-Poulenc
- Aventis (until merger with Sanofi).
- Reliance Innovation Council, Mumbai.
- Sanofi-Aventis (**2010–2011**).
- Novartis Venture Fund.
- and numerous small(er) companies

Co-founder of:

- Therascope (sold).
- Normoxys
- AC Immune
- InCellArt

FIELDS OF RESEARCH OVER THE YEARS

Theoretical Organic Chemistry: Ab initio conformational analysis:

computation of nitrogen and phosphine inversion, of the electronic structure of hydrocarbons, of stereoelectronic effects on chemical reactivity; theoretical

studies of molecular receptors and recognition processes.

Dynamic Nuclear Magnetic Resonance: Studies of conformational rate processes, internal rotation and nitrogen inversion.

Molecular Dynamics and Liquid Structure from Nuclear Magnetic Relaxation data. Nuclear Quadrupole Resonance.

SUPRAMOLECULAR CHEMISTRY:

Cryptates: Design, synthesis and properties of ligands forming stable and selective inclusion complexes with metal ions; **di-** and **poly-**nuclear cryptates; bioinorganic models; **photoactive** and **electroactive** cryptates; cluster cryptates; energy and electron transfer processes.

Molecular Recognition, Molecular Receptors and Coreceptors: Design, synthesis and properties of macropolycyclic complexing agents binding selectively one or several molecular substrates: **metalloreceptors**; **photoactive** receptors; **cyclointercalands**.

Anion Coordination Chemistry: Anion cryptates; receptors and coreceptors for anionic substrates; selective complexation of organic, inorganic and biological anions.

Supramolecular Catalysis: Design and properties of molecular catalysts performing a reaction on bound substrate species; enzyme models; **cocatalysis**.

Transport Processes: Design of selective carriers; transport of anions, cations and molecules; thermodynamic and kinetic properties; transport **regulation**; **coupling** to chemical potentials (protons, electrons) and to light.

Supramolecular Materials: Recognition materials, supramolecular polymers, liquid crystals, vesicles, inorganic materials.

Chemionics: Molecular Photonic, Electronic and Ionic Devices: Photoactive and electroactive cryptates; energy and electron transfer processes; light conversion; photo-antenna; ion transfer; molecular and ionic switching and amplifying processes; molecular protonics.

Semiochemistry: Generation and processing of optical, electronic and ionic chemical signals; ion detection; ion pulses; non-linear optical properties.

Photochemistry and Solar Energy Storage: Photochemical activation of small molecules by means of transition metal complexes; photogeneration of hydrogen and oxygen; **water photolysis**; photoreduction of CO₂; design of photoinduced **charge separation** systems.

Structural and Dynamic Studies by Multinuclear NMR on supramolecular complexes (in collaboration with the NMR Laboratory).

Bioorganic Chemistry and Biological Applications: Models of biological receptors, of enzymes and of biological transport processes; immunological labelling agents, selective nucleic acid reagents, helical and metallo-nucleic

complexes; artificial gene transfer vectors.

Allosteric Effectors of Hemoglobin: Oxygen fixation to haemoglobin; modified red blood cells; biological effects (cardiovascular, oncological).

SELF-ASSEMBLY AND SELF-ORGANIZATION

Programmed Chemical Systems: Design of systems generating given supramolecular architectures by molecular recognition directed spontaneous assembly of the components; self-organization by design and with selection; hydrogen bonding and coordination interactions; multiple expression of molecular information.

Self-Organization of Organic Architectures: Generation of hydrogen bonding entities; hydrogen bonding patterns; polymolecular assemblies, recognition vesicles, recosomes; structural codons and molecular motions.

Self-Organization of Inorganic Architectures: Double and multiple helicates; grid-type architectures; multicomponent self-assembly; nanocylinders; physicochemical properties of multinuclear arrays.

CONSTITUTIONAL DYNAMIC CHEMISTRY – ADAPTIVE CHEMISTRY

Dynamic Covalent Chemistry: Dynamic combinatorial libraries; constitutional dynamic processes; reversible chemical reactions, implementation, efficiency and selectivity; multiple dynamic processes.

Biological Systems: generation and identification of substrates for receptors and enzyme inhibitors; dynamic deconvolution.

Dynamic Materials: Dynamers, dynamic polymers; modulation of properties by component recombination (optical, mechanical, hydrophobic features); biodynamers (glycodynamers, dynamic nucleic acid analogs); controlled release materials.

Adaptation and Selection: Component selection in equilibrium systems; effect of physical and chemical triggers (temperature, electric field, protons, ions, medium, etc.); constituent adaptation in switching processes; adaptation in self-organization; coupling to non-equilibrium processes.

Dynamic Networks: agonistic and antagonistic relationships in constitutional dynamic libraries; responsive systems; agonist amplification.

Self-Organization and Chemical Synthesis

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1. Introduction

An earlier text^[1] elaborated on the theme “Supramolecular Chemistry and Chemical Synthesis – From Molecular Interactions to Self-Assembly”. It is here reworked and complemented by extension to aspects resulting from more recent developments, in particular of dynamic covalent chemistry and its relationships with organic synthesis. In view of the very wide range of topics and the great many studies performed on a wide range of topics, literature citation will be limited to a selection of mainly general presentations (books, reviews) that provide references to the primary literature.

Chemistry has developed a highly powerful *molecular synthetic chemistry*, mastering the combination and recombination of atoms into increasingly complex molecules by means of efficient and selective chemical reactions. The total synthesis of natural products has been the hallmark of the art and science of molecular chemistry and the touchstone on which advances in the discovery and implementation of novel chemical reactions can be evaluated and tested. Highly powerful methodologies have been developed over the years and have been employed for the stepwise build-up of structurally and functionally complex target molecules following efficient and elegant strategies with exquisite control over each step.^[2] Molecular synthesis is achieved at the hand of the chemists, it is a man-made process of progressive edification of a molecular architecture, at times painstaking, at times with brilliant inspiration.

Beyond molecular chemistry, supramolecular chemistry^[3] is harnessing intermolecular forces and processes for the generation of supramolecular entities towards a *supramolecular synthetic chemistry* implementing molecular information carried by electromagnetic interactions acting between complementary molecular components.

