

# Origins and emergences of supramolecular chemistry

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**Abstract** The present paper exposes the field of supramolecular chemistry from the premises of chemistry to recent achievements. As any new event supramolecular chemistry has been claimed to be an emergent field of research. Depending on the definitions of emergence related to hierarchy or scope, supramolecular chemistry is shown to have bottom-up or top-down emergences.

**Keywords** Atoms · Supramolecular chemistry · Emergence

It is often difficult to give a precise date to a scientific event. A discovery is always the achievement of a long process of accumulation of results, of crosschecking, of contradictions and this, even, in the exceptional cases where it occurs with a lightning development (Translated from French by the authors; [1])

A discovery is, above all, a domino reaction, in which successive pieces ultimately make up the whole [2].

First because discoveries only occur through processes widely opaque to their agents. Second because the ‘way of thinking’ of the community of scientists at a

given time for the time being influences the manner in which scientific concepts are built and always impose themselves by coordinating around them groups that promote them. The process of discovery in science can be rationalized only a posteriori: far from being the work of a genius visited by a sudden inspiration, it results from what initially looks like a ‘collective tinkering’ produced by researchers who are associated or rival, some elaborating viable hypotheses, others suggesting wrong ideas but with a fruitful detail (Translated from French by the authors; [3])

As the quick-silver of our experiments at school, scientific ideas follow paths difficult to anticipate. With or without practical designs, they expand, fragment, and hybridize to form new confluences. Their final destiny is always unforeseeable (Translated from French by the authors; [3])

Tracing the birth of a scientific area has quite some arbitrary character. The moment when the seed was planted and the identification of the roots are usually subject to scrutiny only once the tree has grown. This holds also for supramolecular chemistry [4].

The emergence of any novel field of science is linked to the past [5].

It is enough to create new names, estimations and probabilities in order to create in the long run *new things* [Translated from French by the authors] (Nietzsche, *The Gay Science*)

On October 17, 2007, one of us (J.V.) was invited to give a lecture on achievements in supramolecular chemistry at the *International Interdisciplinary Symposium on Supramolecules & Nano-Technology 2007 (IISSNT 2007)*

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Dedicated to Pr Jack Harrowfield and Dr. Jacques Vicens on the occasion of their 65th birthday.

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in Busan, Korea. The inter-disciplinary nature of this meeting made for an ideal opportunity to present a lifetime of studies within a wider framework of supramolecular chemistry, encompassing origins, foundations, principles, applications and philosophy of this now >50-year-old field. The lecture presented at this symposium served as the inspiration for the historical section of the present account. Here, in addition, the supramolecular chemist—the father—was joined by a molecular biologist—the son (Q.V.)—to review some examples illustrating how other scientific disciplines such as biology have informed chemistry, leading to the emergence of supramolecular chemistry, one of its principal branches today.

The arrival of supramolecular chemistry is as revolutionary to the field of chemistry as the arrival of Pablo Picasso's artwork to the world of painting. *Les Femmes d'Alger (O. J. R. M.)* (1907) was a vigorous opening to the art of the twentieth century. Likewise, the pioneering work of Pedersen [6], Lehn [7] and Cram [8] in the 1960s was an energetic impetus to chemistry, and in particular to organic chemistry, which was about 200 years old at that time [9–11]. The parallel between chemistry and painting can be drawn even further, through a similitude between the expression *Supramolecular Chemistry* and the word *Surrealism*. *Supramolecular chemistry* is 'the chemistry beyond the chemical bonds' and deals with *supermolecules* [7]. Similarly, *surrealism* is a type of art beyond realism. Wikipedia dictionary says: 'The English word 'Surrealism' is a mis-translation of the French word 'Surréalisme'. The correct translation should be 'Superrealism'. André Breton (one of the founder) somewhere said that the "'surréal' is to the 'réel' what the 'surnaturel' is to the 'naturel'. English-speakers say 'supernatural'" (<http://en.wikipedia.org/wiki/Surrealism>). Furthermore, *supramolecular chemistry* and *surrealism* have in common the ability to describe and reproduce or build objects found in Nature, and to assemble these objects in unusual ways. New ideas and concepts often emerge from the association of these objects, even in the absence of connection between these objects in Nature.<sup>1,2</sup>

The field of supramolecular chemistry is among one of the most interesting and promising ones in chemistry.

<sup>1</sup> On many levels, and to many people, chemistry and art are not easily correlated. From the DaVinci Project a conceptual framework for the development of project materials and activities was identified. This framework was based on three levels of complexity of ideas: structures, interactions between and among structures, and applications of structures and interactions to the everyday, observable environment. The development of higher thinking skills was fostered during the entire project the entire project, especially during the development of the third phase of the DaVinci Multimedia System. The conclusion that chemists and artists behave similarly creative for reasons evidenced during the DaVinci Project are given in Simonson and Schlosser [81].