There is then the next step where, beyond the edification of immutable (static!) monuments, molecular chemistry acquires the dynamic features intrinsic to supramolecular chemistry, leading from the latter, dynamic non-covalent chemistry

(DNCC), to an intentionally enforced dynamic covalent chemistry (DCC) which extends the supramolecular type of synthetic operations to molecular/covalent chemistry. Molecular synthesis becomes dynamic by virtue of reversible covalent bond formation, generating collections of interconverting molecules, rather than static ones. Taken together, DCC and DNCC may be placed under the common roof of a *constitutional dynamic chemistry* concerning both molecular and supramolecular chemical entities, on the way towards *adaptive chemistry* (see below).

The master word becomes *self-organization*, the process that drives the formation, the synthesis, of complex matter in our universe, from primordial nucleosynthesis to living and thinking matter.^[4,5] At the hands and mind of the chemist, it involves the generation of organized chemical entities from designed molecular building blocks by controlled self-assembly, amounting to a sort of *self-synthesis*^[6] and, in the present context, beyond the molecule, the ultimate synthesis! Molecular synthesis builds the basis on which self-organization can flourish.

2. Supramolecular Chemistry and Chemical Synthesis

The contribution of supramolecular chemistry to chemical synthesis has two main aspects: on one hand the generation of non-covalent supramolecular entities themselves and on the other hand, the exploitation of supramolecular processes for enabling the synthesis of covalent molecular structures. Supramolecular chemistry, of course, requires and depends on molecular synthesis for the construction of the covalent entities on which it is built. Controlling the outcome (although not necessarily the intervening steps) of the synthetic assembly process requires the design of the building blocks carrying the relevant molecular information, so as to already draw the assembly plan based on the interaction patterns that define a self-assembling supramolecular algorithm.^[3a,7]

2.1. Supramolecular synthesis

There is an important twist in chemical synthesis concerning supramolecular synthesis. First, the connections between the building blocks, the molecular components of a supramolecular entity, are ensured by physical interactions, not by bond formation through chemical reactions, and second, the synthetic process rests on molecular recognition between complementary interactive patterns, not functional recognition between complementary reactive groups. Supramolecular synthesis consists in the designed association of molecular components directed by the physico-chemical features of intermolecular forces to generate specific supramolecular architectures; like molecular synthesis, it requires strategy, planning and control. The conception of the components must, at the outset, already *incorporate the supramolecular project*.

Supramolecular synthesis may therefore be considered to involve two steps: – the

design and synthesis of the instructed molecular components based on covalent bonds; – the generation of the supramolecular entities by designed association of the molecular components in a pre-determined arrangement by means of comparatively weak and kinetically labile interactions following the built-in intermolecular plan; – the latter may, in addition, follow a given sequence and hierarchy of operations.

Supramolecular synthesis thus requires expertise at *both* the intramolecular and the intermolecular levels. The synthesis of a supramolecular architecture requires similar efforts on the intermolecular scene as molecular synthesis on the intramolecular one. In the realm of synthetic chemistry, supramolecular chemistry must claim and engage in the same pursuit of design and control as molecular chemistry, and requires, in addition, the correct storage of an intramolecular program into a covalent framework.

In the last fifty years, chemistry has entered the confines of the supramolecular world. Great feats in synthetic power for the elaboration of ever more complex architectures have been achieved and even more lie ahead, in the same manner as there has been a rich and exciting but long road of tribulations from the synthesis of urea in 1828 to that of highly complex molecular structures (see above and for instance ref. 2).

The *synthesis of materials* must be mentioned although it cannot be developed here. Materials are polymolecular assemblies of either covalent constituents or of non-covalent ones. However, all materials necessarily involve a supramolecular contribution as their properties result from both the structural features of the constituents themselves and from their interactions as they associate into a material. Such is the case for instance for soft materials based on either covalent polymers or on supramolecular polymers.^[8,9] The latter are in fact doubly supramolecular, as both the constituents themselves and their assembly in a material are of supramolecular nature.

2.2. Supramolecular assistance to Synthesis

Supramolecular association may be implemented for positioning components as an aid towards the synthesis of complex covalent species by *post-assembly modification*. Reactions deliberately performed on the pre-organized species or occurring spontaneously within them, lead to the generation of the desired molecular architecture. Dismantling of the intermolecular connection(s) may follow, thus liberating the covalently connected structure. This strategy amounts to *supramolecular assistance to synthesis* that may specifically become *self-replication* if spontaneous reproduction of one of the initial species takes place. Intermolecular interactions and metal coordination have been used very effectively for the synthesis of novel organic and inorganic entities that would

otherwise be of very difficult access.

Inorganic templating provides coordination compounds whose geometries make possible the synthesis of a great variety of complex molecular architectures by post-assembly modification.

Organic templating may similarly be implemented to position partners for subsequent reaction, amounting to a template-assisted organic synthesis.

Such methodologies have enabled in particular the development of a *topological chemistry* and have been instrumental in the synthesis of highly complex mechanically interlocked entities and knotted structures which involve the preformation, by self-assembly, of a threaded supramolecular species.^[10] Supramolecular assistance adds a new direction with powerful means to organic synthesis.

2.3. Replication – Self-replication

Self-assembled template-directed systems containing reactive groups provide pathways towards systems displaying copying, information transfer and replication. Replicating molecules are of interest both chemically and biologically in view of their relation to the origin of life.

Self-replication is a sort of synthesis of the self. It takes place when a molecule catalyses its own formation by acting as a template for the constituents whose reaction generates a copy of the template. A problem is the occurrence of product inhibition, when the product of the first condensation round, is too stable to be easily dissociated by the incoming components for a new cycle.

The investigation of self-replicating systems is subject to increasing activity.^[11]

The information processing that operates in molecular recognition and self-assembly plays a major role, coupled to chemical reactions for connecting the building blocks.

3. Self-assembly. Self-organisation

Beyond molecular recognition, reactivity and transport processes, supramolecular chemistry has been actively exploring systems undergoing *self-organization*, i.e. systems capable of spontaneously generating organized, functional supramolecular architectures by self-assembly from their components, under the control of *molecular recognition* events based on interaction patterns forming the processing algorithms. They represent *programmed chemical systems*^[3a, 7] involving the explicit implementation of molecular information for controlling the generation of supramolecular species and devices as they emerge from the assembly of their components and operate through *self-processes*.