Although relatively young, it has advanced rapidly over the years and has reached a high level of sophistication and maturity. The terms of supramolecular chemistry as an emerging field were introduced in 1978 by Jean-Marie Lehn as a development and generalization of earlier works: 'As there is a field of molecular chemistry based on covalent bond, there is a field of molecular assemblies and of intermolecular bonds' reformulated later as 'Supramolecular chemistry may be defined as 'chemistry beyond the molecule' [12]. This successful attempt to organize old and novel chemistries represents the moment when supramolecular chemistry was clearly established and gave rise to a new language, new concepts, and applications [13].

Supramolecular chemistry dealing with *supermolecules* has historical roots in organic synthetic chemistry. In the present paper, we will show how the accompanying concepts and ideas of atoms, molecules, chemical transformations, synthesis, and other tools of organic chemists have been developed to reach our present view of supermolecules. For this purpose, we shall first make a short history of chemistry, atoms and molecules, and organic chemistry.

### The first men on Earth discovered chemistry "without" atoms

Millions of people have contributed, consciously and unconsciously, to make chemistry what *it* is today. These people have worked either independently or by communicating their observations and their results. The development of chemistry has occurred with scattered observations, reasoning, arguments, ideas, desires, cravings, prejudices of conclusions, and assumptions, all coming from these ordinary or educated people who had problems and questions of their time, much like present chemists. Drawn conclusions and proposed assumptions, even wrong, can always be justified and always represent the truth and the reality of someone, the truth and the reality of a moment, the truth and the reality of a place. Therefore, the development of chemistry does not follow a straight line. One cannot report a single history of chemistry, with well defined steps and long-term explanations. Chemistry has developed from philosophies, religions, wars, beliefs, wisdoms, laws, travels, other sciences and more generally other knowledges and other memories. Chemistry was first a science of observation of natural things, then the science of events provoked by men with

<sup>2</sup> One example can be found of supramolecular chemistry giving rise to art works due to the fascinating shapes of molecules: Balzani et al. [82].

natural objects. Chemistry has no birth. *Chemistry has always been.*<sup>3</sup>

Nevertheless, chemistry is historically the study of *matter* and its transformations. Matter is anything that has mass and occupies space. Matter is what *substances* are composed of. But what is meant by substances? How is organized our view of matter (natural or artificial) and its properties? Answering these questions is a long journey that started at the beginning of humanity, when people began to admire, try to understand, interpret, and be part of the transformations of matter.

During the Paleolithic age, men mastered fire. Some of the first matters to be used were probably soil, rocks and wood. Several uses of matter were discovered. Bees wax or animal fats allowed lighting. Natural bitumen was exploited for mummification and for stainless boat making. Charcoal and natural pigments were used for the prehistoric paintings. Processes were invented to isolate metals. Native gold was discovered. Limestone was heated to afford limes. Subsequently, in the ancient civilizations of Egypt and Mesopotamia, substances were used for mummification, constructions, and fish-preserving. Bronze, iron, and steel were discovered. One uses glass. One perfumes himself. Besides this utility aspect, the sense of divine and science intersect. *Thot* was the messenger of the god *Sun* and the god of the knowledge given to men. The link between science and religion was made.

Like any other object or thing, the matter was described by using symbols. So did symbolized chemistry start. When the Egyptian, and later Greek and Roman scientists and alchemists described their experiments, they used symbols, making no difference between substances, compounds and atoms: the same symbol was used for gold, whether to describe the content of a flask or a prescription. Greek and Roman scientists were at the origin of the elimination of a divine involvement in science by introducing the idea of a junction between *thinking* and *knowing*. With the Greek philosophers, a new way to learn the transformation of matter appeared. Science associated the observation of Nature with the philosophical logic. Philosophy differentiated and opposed the mythology to the first chemical observations. A relationship was found between water, air, earth, and fire. Plato (ca. 430–350 BC) introduced the description of these four elements by polyhedrons and invented the representation of chemical

reactions. *Geometrical transformations* would correspond to matter transformations.

### The advent of atoms and molecules: a progress in stages over 2,500 years

#### Birth and abandonment of the concept of atoms

Much of the scientific history involves a succession of subjects that have made the transition from philosophy to science. Well-known examples are space and time, the nature of matter and life, varieties of causation, and cosmology, all of which were already subjects of rich philosophical discourse at the time of ancient Greece. Of all the topics deliberated upon ancient Greek philosophers, the one which has had the greatest impact on the scientific view of the world is the atomic hypothesis. Richard Feynman once remarked that if all scientific knowledge were to be lost save for one key idea, *the atomic theory of matter* would be the most valuable [14].

The concept of *atom* was first proposed by Leucippus (ca. fifth century BC). The divisibility of matter was then considered to have limits which were defined by atoms; the term ‘atom’ comes from the Greek word ‘a-tomos’, meaning ‘indivisible’. Then, Leucippus’ follower Democritus (ca. 460–370 BC) proposed that matter was constructed by corpuscles in never-ending movement. These corpuscles were suggested to be small, invisible, hard, and immutable, and to possess infinity of forms, accounting for the diversity of objects observed in the environment. One century later, Epicure (341–270 BC) proposed the notion of *clinamen* issued from gravitation, implying that atoms could slowdown and aggregate to give material forms. Atoms were still seen as being inert and composing objects. Finally, Lucreces (98–55 BC) came back to the concept of atoms in ‘*De natura rerum*’. He proposed that atoms had a volume, a shape, a specific form, that they would associate and that they would be separated by *vaccum*.

During the Middle Ages (roughly fifth to fifteenth century AD), the idea of atoms sank into oblivion. However, alchemists readily worked on *chemical techniques* that would contribute to the development of *controlled chemical reactions*. Materials were treated and substances were separated and isolated. Many chemical instruments still in use today were invented at that time. Some symbols first used then remain today. For example,  $\Delta$  represented ‘ignus’ which today means ‘reflux’ or ‘boiling’ in organic chemistry. The same sign but upside down was for ‘aqua’ (‘water’ in Latin) and now refers to ‘hydrolysis’. Among the amounts of work performed during this period, some

<sup>3</sup> Words of French philosopher Michel Foucault describe this type of thinking: ‘J’aurais aimé m’apercevoir qu’au moment de parler une voix sans nom me précédait depuis longtemps: il m’aurait suffi alors d’enchaîner, de poursuivre la phrase, de me loger, sans qu’on y prenne bien garde, dans des interstices, comme si elle m’avait fait signe en se tenant, un instant, en suspens. De commencement il n’y en aurait donc pas.’ L’ordre du discours, Leçon inaugurale. Collège de France [83].

ideas became paramount. Roger Bacon (1214–1294), a British monk and philosopher, preferred observation and rationalisation to philosophy. He introduced the use of the balance and the weight in *Alchemy*. One knows the importance of weighting in chemistry, as it later helped the French chemist Antoine-Laurent de Lavoisier (1743–1794) to enunciate the famous principle: ‘*Rien ne se perd, rien ne se crée, tout se transforme*’. Arnaud de Villeneuve (1238–1311), a French doctor in medicine, isolated the *spirit of wine* or *aqua vitae* from grapes, which is known as alcohol (‘al-kohl’ in arab). With Paracelsus (1493–1541), a Swiss physician and chemist, came experimental chemistry. He showed for example the importance of isolating pure substances in order to be able to reproduce experiments. He was the first to be convinced that food digestion was linked to fermentation. By distillation, chemists isolated mercury, sulphur and salts that were used as medicines.

### Modernization of atomic theories

At the end of this era, with the event of the *Renaissance*, Pierre Gassendi (1592–1655), a French priest who was also philosopher and scientist, brought back the atomism of Democritus and Epicure to the forefront. He conceived the world as a material construction of elemental bricks, the atoms. In 1661, Robert Boyle (1627–1691) an Irish mathematician made a distinction between mixtures and chemical combinations. He proposed that matter was made of simple substances. Mixtures were separable into simple substances while complex compounds were formed from simple elements. The distinction between mixture and chemical species allowed understanding that a chemical combination results from the reaction of one substance with another. This was the first evidence of a *linkage* between atoms and made for a quantum leap towards the notion of *molecule*.

Around the time of the French Revolution, Lavoisier wrote a *Traité Élémentaire de Chimie* (Elementary Treatise of Chemistry, 1789), which is now considered to be the first modern chemical textbook. It presents a unified view of new theories of chemistry, contains a clear statement of the Law of Conservation of Mass, and denies the existence of *phlogiston*, a fifth element that had been proposed to be responsible for oxidation processes. Also, Lavoisier clarified the concept of an element as a simple substance that could not be broken down by any known method of chemical analysis, and he devised a theory of the formation of chemical compounds from elements. Hence, he discovered that one element could not associate with an infinite number of other elements, but rather would combine in a specific manner. This announced the notion of *valence*. Lavoisier also devised a chemical *nomenclature*, or a system of names describing the composition of chemical

compounds. He described this nomenclature in *Méthode de nomenclature chimique* (*Method of Chemical Nomenclature*, 1787). The system facilitated communication of discoveries between chemists of different backgrounds and is still largely in use today, as it includes names such as “sulfuric acid”, “sulfates”, and “sulfites”.

### Classification of atoms

Throughout the nineteenth century, a few prominent chemists further delineated the foundations of modern chemistry. In 1813 and 1814, Jöns Jacob Berzelius (1779–1848), a Swedish chemist, published two essays that appeared in *Annals of Philosophy*, making him one of the founders of modern chemistry. He was especially recognized for his determination of atomic weights, his development of modern chemical symbols, his electrochemical theory, the discovery and isolation of several elements, the development of classical analytical techniques, and his investigation of isomerism and catalysis, phenomena that owe their names to him. He proposed to designate the elements by the one or two-first letters of their Latin or Greek name: S = sulphur, Si = silicium, St: stibium (antimony), Sn = stannum (stain), Cu = cuprum (copper), C = carbonicum (carbon), O = oxygen and to note the chemical combinations and reactions by association of the symbols: *oxidum cuprosum* became Cu + O, which is now CuO. John Dalton (1766–1844), an English chemist, also exposed his theory on atoms in *A New System of Chemical Philosophy* (1808). Compounds were listed as binary, ternary, etc. depending on the number of atoms a compound had in its simplest, empirical form. He hypothesized the structure of compounds could be represented in whole number ratios. Thus, one atom of element X combining with one atom of element Y would constitute a binary compound. Furthermore, one atom of element X combining with two elements of Y or vice versa, would make a ternary compound. Many of the first compounds listed in the *New System of Chemical Philosophy* were listed correctly, although others were not. Dalton used his own symbols to visually represent the atomic structure of compounds. Many of Dalton’s ideas were acquired from other chemists at the time. However, he was the first to put the ideas into a universal atomic theory.