Self-organization (passive, thermodynamically controlled, or, active, out-of-equilibrium, dissipative) results in the build-up/synthesis of an output entity along a multicomponent synthetic pathway with more or less numerous “hidden

steps". In presence of a kinetic bottleneck, it may become possible to detect and identify these steps and the intermediates along the path(s). One may mention that transformations involving several "hidden" steps in a single "operation" of course may also occur in molecular synthesis (for instance in the two-step Robinson annulation reaction or the multistep polyene cyclization).^[12]

Numerous self-organization processes have been explored concerning both organic and inorganic entities. They participate in supramolecular synthesis approaches discussed below. Depending on the subunits involved, they may lead either to *discrete supramolecular entities* or to *organized polymolecular assemblies and materials*, such as membranes, molecular layers and films, mesophases, polymeric species or solid state lattices. Their operation follows three steps of information input: 1) molecular *recognition* for the *selective binding* of the basic components; 2) *growth* through binding of the components in the correct relative disposition; 3) *termination* of the process, in case of discrete assembled entities, requiring a built-in feature, a *stop signal*, that specifies the end point and signifies that the process has reached completion. Furthermore, multistep assembling is required for bridging dimensions from nanoscale to mesoscale, each assembly step setting the stage for the next one in a sequential and/or hierarchical fashion.^[13]

3.1. Self-organization of organic supramolecular architectures

The spontaneous but controlled generation of organized organic supramolecular species requires knowledge of the strength and of the dependence on distances and angles of interactions put to use: electrostatic, hydrogen bonding, Van der Waals, stacking or donor-acceptor types, similar to those found in proteins, nucleic acids, liquid crystals, and molecular complexes. It depends on the design of molecular components capable of self-assembling into supramolecular entities presenting the desired architectural and functional features. The nature of the species obtained will depend on the information stored in the components. If these molecular units present specific optical, electrical, magnetic, binding, etc. properties, their ordering may induce a range of novel features in a functional device fashion. For instance, variety of discrete hydrogen-bonded supramolecular assemblies have been reported.^[14]

3.2. Self-organization of inorganic, metallo-supramolecular architectures

The interaction of suitably designed organic ligand molecules with metal cations results in the spontaneous generation of well-defined metallo-supramolecular architectures. The cations serve as connectors holding the ligands together and positioning them in orientations determined by the coordination geometries. They offer powerful means for providing inorganic assistance to synthesis as

discussed above. They have properties of special interest as linkers for self-assembly as they provide a range of coordination geometries, binding strengths and formation and dissociation kinetics. In the process, full use is made of the structural and coordination features of both types of components which, in addition, convey electrochemical, photochemical or chemical functionality depending on their nature.

The generation of metallo-supramolecular structures of numerous types has been achieved, based on ligand design and on the use of suitable coordination geometries that act as the assembling algorithm (see also above). A great variety of architectures of different levels of complexity, involving in particular multiple components, have been obtained: multiply-stranded helical metal complexes (helicates),^[15a] grid-like arrangements,^[15b] nanocylinders, circular architectures, knotted structures, etc..^[10, 15c]

4. Constitutional dynamic chemistry and Chemical Synthesis: dynamic covalent and non-covalent synthesis

Supramolecular entities are by nature dynamic in their constitution as they are built on labile non-covalent interactions. They are prone to dissociate into their molecular components and to re-associate by breaking and forming non-covalent interactions, thus defining a Dynamic Non-Covalent Chemistry (DNCC) that is intrinsic to supramolecular entities. Traditionally, the objective of molecular chemistry and synthesis is to generate static “stable” molecules. However, molecules can also be made dynamic in their constitution by the intentional introduction of reversible covalent bonds formed by reversible chemical reactions. They become endowed with the ability to continuously modify their constitution by breaking apart into components and regenerating with recombination and exchange of components under thermodynamic control. Such processes define a Dynamic Covalent Chemistry (DCC).^[16]

The dynamic molecular (DCC) and supramolecular (DNCC) fields may be joined together under the general heading of *Constitutional Dynamic Chemistry* (CDC) encompassing chemical entities dynamic in their constitution, able to undergo a continuous change in constitution by reorganization and exchange of building blocks.^[17] CDC introduces a paradigm shift with respect to constitutionally static chemistry. The latter relies on design and stepwise build-up for the generation of a target entity, whereas CDC takes advantage of dynamic diversity to allow variation and selection. In line with the theme of the present opus, one may consider that DNCC, DCC and CDC represent on the synthetic scene the generation of the corresponding dynamic entities by dynamic non-covalent synthesis and dynamic covalent synthesis, with constitutional dynamic synthesis bringing both areas together.

Particularly remarkable is the spontaneous synthesis of highly intertwined architectures resulting from a combination of preorganization by metal ion coordination, of metallo-dynamics and of covalent dynamics, whereby the ligands within a metallo-supramolecular architecture are connected via reversible imine formation in a post-assembly step.^[16a, 16j] Particularly impressive examples are for instance the sumptuous synthesis of Borromean rings in a single step and in high yield from suitably designed molecular components and the appropriate metal ions^[10f, 18a,b] as well as the impressive synthesis of metallo-supramolecular knots derived from circular complexes (circular helicates),^[19] based on functionalized ligands connected through bis-imine bridges.^[18c,d,e]

4.1. Adaptive Chemistry: Towards Adaptive Synthesis ?

CDC enables the implementation of selection in chemistry introducing thus a fundamental change in outlook. Whereas *self-organization by design* strives to achieve full control over the output molecular or supramolecular entity by explicit programming, *self-organization with selection* operates on dynamic constitutional diversity in response to either internal or external factors to achieve *adaptation*, leading to the emergence of *adaptive chemistry*.^[5,17a,c] By the same token one may consider these processes to represent a *constitutional dynamic synthesis* opening towards *adaptive synthesis*, where the produced “synthetic” target entity is able to undergo modification in response to physical stimuli and/or chemical effectors, in particular to supramolecular interactions with an effector molecule. Similar considerations apply also to materials science with the advent of dynamic and adaptive materials.^[9]

Supramolecular/non-covalent and molecular/covalent self-organization may thus be considered as a sort of ultimate synthetic chemistry, whereby chemical objects at both levels build themselves up under the action of specific physical or chemical factors, such as recognition processes involving either interactional or reactional features.

Non-covalent interactional and covalent reactional recognition, dynamic and adaptive behavior and self-processes are providing a range of novel perspectives to chemical synthesis and to chemistry in general. They lead toward a science of complex matter, of informed, self-organized, evolutive matter. The goal is to progressively discover, understand, and implement the rules that govern its evolution from inanimate to animate and beyond, to ultimately acquire the ability to create new forms of complex matter. The perspectives opened up become wider and wider as progress is being made and will constitute horizons of the future for quite some time!

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*Introductory Perspective
Toward complex matter:
Supramolecular chemistry and self-organization
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As the wind of time blows into the sails of space, the unfolding of the universe nurtures the evolution of matter under the pressure of information. From divided to condensed and on to organized, living, and thinking matter, the path is toward an increase in complexity through self-organization.

Thus emerges the prime question set to science, in particular to chemistry, the science of the structure and transformation of matter: how does matter become complex? What are the steps and the processes that lead from the elementary particle to the thinking organism, the (present!) entity of highest complexity?

And there are two linked questions: an ontogenetic one, how has this happened, how has matter become complex in the history of the universe leading up to the evolution of the biological world, and an epigenetic one, what other and what higher forms of complex matter can there be to evolve, are there to be created?

Chemistry provides means to interrogate the past, explore the present, and build bridges to the future.

Molecular chemistry has created a wide range of ever more sophisticated molecules and materials and has developed a very powerful arsenal of procedures for constructing them from atoms linked by covalent bonds.

Beyond the molecule, supramolecular chemistry aims at developing highly complex chemical systems from components interacting by noncovalent intermolecular forces (1, 2). It has over the last quarter of a century grown into a major field and has fueled numerous developments at the interfaces with biology and physics, thus giving rise to the emergence and establishment of supramolecular science and technology, as a broad multidisciplinary and interdisciplinary domain providing a highly fertile ground for the creativity of scientists from all origins. The breadth and depth of its scope is evidenced and illustrated by the wide selection of many of the major players in the field gathered in the Special Feature in this issue of PNAS.

Rather than adding another facet to this already breathtaking panorama, it appeared appropriate here to emphasize perspectives and provide a vision. This essay therefore

will not be extensively documented (numerous reviews and books are available) but rather outline some conjectures for the future, mainly based on, illustrated by, and extrapolated from work performed in the author's laboratories. Looking toward the horizon of supramolecular chemistry, and more generally of supramolecular science (1, 3), special attention will be given to exposing the forest(s) rather than to describing the trees!

Supramolecular Chemistry and the Information Paradigm

One of the major lines of development of chemical science resides in the ever clearer perception, deeper analysis, and more deliberate application of the information paradigm in the elaboration and transformation of matter, thus tracing the path from merely condensed matter to more and more highly organized matter toward systems of increasing complexity. In chemistry, like in other areas, the language of information is extending that of constitution, structure, and transformation as the field develops toward more and more complex architectures and behaviors. It will profoundly influence our perception of chemistry, how we think about it, how we perform it.

Supramolecular chemistry has paved the way toward apprehending chemistry as an information science through the implementation of the concept of molecular information with the aim of gaining progressive control over the spatial (structural) and temporal (dynamic) features of matter and over its complexification through self-organization, the drive to life (4–6).

Supramolecular chemistry has developed as the chemistry of the entities generated by intermolecular noncovalent interactions (1, 2). Through the appropriate manipulation of these interactions, it became progressively the chemistry of molecular information, involving the storage of information at the molecular level, in the structural features, and its retrieval, transfer, and processing at the supramolecular level, by interactional algorithms operating through molecular recognition events based on well-defined interaction patterns (hydrogen bonding arrays, sequences of donor and acceptor groups, ion coordination sites, etc.). This venture involved the design and investigation of more or less strictly preorganized molecular receptors of numerous types, capable of binding specific substrates with high efficiency and selectivity.

Three overlapping phases may be considered in the development of supramolecular chemistry, each exploring a main theme.

The first is that of molecular recognition and its corollaries, supramolecular reactivity, catalysis, and transport; it relies on design and preorganization and implements information storage and processing.

The second concerns self-assembly and self-organization, i.e., self-processes in general; it relies on design and implements programming and programmed systems.

The third, emerging phase, introduces adaptation and evolution; it relies on self-organization through selection in addition to design, and implements chemical diversity and “informed” dynamics.

From Preorganization Toward Self-Organization and Programmed Systems: Design

Supramolecular chemistry has first relied on preorganization for the design of molecular receptors effecting molecular recognition, catalysis, and transport processes (1, 2).

Supramolecular preorganization also has provided new ways and means to chemical synthesis (1, 7–9). Supramolecular, noncovalent synthesis, i.e., the construction of the supramolecular entities themselves, rests on the making and breaking of noncovalent bonds following an Aufbau strategy incorporated into the design of the molecular components. On the other hand, supramolecular assistance to synthesis provides a powerful tool involving first the noncovalent synthesis of a supramolecular architecture, which positions the components, followed by post-assembly modification through covalent bond formation. Both areas will continue to provide in the future a range of highly sophisticated noncovalent as well as covalent entities. A particularly impressive illustration of the latter is the synthesis of interlocked compounds (see below).

Beyond preorganization lies the design of systems undergoing self-organization, i.e., systems capable of spontaneously generating well-defined, organized, and functional supramolecular architectures by self-assembly from their components, thus behaving as programmed systems (1, 10). Chemical programming requires the incorporation into molecular components of suitable instructions for generation of a well-defined supramolecular entity. The program is molecular, the information being contained in the covalent structural framework; its operation is supramolecular, making use of recognition algorithms based on specific interaction patterns. Understanding, inducing, and directing self-processes is key to unraveling the progressive emergence of complex matter. Self-organization is the driving force that led up to the evolution of the biological world from inanimate matter (4–6).