Dalton’s work is probably at the origin of the periodic table of elements of Mendeleiev. By attempting to classify 29 of the 63 chemical elements known at that time by the atomic weight, Dmitri Mendeleiev (1834–1907), a Russian chemist, created the first version of the periodic table of elements published in *Zeitschrift für Chemie* (1869). Unlike other contributors to the table, Mendeleiev predicted the properties of elements yet to be discovered. The table of Mendeleiev was another quantum leap, in the sense

that any matter existing on Earth is made of atoms described in the periodic table. Alexander Crum Brown (1838–1922), a Scottish chemist, represented *molecules* consisting of associations of atoms. He drew small circles as first designed by Dalton, in which letters indicated the symbols of Berzelius. These symbols were also linked by segments, thereby satisfying the notion of valence. His first publication appeared in 1864 in the *Journal of the Chemical Society*. The word ‘molecules’ comes from Latin ‘moles’ (mass, structure) and molecules mean ‘small mass’. In 1873, another Scottish physicist, James Clerk Maxwell (1831–1879) clearly stated: ‘*an atom is a body which cannot be cut in two; a molecule is the smallest possible portion of a particular substance*’.

Observations of atoms and description of their interactions

At the turn of the twentieth century, atoms became physical evidence due to the work on cathodic rays of a British physicist, Joseph John Thomson (1856–1940), who showed that electrons could be extracted from matter. He also discovered positive particles and deduced that the atom is a sphere full of positive substances with negative electrons like in a ‘pudding’. One of his students, the New Zealander physicist Ernest Rutherford (1871–1937), explained the ability of atoms to loose and exchange electrons to form molecules because they revolve around a positive nucleus like planets around the sun. Thanks to the work of Rutherford and a German physicist, Max Planck (1858–1947), Niels Borg (1885–1962), a Swedish physicist, elaborated an atomic model in which electrons had different levels of energy. To explain the formation of molecules, Gilbert Newton Lewis (1875–1946), an American chemist, proposed a model to elaborate molecules: a *covalent bond* results from two atoms sharing two electrons. The concept of “covalent bond” was important because it launched investigations of reaction conditions that would cause bond formation or breakage, to eventually build larger covalent structures from smaller molecular elements. For example, target-molecule with a desired shape and functional properties could now be synthesized.

From then on, according to the reactivity of atoms deduced from the periodic table, each atom was described as a cube having a various number of electrons to be shared. The view of Rutherford was expanded so that the electrons were proposed to orbit around the nucleus in a defined path, like a planet moves around the sun. Electrons inhabit regions of space known as *orbitals*. Orbits and orbitals sound similar, but they have quite different meanings. The *Heisenberg Uncertainty Principle* says that one cannot know with certainty both where an electron is and where it will be. Linus Pauling (1901–1994), an

American chemist, published in 1931 an article in which the geometry of molecules were obtained from quantum mechanics. More recently, the Nobel Prize of Physics in 1986 was attributed to a German, Eric Ruska and two Russian physicists, Gerd Binnig and Heinrich Rohrer for their fundamental work in electronic optics leading to the first STM (Scanning Tunnelling Microscope), which allows the visualization of atoms and molecules on metallic surfaces. This discovery was highly important since today chemists can see and thereby *touch* their molecules as ordinary objects. Recently, a group of scientists at the Scripps Research Institute in La Jolla (California, US) has developed a technique for ‘*touching molecules with your bare hands*’ and interacting with molecules so small that they cannot be seen with the world’s most powerful microscope (<http://www.scripps.edu/news/press/032405.html>). Starting from the philosophical concept of atoms, atoms and molecules, are now atomic objects that one can ‘see and touch’.

### Organic chemistry leads to the emergence of supramolecular chemistry

Supramolecular chemistry takes its origin in organic chemistry, which itself derives from studying the chemistry of living systems. The synthetic power of organic chemistry made possible to synthesize useful natural products and to prepare complex artificial pharmaceutical molecules. Nicolaou recently presented inspirations, discoveries and future perspectives in total synthesis, tracing the evolution of the art of chemical synthesis to its present sharp condition [15, 16]. Until the end of the eighteenth century, chemists were working without differentiating mineral and organic bodies. When publishing his *Cours de Chymie* in 1690, Nicolas Lèmetry (1645–1715), a French apothecary and physician, separated the mineral world from the living one without knowing he was distinguishing ‘mineral chemistry’ and ‘organic chemistry’. The difference was based on the existence of a *vital force* or *assimilation*, from a divine source, and which allowed the chemical transformations of living substances: Living substances are produced from mineral elements by processes which cannot be done by men. Chemists were eventually able to transform products extracted from natural substances, which led Berzelius to coin the expression of ‘organic chemistry’ to name this branch of chemistry. In 1808, in the first volume of *Läbork i chemie*, he used this word, derived from the word ‘organ’ corresponding to an organisation characterizing the physical, chemical and mechanistic perfection of the living systems induced by the vital force. Twenty years later, Friedrich Wöhler (1800–1882), a German chemist, published an article in *Annalen der*

*Physik und Chemie*, entitled ‘*Production of artificial urea*’ reporting the synthesis of *urea*, a compound originally extracted from living systems by pyrolysis of ammonium cyanide issued from two mineral materials. This result put an end to the idea of a *divine* or *vital force* that produces living entities. At the same time, this opened the way to *organic chemical synthesis*. Marcellin Berthelot (1827–1907), a French chemist, developed organic syntheses not only by producing and transforming products from life such as ethanol, methanol, methane, and benzene, but also by producing the first system of reactions to prepare artificial substances such as fats, hydrocarbons and some synthetic sugars. In 1860, he published the *Chimie organique fondée sur la synthèse*, showing the positive behaviour of organic synthesis to give rise to a creative chemistry that is self-developing.

During the twentieth century, organic chemistry grew up, affording a large number of organic reactions and products for industry, companies and fundamental research. In 1965, the American Robert Burns Woodward (1917–1979) was awarded the Nobel Prize of Chemistry for the total synthesis of vitamin B12 [17]. This achievement demonstrated that organic chemists were able to synthesize complex molecules by forming *covalent* chemical bonds.<sup>4</sup> In parallel, the synthesis of unnatural molecules having special properties was developed. For example, the synthesis of intramolecularly overcrowded helicenes showed that organic chemists were now able to *invent* or *create* molecules from their imagination, thus producing new materials [18]. These ideas were reflected in the words of Nicolaou: ‘Chemical synthesis is an exceedingly exciting, challenging, and fulfilling field, one that will always appeal to those talented youngsters who are destined to shape it further and ensure the continuation of its proud tradition as they strive to equal or even *surpass Nature* at her own game’ [15]. Among the driving forces of the development of organic synthesis was Molecular beauty, often associated to symmetry. In 1991, Hoffman wrote an article showing how the beauty of certain molecules of the 1960s ‘*appeals directly to the mind*’ [19]. And he gave as one example, the first preparation of interlocking molecules, thanks to the concept of chemical

topology and topological isomerism [20, 21, 22]. A special issue on aesthetics in chemistry was recently published.<sup>5</sup>

In addition to allowing for the preparation of almost any target molecule, synthesis has another advantage: ‘*Synthesis offers a different strategy. Instead of a ‘probe and model’ paradigm, synthesis uses a symmetrical double paradigm: if you understand it, then you can make it; if you can make it, then you can say that you understand it*’ [23]. It is in this context of a ‘healthy’ development of organic synthesis, that about forty years ago, in 1967, the first of Charles Pedersen’s papers on the synthesis and metal binding properties of crown ethers was published in the *Journal of the American Chemical Society* [24]. Twenty years later, in 1987, Pedersen (1902–1979) [6], Lehn [7] and Cram (1919–2001) [8] were awarded the Nobel Prize in chemistry in recognition of their pioneering work in supramolecular chemistry.

### Stereochemistry, topology of molecules, and molecular models

Besides the synthetic skill developed by organic chemists, another consideration was very important for the emergence of supramolecular chemistry: the third dimension. Molecules exist as spatial entities. From an interview of Lehn, Goodman writes in *Nature Chemical Biology* [25]: ‘He (J.-M. Lehn) remembers, “*This was a question of trying to selectively bind a sphere in a collection of spheres. Then you think about molecular recognition, because that’s all this binding is—a recognition process*”’ as an echoes to earlier words in 1969 about the inclusion of an object within a 3D structure: ‘I thought that the ring structures described by Pedersen were nice but not really what you want, because you want something that is 3-dimensional. A spherical ion is 3-dimensional – you don’t want a ring, you want spherical cavities. And so we started to make the macrobicyclic cryptand cavity compounds—and obtained their selective inclusion complexes, the cryptates, with alkali cations. That was the beginning’ [11].

This statement reflects the development of supramolecular chemistry and its relationship to the stereochemistry and topology of molecules, which dates back to the nineteenth century. If the matter occupies a volume, if molecules are composed of atoms which are bricks, and if molecules are the smallest portion of a substance that occupies space, one cannot understand why molecules are seen and represented flat. This probably was coming from the fact that chemistry was written on paper and chemists could not figure out that molecules actually had three dimensions. However, in 1865, German chemist August

<sup>4</sup> A covalently formed bond can be considered to be as strong as an irreversible linkage between atoms. This property has been synthetically exploited, from forming one bond at a time, to methodically building larger and larger covalent structures from smaller molecular starting materials. For a long time, this was the only available method to produce a molecule with a desired shape and function, with common molecular targets having less than 100 covalent bonds and molecular weights of several hundred Daltons. Some of the largest structures synthesized at the upper limits of covalent synthesis, palytoxins, have molecular weights of several thousand Daltons and lengths of around one nm. See as an example Armstrong et al. [84].