Whereas self-assembly may be taken as simple collection and aggregation of components into a confined entity, we shall here consider self-organization as the spontaneous but information-directed generation of organized functional structures in equilibrium conditions. A relevant biological example is for instance the formation of a virus particle from its components, genomic nucleic acid and coat proteins. The inclusion of dissipative, non-equilibrium processes, as present in the living world, constitutes a major goal and challenge for the future (4–6).

Abbreviations: CDC, constitutional dynamic chemistry; DCC, dynamic combinatorial chemistry.

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A self-organization process may be considered to involve three main stages: (i) molecular recognition for the selective binding of the basic components; (ii) growth through sequential and eventually hierarchical binding of multiple components in the correct relative disposition; it may present cooperativity and nonlinear behavior; and (iii) termination of the process, requiring a built-in feature, a stop signal, that specifies the end point and signifies that the process has reached completion.

Suitable encoding by manipulation of structural subunits and processing through interactional algorithms should give access to a variety of systems. More or less strict programming of the output species may be achieved depending on the robustness of a given directing code (for instance, of hydrogen bonding or metal coordination nature), i.e., on the extent to which it is sensitive to perturbations. In a robust system the instructions are strong enough for ensuring the stability of the process, i.e., the self-organization is resistant, stable toward interfering interactions (such as secondary metal coordination, van der Waals stacking, etc.) or toward modifications of parameters (such as concentrations and stoichiometries of the components, presence of foreign species, etc.). When the assembly occurs only in a narrow range of conditions, the system is unstable and presents a singularity; it may also display a bifurcation or a switching point between different assemblies. On the other hand, sensitivity to perturbations, while limiting the operation range, introduces diversity and adaptability (3) in the self-organization process.

Self-selection with self-recognition occurs when the structural instructions are sufficiently strong, as is the case in the “correct” pairing of strands of different lengths in the assembly of helicates, inorganic double helices (11). The process bears relation to the implementation of combinatorial chemistry in its “dynamic” version (see below). It reveals a broader perspective with a paradigm shift, from “pure compounds” to “instructed mixtures”, from “unicity” to “multiplicity + information” (11). Rather than pursuing mere chemical purity of a compound or a material, one seeks to design instructed components, which, as mixtures, allow the controlled assembly of multiple well-defined supramolecular species, following specific programs and interactional algorithms. The implementation of this instructed mixture paradigm is crucial for the development of complex chemical systems, as witnessed by the build-up of organized species and the execution of highly integrated functions that take place side-by-side in the assembly and operation of the machinery of the living cell.

Intense activity has been devoted to the explicit application of molecular recognition to control the formation, from their components, of organized supramolecular entities presenting specific physical and chemical properties. Three main types of investigations have been pursued, based on the use of hydrogen bonding, donor acceptor, and metal coordination interactions for controlling the processes and holding the entities together (12–18). The latter have been instrumental in the initial introduction of the notions of self-assembly into supramolecular chemistry (1, 10).

The clever exploitation of templating and self-organization has given access to a range of molecular and supramolecular entities of truly impressive structural complexity, which otherwise would have been considered impossible to construct, such as interlocked entities, whose components are mechanically held together (15, 19) and multicomponent organic or inorganic architectures (1, 12–18).

Because it is a time-dependent process, self-organization also involves temporal information and may display kinetic control, generating kinetic products before reaching the thermodynamic one(s). This is the case in the initial assembly of a triple helical complex that evolves toward a circular helicate (20). Such a process may either be sequential, if the kinetic product is an intermediate located on the pathway toward the final product, or it may be bifurcated, if this is not so.

A sequential process may be either commutative, if given steps may be interchanged along the overall pathway leading to the final superstructure, or it may be noncommutative if its progressive build-up occurs through a defined sequence of molecular instructions and algorithms, where the generation of a given intermediate depends on the previous one and sets the stage for the next one. For example, discotic liquid crystals form by the assembly of “sector”-shaped components into disks, which thereafter organize into columns (21), and template binding by molecular strands induces wrapping into helical disk-like objects, which then aggregate into large supramolecular assemblies (22).

The generation of supramolecular architectures and materials through a non-commutative sequence of steps amounts to multilevel hierarchical self-organization, along primary, secondary, tertiary, etc. structures. Such conditional processes enable the progressive build-up of more and more complex systems in a directed, temporally ordered fashion; they also offer the intriguing possibility to intervene at each step so as either to suppress the following ones or to reorient the subsequent evolution of the system into another direction, toward another output entity.

Multiple Self-Organization Through Multiple Processing/Expression of Molecular Information

The generation of a given superstructure through self-organization results, in its simplest form, from the operation of a single-code assembly program. A step beyond consists in devising systems of higher complexity that operate in multimode fashion through the implementation of several codes within the same overall program, resulting in multiple self-organization processes (3, 23).

Such behavior may take place in the generation of different metallo-architectures from the same ligand when using different sets of metal ions/coordination algorithms for reading the binding information, as in the generation of two different helicates from the same strand (3, 24) and in the assembly of ligands containing two different subunits coding, respectively, for the formation of a helicate and a [2 X 2] grid-type

complex (25). Similarly, the differential expression of hydrogen bonding information contained in a molecular strand may yield different supramolecular structures depending on the processing mode (angular or linear) defined by the recognition algorithm of the bound effector (22). These considerations lead to conjectures that may have far-reaching implications and open novel perspectives within the general framework of self-organizing, programmed chemical systems (23).

The processing of the same ligand information by different interaction algorithms (e.g., through the use of different sets of metal ions or of different H-bonding effectors) allows the controlled self-organization of different output architectures, resulting in multiple expression of molecular information, through postinformational (postgenomic!) operations. Such a one code/several outputs scheme, in addition to the one code/one output (product) mode, also has in principle significant implications in biology.

Multisubroutine self-assembly may display three types of behavior: (i) it may behave as a linear combination of the subprograms, each running independently to generate its own encoded output; self-recognition (11) is a related process; (ii) it may present crossover, when the subprograms operate in a combined fashion; or (iii) it may also be of dominant/recessive type, one of the subprograms imposing its own output over the other one(s) (26).