<sup>5</sup> For further reading on molecular beauty and chemists’ imagination see also: Spector and Schummer [85].

Wilhelm von Hofmann (1818–1892) built stick-and-ball molecular models. The atoms were represented by balls of billiards with different colours: carbon = black, nitrogen = blue, oxygen = red; hydrogen = white; sulphur = yellow; chlorine = green. Remarkably, the very same choice of colours is in use in today's molecular models. Yet, in his first molecular model, the molecule of methane was represented with a flat tetravalent carbon. A few years later, Jacobus Henricus van't Hoff (1852–1911), a Dutch physical and organic chemist, and Joseph Achille Le Bel (1847–1930), a French chemist, independently proposed that the phenomenon of optical activity of some organic compounds could be explained by assuming that the chemical bonds between carbon atoms and their neighbors were directed towards the corners of a regular tetrahedron, which could give rise to mirror-image isomers. To illustrate his theory, van't Hoff built hand-made cardboard tetrahedral models of various organic molecules with various colours on each face.<sup>6</sup> Henceforth, the way of writing a carbon substituted with four substituents changed, and the carbon became tri-dimensional. Subsequently, von Hofmann revisited his models to give a tetrahedral carbon to the methane and his models were built in three dimensions. It took a while for chemists to comprehend the implications of these 3-dimensional molecular models, and Pierre Laszlo has stressed that chemists were playing as children with them [26]. The use of molecular models proved to be so practical that many calculations-based molecular modelling softwares were programmed to allow many kinds of representations of various types of molecules, as well as to calculate distances, to evaluate the shape of cavities, to visualize the contacts between molecules. In short, these models helped to quantify the properties of supramolecular systems.

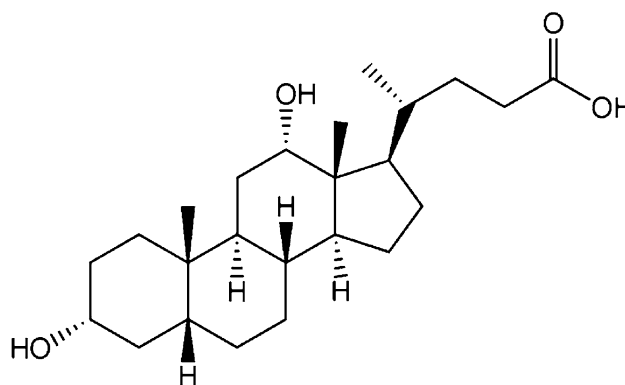
### Representation of molecules: expanding visual thinking

The representation of molecules by models is important to chemists. The development of organic chemistry was accompanied by the representation of structural formulas or

<sup>6</sup> Van 't Hoff is not only one of the fathers of 3D-chemistry as we know it today, but he is probably also the father of *Molecular Origami's*. Origami is a Japanese word to designate the art of folding (oru) the paper (kami). Molecular origami's use this art and the way of cutting and folding to represent molecules or crystalline solids. It is related to the knowing of matter by X-ray diffraction. It is used by chemists and biologists. For example the work of R. M. Hanson (Ed.) *Molecular Origami Mass Scattered Paper Models* proposes the precise-scale construction in 3D with angles and distances with variously coloured papers. Molecular Origami's images are also used by softwares to calculate molecular structures as large as the ones of nanochemistry. This type of modelisation-representation has been extended to DNA and related molecules which can be seen with CACHE programs [86].

chemical structures (disposition of atoms and bonds). These were drawn by the chemists to communicate and generate new molecular objects that they sought to synthesize out of curiosity or for special needs. Studies on the importance of chemical structures and representation of molecules for the communication of organic chemistry have been reported by Cooke [27], Hoffman and Laszlo [28], and Goodwin [29]. Significantly, chemists '*make visual imagery for problem-solving, in order to sort out and organise information to find analogies, to think*' [28]. A chemical formula represents the structure of a molecule, i.e., the arrangement and the connectivity of atoms in space. A single bond is stronger than double or triple bonds, which are more able to give rise to reactions. This bonding organization therefore indicates the localization of functions that can be used for further reactions. Organic chemists use the concept of molecular graph<sup>7</sup> and read a formula like an ideogram [30, 31]. They have developed a *visual thinking*.<sup>8</sup>

A direct consequence of visual thinking is that organisation and creation are connected [32]. Thus, organic chemists enhance their ability to think and create visually, and communicate ideas in visual ways. For example, the following formula:



<sup>7</sup> Curiously, the concept of molecular graph was first conceived by Arthur Cayley (1821–1895), a British mathematician in 1847. Two types of molecular graphs were proposed: plerograms and kenograms. Plerograms are molecular graphs in which all the atoms are represented by vertices. Kenograms are what nowadays is referred to as hydrogen-suppressed or hydrogen-depleted molecular graphs. See Cayley [33, 87] and [88].

<sup>8</sup> Picture or visual thinking is the ability of thinking through images and not through words using the part of the brain that is emotional and creative to organize information in an intuitive and simultaneous way. Thinking in pictures, is one of a number of other recognized forms of non-verbal thought such as kinesthetic, musical and mathematical thinking. It is nonlinear and often has the nature of a computer simulation, in the sense that a lot of data is put through a process to yield insight into complex systems, which would be impossible through language alone. 'Visual thinking calls for the ability to see visual shapes as images of the patterns of forces that underlie our existence—the functioning of minds, of bodies or machines, the structure of societies or ideas.' are the words of Arnheim [32].

is the formula of the *deoxycholic acid* (DOCA). Even if a chemist is unaware of this fact, at a glance he can deduce the following properties about this molecule: (1) it is a solid substance, (2) it is a natural product, (3) it belongs to the steroids family, (4) it has three reactive positions, and (5) it is colourless. *A supramolecular chemist adopts an expanding visual thinking as he identifies the molecule in a different way from organic chemists.* DOCA is no more a ‘synthon’ for preparing organic derivatives but rather a building block able to produce intermolecular interactions via its functionalities, with the possible formation of (inclusion) complexes or clathrates. DOCA can form hydrogen bonds, it can form Van der Waals interactions, it has a hydrophobic region, etc. Indeed, DOCA was preliminary used as an intermediate for the production of corticosteroids, which have anti-inflammatory indications [33]. Then, a different (supramolecular) use of DOCA was as a biological detergent to lyse cells and solubilise cellular and membrane components (<http://www.nzp.co.nz/products.php?cid=2&pid=2>).

In a more general sense, the functions which are used as *reaction centers* for organic synthesis are used to promote *molecular interactions* in supramolecular chemistry. Supramolecular chemists say that molecules bear *functional informations* to recognise and complex an entity and to create complexes in which the components are not chemically transformed. This introduces the concept of *molecular information* and *recognition*. This molecular information consists in several functions placed at the right position in the molecular framework to fit the size and shape of the partner. It is also used to organize matter into organised systems undergoing so-called *self-organization*, i.e. systems capable of spontaneously generating well-defined functional supramolecular architectures by assembling their components. From a philosophical point of view a new field opened in which understanding the origins of ‘information and interactions [was] however, beyond the authors and probably most of the readers’ [34].

### Some events related to topology and self-organization in the 1940–1960s

Supramolecular chemistry, its concepts and vocabulary were developed since the 1960s [11]. We have noticed the importance of molecular topology to organize and create complexes or molecular assemblies by self-organization. In the 1940–1960s, just before the birth of supramolecular chemistry, a certain number of important events in science were related to molecular *topology and self-organization in chemistry, physics, and biology*, offering to these separated fields of research a common denominator. One can assume that this ‘ambient mood’ for topological problems guided

chemists in the enunciation of rules and concepts in supramolecular chemistry.

A major event in the 1940–1950s was the race for the discovery of the topology and the structure of deoxyribonucleic acid, DNA. After several propositions that DNA adopted a triple helix (see for example ref. [35]), Francis Crick (1916–2004) and James Watson (born, 1928), with the contributions of Maurice Wilkins (1916–2004) and Rosalind Franklin (1920–1958), proposed the model of the ‘double helix’ structure of DNA [36, 37, 38, 39, 40]. The *specific pairing* of purine and pyrimidine bases was a key feature of the Watson and Crick model of DNA, based on Chargaff’s (1905–2002) observations that in the DNA from many different sources, the amount of guanine (G) was equal to that of cytosine (C), and that the amount of adenine (A) was equal to that of thymine (T) [41]. By using the keto rather than the enol tautomers of G and T, Watson and Crick accounted for Chargaff’s findings by base pairing A with T and G with C through the formation of hydrogen bonds. The model of the double helix thus stemmed from the similarity in shape and size of the A:T and G:C pairs. Furthermore, Watson and Crick’s model suggested the two complementary strands of DNA could be unzipped for replication, further supporting the evidence that DNA was the depository of genetic information [42, 43].