Multiple processing capacity represents a further step in the design of programmed chemical systems of increasing complexity capable of producing a variety of more and more complex architectures as outputs.

Parallel processing, extending eventually to massively parallel systems, would involve the simultaneous operation of multiple self-organization processes toward the generation of a single functional entity or several different ones. The side-by-side formation of different helicates (11) or helicates and inorganic grids (D. Funeriu and J.-M.L., unpublished work) in a mixture of the corresponding ligands and suitable metal ions may be seen as prototypes on a simple level.

Multiple processing of a single set of instructions allows the generation of diversity, because multiple outputs may either coexist, or be potentially accessible (virtual diversity) (27). It thus meets dynamic combinatorial chemistry (DCC) (see below).

Conversely, such chemical systems also open perspectives for information science, inasmuch as they raise the question of going beyond the usual one-to-one correspondence, established by a given program, between the input information and a single output, toward multiple outputs generated by different modes of processing the same information.

The combination of different recognition/instruction features in a molecular program opens a door to the design of self-organizing systems capable of performing molecular computation. Computing by self-assembly may yield a powerful alternative to conventional models (28, 29). Recent studies described the use of

biomolecules and DNA-based protocols to solve computational problems (30–32). An approach making use of specifically designed non-natural components could provide higher diversity, better resistance to fatigue, and more compact/smaller size. Such potential is latent in the coordination-controlled assembly of double helicates (3, 24) and metallocsupramolecular architectures (25), as well as in the differential folding processes induced by effector H-bonding (22). Numerous types of interactions and recognition units, be they of inorganic or organic nature, are available for exploring these avenues.

The combination of multiple expression with reversible diversity generation suggests the notion of dynamic computing through dynamic information generation and processing, defining adaptive/evolutionary programmed systems. Evolutionary computation may be envisaged with biomolecules (28, 32, 33), but entirely synthetic molecular systems or mixed abio/ bio ones should in the future be amenable to similar feats, with probably advantages in design, control, and diversity.

Dynamic Chemistry and Constitutional Diversity: Selection

Supramolecular chemistry is by nature a dynamic chemistry in view of the lability of the interactions connecting the molecular components of a supramolecular entity. The reversibility of the associations allows a continuous change in constitution, which may be either internal, by rearrangement of the components with modification of the connectivity between them, or external, by exchange, incorporation, or extrusion of components, therefore conferring constitutional plasticity to the system. Thus, supramolecular chemistry is a constitutional dynamic chemistry (CDC).

Dynamic chemistry also can be just morphological, involving reversible changes in shape through molecular or supramolecular conformational or configurational modifications, without change in (internal or external) constitution and resulting in motional processes.

CDC may be molecular as well as supramolecular when the components of the molecular entity are linked by covalent bonds that may form and break reversibly. This ability to undergo continuous and reversible change by reorganization, deconstruction, and reconstruction (alike or different) generates constitutional dynamic diversity. It allows us to perform selection of a given constituent, made up of a well-defined set of components in the pool of compounds having all possible constitutions, under the pressure of either internal [intrinsic stability of the species, as in helicate self-recognition (11)] or external [interaction with species in the environment, as in anion binding by circular helicates (34, 35)] factors.

CDC constitutes thus a general area of which one specific expression, when under combinatorial conditions, is DCC that has actively developed in recent years (27, 36, 37). It relies on the dynamic generation of molecular and supramolecular diversity through the reversible combination of covalently or noncovalently linked building

blocks (components). Whereas combinatorial chemistry itself is based on extensive libraries of prefabricated molecules, DCC implements the reversible connection of pools of basic components to give access to virtual combinatorial libraries (VCLs) whose constituents comprise the full set of all possible combinations that may potentially be generated in dynamic equilibrium. The constituents actually expressed among all those accessibles are expected to be those presenting the strongest interaction with a given target, i.e., the fittest. DCC bypasses the need to actually synthesize the library constituents and lets the target select the optimal partner by inducing its preferential assembly from its components, eventually with a facilitation of the connecting reaction. It is thus a target/function-driven self-organization, i.e., a self-design process (see below). The basic features of the DCC/VCL approach have been presented together with its implementation in different fields and the perspectives it offers in a variety of areas of science and technology, such as the discovery of biologically active substances, new materials, and catalysts, etc. (27). CDC introduces a profound change in paradigm and opens a range of novel perspectives with respect to constitutionally static chemistry (see also refs. 38 and 39). Whereas the latter relies on design for the generation of a target molecule or supermolecule, CDC takes advantage of dynamic diversity to allow variation and implements selection to achieve adaptation in a darwinistic fashion.

Self-Organization by Design and Selection: Self-Design

Whereas preorganization relies entirely on design, supramolecular self-organization introduces in addition the possibility to let the system build up by selection.

Self-organization by design has been pursued with the goal to achieve full control over the output supramolecular entity by means of correctly instructed components, specific interaction algorithms, and (as much as possible) strict programming. Design is knowledge-based and has an explicit information content.

Self-organization by selection requires dynamic diversity (constitutional and/or morphological) on which to operate. This is made possible by the implementation of CDC responding to the pressure of either internal or external factors. Selection has an implicit information content. It is also truly a supramolecular process, because it occurs in relation to interactions with surroundings (which may be either the medium or a more or less distant part of a folded macromolecule).

The introduction of the selection paradigm into (supramolecular) chemistry brings about a fundamental change in ways, means, and outlook. Of course, the question is not to replace the deliberately planned linear process of design by a multipronged trial-and-error process of selection. Design and selection are not mutually exclusive but are complementary for reaching systems of higher complexity through self-organization. The ultimate goal is to merge design and selection in self-organization to perform self-design, where function-driven selection among suitably instructed

dynamic species generates the optimal organized and functional entity. In fact, self-recognition in helicate self-assembly from mixtures of ligand strands (11), the selection of monomers in the synthesis of molecular helices under the pressure of folding (40) as well as the formation of dynamic helical polymers (J.-L. Schmitt and J.-M.L., unpublished work) may be perceived as such internally driven systems. Altogether, harnessing the power of selection for adaptation and evolution on the molecular scene is ushering in a darwinistic era into chemistry, where the fittest species survive.

Self-Organization of Functional Supramolecular Systems

The self-organization of functional supramolecular entities concerns either discrete species or, on the other hand, extended assemblies in one (e.g., polymolecular chains, fibers), two (e.g., layers, membranes), and three (e.g., solids) dimensions.

Functional supramolecular devices are based on the structural organization and functional integration of active components operating with photons, electrons, and ions or presenting chemical reactivity.

Photoactive and electroactive devices performing energy or electron exchange/transfer processes form the core of molecular and supramolecular photonics and electronics (41–45). They have, for instance, led to labeling and detection procedures of interest for biological studies and medical diagnostics based on energy transfer. Redox processes have been used for developing prototypes of molecular electronic components, such as molecular wires, batteries, and rectifiers. The combined operation of photo- and electro-effects gives rise to photoinduced electron transfer and charge separation, so that a major thrust has been toward the mimicking of the first steps of photosynthesis (45). The search for artificial ion carriers and ion channels provides the basis for (supra)molecular ionics (41,42,46, 47). Controlling the transfer of photons, electrons, and ions sets the stage for semiochemistry (10), the chemistry of signal generation and processing, of interest for instance in devising sensing and logic functions (48, 49). Developments toward supramolecular technology have been actively pursued, concerning in particular sensors and other optical or electronic devices, possibly of interest for “molecular computing” (42, 50).

Mechano-devices, effecting triggered molecular motions, belong to a general area of dynamic devices. Molecular motions and changes in molecular shape may be produced through external stimuli in various systems, e.g., cis-trans isomerization in azobenzene derivatives and optical changes in photochromes are accompanied by large geometric variations. Interlocked and intertwined structures have been used for the photochemical or electrochemical induction of relative motion between the mechanically linked components. They have given access to a range of intriguing processes (e.g., shift registers, circular displacements) related in particular to the design of “molecular machines” and the induction of directional motion (51–53).

While the above devices present physical functionality, chemically reactive self-organized entities are formed when the assembling brings together components bearing reactive functional groups. Through the appropriate disposition of specific subunits in an organized pattern, they may be amenable to perform efficient and selective reactions and catalysis. Such supramolecular processes involve first a substrate recognition step followed by a chemical transformation on the bound entity (1), resulting in an activity of artificial enzyme type. When the reactions occur within the self-assembled entity, they amount to self-transformation and may in particular result in replication and self-replication processes (39, 54, 55). They may present autocatalysis, a behavior that together with the establishment of networks of reactions and coupled catalytic cycles amounts to self-organization on the chemical reactivity level, presenting features such as self-regulation, feedback, and amplification. The controlled self-organization of functional systems displaying reactivity and catalysis is crucial for the development of chemical systems of both structural and reactional complexity. It has played a key role in biological evolution (4) and presents a major challenge to chemistry.

Functional Supramolecular Materials

The properties of a material depend both on the nature of its constituents and the interactions between them. Supramolecular chemistry may thus be expected to have a strong impact on materials science by means of the explicit manipulation of the noncovalent forces that hold the constituents together. These interactions and the recognition processes that they underlie allow the design of materials and the control of their build-up from suitable units by self-organization. Thus, supramolecular chemistry opens new perspectives in materials science toward an area of supramolecular materials, “smart” materials whose features depend on molecular information. For instance, liquid-crystalline polymers of supramolecular nature have been obtained by the self-assembly of complementary subunits (56–58).

Supramolecular materials are by nature dynamic materials, materials whose constituents are linked through reversible connections and which may undergo assembly/ deassembly processes in specific conditions. Because of this intrinsic ability to exchange their constituents, they are constitutionally dynamic materials and may in principle select their constituents in response to external stimuli or environmental factors. Supramolecular materials thus are instructed, dynamic, and combinatorial and behave as adaptive materials (3).

A rich domain emerges from the combination of polymer chemistry with supramolecular chemistry defining a supramolecular polymer chemistry (56–58). It involves the designed manipulation of molecular interactions (hydrogen bonding, donor-acceptor effects, etc.) and recognition processes to generate main-chain (or side-chain) supramolecular polymers by the self-assembly of complementary

monomeric components (or by binding to lateral groups). In view of their lability, these associations present features of reversible, "living" polymers capable of growing or shortening, of rearranging or exchanging components. Supramolecular polymers are thus constitutionally dynamic materials, based on dynamic polymer libraries whose members possess constitutional diversity determined by the nature and variety of the different monomers. The components effectively incorporated into the polyassociations depend in particular on the nature of the recognition and core groups, internal structural compatibility, as well as the interactions with the environment. These features give access to higher levels of behavior such as healing, adaptability, response to external stimulants (heat, light, additives, etc.) by association/growth/ dissociation sequences.

The selective, recognition-controlled incorporation of components presenting specific functional properties (energy transfer, electron transfer, ion binding, etc.) allows us to envisage applications for such diverse purposes as drug delivery, gene transfer, mechanical action (e.g., triggered changes in shape or size), viscosity adjustment, hydrophilicity/hydrophobicity modulation, optical and electronic effects, etc.

Supramolecular versions of the various species and procedures of molecular polymer chemistry may be imagined and implemented, providing a wide field of future investigation that may offer a wealth of novel entities and functionalities. Similar considerations apply to the generation of supramolecular liquid crystals (56–58).

Molecular recognition may be used to induce and control self-organization in two and three dimensions for performing supramolecular engineering of polymolecular assemblies and materials, layers, films, membranes, micelles, gels, mesophases, and solids as well as on surfaces or at interfaces.

Surfaces modified with recognition units may display selective surface binding on the microscopic level and recognition-controlled adhesion on the macroscopic scale. Intermolecular interactions may be brought to induce the controlled assembly of macroscopic objects as is the case with capillary forces (59).

Self-organization of polymolecular assemblies reaches a second level in the self-organization of objects that are themselves self-organized. Vesicles are of special interest in this respect, because compartmentalization must have played a major role in the self-organization of complex matter and thus in the evolution of living cells and organisms. One may envisage the controlled build-up of architecturally organized and functionally integrated polyvesicular systems toward the design of artificial cells and polymolecular systems of tissue-like character, implementing specific intravesicular and intervesicular processes (60, 61). The manipulation of the features of vesicles and their behavior is a step in this direction; thus, liposomes decorated with recognition groups, recosomes, present features such as selective interaction with molecular films, aggregation, and fusion (62, 63).

Molecular recognition interactions also provide a powerful entry into solid-state

chemistry and crystal engineering. The increasing ability to control the way in which molecules associate gives means for the designed generation of supramolecular architectures in the solid state (64).

The generation of self-organized nano-structures, organized and functional species of nanometric dimensions, defines a supramolecular nanochemistry.

Supramolecular Nanochemistry and Nanomaterials

Nanoscience and nanotechnology are receiving great attention in view of both their basic interest and their potential applications (65, 66). Here again, supramolecular chemistry and self-organization contribute a fundamentally novel outlook of deep impact. Three approaches to these areas may be considered.

(i) The miniaturization, top-down “size-shrinking” approach, mainly pursued up to now, has led to the tremendous achievements of the microelectronics technology and is pushing down the limits of size and compactness of components and devices.

(ii) The nanofabrication and nano-manipulation bottom-up approach to molecular nanotechnology, takes advantage of novel nanolevel materials and methods (e.g., near-field scanning microscopies) to generate nanoentities presenting intriguing potential, such as electrical devices built on carbon nanotubes (for two recent examples, see refs. 67 and 68) or optical devices like optical sieves (69).

(iii) The supramolecular self-organization approach, where the goal is not smaller size or individual addressing but complexity through self-processing, strives for self-fabrication by the controlled assembly of ordered, fully integrated, and connected operational systems by hierarchical growth.

The first two approaches rely on design and implement physical procedures. Self-organization may take advantage of both design and selection, through its informed, dynamic and adaptive features, and finds inspiration in the integrated processes of biological systems.

Indeed, the spontaneous but controlled generation of well-defined, functional supramolecular nanostructures through self-organization offers a very powerful alternative to nanofabrication and nano-manipulation, bypassing the implementation of tedious procedures and providing a chemical approach to nanoscience and technology. Rather than having to top-down prefabricate or to stepwise construct nanostructures, more and more powerful methodologies resorting to self-organization from instructed components will give access to highly complex functional architectures (1). Their dynamic features, allowing constitutional modification through exchange of components, confer to them the potential to undergo healing and adaptation, processes of great value for the development of “smart” nanomaterials. Of course, various combinations of self-organization and fabrication procedures may be envisaged and implemented at different stages.

Fabricating, manipulating, and implementing nano-size chemical entities offer a wide

range of potential applications of great value for science and technology (70). Reducing size to the nano-object and addressing it are admirable feats that provide entirely new insight into the properties and functioning of chemical as well as biological systems. However, in the long run, the goal is complex organization and collective operation rather than smaller size and individual addressing. And here the path is traced by self-organization, covering a full range of self-processes that determine the internal build-up and the operation of the entity (self-selection, self-wiring), as well as its interaction with the environment (self-connection for addressing and sensing). It follows also a bottom-up scale change by growth from the nanolevel to the meso level and to the macrolevel with internal structural organization, functional integration, and external connection. Indeed, the most complex object around, the brain, builds up by self-organization and is self-wired and self-integrated as well as self-connected through our senses!

Toward Adaptive and Evolutive Chemistry

The combination of the features of supramolecular systems—information and programmability, dynamics and reversibility, constitution and diversity—leads toward the emergence of adaptive/evolutive chemistry (3). It is, by essence, of supramolecular nature because it is determined by interaction with an external entity. It may be constitutional and/or morphological (as occurs in “induced fit” for instance). Adaptive chemistry implies selection and growth under time reversibility. Implementing both design and selection, self-organization offers adjustability (through self-correction, self-healing under internal dynamics); adjustability leads to adaptation (through reorganization under interaction with environmental effectors); adaptation becomes evolution, when acquired features are conserved and passed on. Adaptation is illustrated by functionally driven optimization through selection from pools of dynamically interconverting supramolecular species. Evolutive chemical systems suppose multiple dynamic processes with sequential selection/acquisition/fixation steps and undergo progressive change of internal structure under the pressure of environmental factors. But the world of selection is a brutal world, where only the fittest survives. It is ultimately for thought and design to open up a post-Darwinian era by recruiting the forces of information to override the dictate of selection!

Beyond programmed systems and in line with an evolutive chemistry, the next step in complexity consists in the design of chemical “learning” systems, systems that are not just instructed but can be trained (see for instance ref. 71).

The incorporation of the arrow of time, time irreversibility, leads to self-organization in nonequilibrium, dissipative systems through irreversible processes (4, 5). It implies the passage from closed systems to open and coupled systems that are connected spatially and temporally to their surroundings.

Supramolecular Science, the Science of Informed, Complex Matter

In the long-range perspective, the development of chemical science is toward complex systems, spanning the broadest outlook from divided to condensed matter then to organized and adaptive matter, on to living matter and thinking matter, up the ladder of complexity. Complexity implies and results from multiplicity of components, interaction between them and integration i.e., correlation, coupling, and feedback (1). The species and properties defining a given level of complexity result from and may be explained on the basis of the species belonging to the level below and of their multibody interaction, e.g., supramolecular entities in terms of molecules, cells in terms of supramolecular entities, tissues in terms of cells, organisms in terms of tissues and so on, up to the behavior of societies and ecosystems along a hierarchy of levels defining the architecture of complexity. At each level of increasing complexity novel features emerge that do not exist at lower levels, which are deducible from but not reducible to those of lower levels.

Supramolecular chemistry provides ways and means for progressively unravelling Together with the corresponding areas in eling the complexification of matter through self-organization. The Special Feature in this issue of PNAS takes stock and outlines prospects for many of the activities pursued in the field.

Together with the corresponding areas in physics and biology, supramolecular chemistry builds up a supramolecular science whose already remarkable achievements point to the even greater challenges that lie ahead. They lead toward a science of complex matter, of informed, self-organized, evolutive matter. The goal is to progressively discover, understand, and implement the rules that govern its evolution from inanimate to animate and beyond, to ultimately acquire the ability to create new forms of complex matter. The perspectives opened up become wider and wider as progress is being made and will constitute horizons of the future for quite some time!

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