The pairing of A with T and of G with C illustrates that conceptually, all biological phenomena depend in one way or another on *specific molecular recognition*. At the end of the nineteenth century, Emil Fischer (1852–1919) coined his famous *lock-and-key* analogy to picture the specificity of enzyme reactions, which are a molecular premise of life [44, 45]. The enzyme was considered to be a rigid catalyst to which the substrate had to fit as a key into a lock. Over the years, however, it became apparent that a rigid fit between preformed molecular structures could not explain all aspects of enzyme catalysis [44, 45]. For example, how could a smaller substrate fit into the active site of an enzyme designed for a larger substrate? Or why were some enzymes highly selective while others could accommodate several structurally different substrate molecules? In 1958, Daniel E. Koshland (1920–2007) formulated the theory of the *induced fit* to account for these observations [46, 47]. To facilitate the enzymatic reaction in the absence of a precise fit, he postulated that: ‘*the substrate may cause an appreciable change in the three-dimensional relationship of the amino acids at the active site*’. The idea of a precise fit was retained from the lock-and-key image, but is the new concept stated explicitly that the fit ‘*occurs only after the changes induced by the substrate itself*.’ This concept was rapidly adopted and used to explain all kinds of molecular recognition processes far beyond enzyme-substrate reactions. Indeed, structural analysis of interacting biomolecules such as RNA and proteins further established



that a complex and its free component molecules may differ in fine details of structure, in support of recognition by induced fit [48]. A good case in point was provided by several antigen-antibody complexes for which spatial adaptation was demonstrated by high-resolution crystal structure analysis. These principles of lock-and-key and induced fit were accepted and used by supramolecular chemists from the beginning. Furthermore, the tenet of the *best fit* and/or *preorganisation* with complementarity of shape and functions was introduced by Donald Cram (1919–2001) [7]: the fact that a receptor has to rearrange itself to reach the best fit is often translated in terms of entropy.

The elaboration of the allosteric theory during the years 1961–1967 is directly related to Koshland's induced fit theory. In 1965, Jacques Monod (1910–1976), Jeffries Wyman (1901–1995) and Jean-Pierre Changeux (born, 1936) proposed the model of allosteric effects in which there is a relation between two binding sites of a protein [49, 50]. The words of the original publication are as follows: '*indirect interactions between distinct specific binding-sites (allosteric effects)*' and '*It must be assumed that these interactions are mediated by some kind of molecular transition (allosteric transition) which is induced or stabilized in the protein when it binds an 'allosteric ligand'*' [49, 50]. This concept would be later revisited by supramolecular chemists who would design molecules able to change shape to perform a particular function (e.g., to bind a ligand), only after an effector molecule would bind [51].

In parallel to these advances in biology, organic reactions in the solid state were widely developed in the 1960s. A great impetus to this field was given by late Gerhardt M. J. Schmidt (working at the Weizmann Institute in Israel), with the observation that in some photochemical reactions the nature of the product may be explained by the crystal structure of the starting material [52]. One interesting property of such reactions was the possibility of acting on the reaction events such as transition states by engineering the structure of the reacting crystal whose close packing is organized by molecular interactions. The reaction is occurring with a '*minimum of movement*' of atoms and functionalities involved in the process. This topological principle found applications in the design of molecular crystals or '*crystal engineering*' for creating absolute asymmetric syntheses and obtaining highly selective reactions [52].

Simultaneously to these topological and structural behaviours, organisation and self-organisation, information as a function, assembly theories, and evolution of systems in general were developed. Methods employing '*transitional machinery organized by a sufficient amount of information*' were developed by Manfred Eigen who received the Nobel Prize in 1967 for his research on very rapid chemical kinetics. Already in 1971, his scientific

interest was focused almost exclusively on problems concerning evolution. And in 1977 he published with Peter Schuster a pioneering paper of a trilogy dealing with two new concepts: the '*self-organization of matter*' and the '*evolution of biological macromolecules*' [53]. These are classical concepts in the field of evolution. Laws of Nature are, in a sense, biased so that they tend locally to direct matter toward states of increasing *complexity* and *order*. Manfred Eigen is among those who have investigated the effect of connected, self-organizing chemical processes in generating complex molecular arrangements in relationship to selection and evolution of RNA or DNA molecules.

A new structure resulting from self-organisation was called a '*dissipative structure*' because it occurs spontaneously and is directed or controlled by a centralized, hierarchical '*command and control*' center. As a result, whole systems self-organise when they are pushed far from their stable state. Order emerges through a process of self-organisation. First studied in physical systems by Ilya Prigogine (1917–2003), a Belgium physicist and chemist, also in the 1960s, self-organization is now studied primarily through computer simulations such as cellular automata, boolean networks, and other phenomena of Artificial Life [54]. In a quite different field of research, some topological behaviours and dynamic systems are also investigated by the French mathematician René Thom (1923–2002) [55]. The catastrophe theory [56–58] is a special branch of dynamical systems theory. It studies and classifies phenomena characterized by sudden shifts in behaviour arising from small changes in circumstances. Catastrophes are bifurcations between different equilibria, or fixed point attractors. Catastrophe theory has been applied to a number of different phenomena, such as the movements of waves of the sea, bridge collapse, and, more particularly gave rise to mathematic models of morphogenesis [55–58]. Although these few last examples are not directly related to 'pure' chemistry they may have some influence in the thinking of beginners in supramolecular chemistry.

### The three seasons of supramolecular chemistry

According to Lehn [59], '*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’. These three seasons of supramolecular chemistry roughly corresponds to three review articles of Lehn [4, 5, 60] and are reflected by the words of the title of an important review article of Gale: ‘Supramolecular chemistry: from complexes to complexity’ [61]. The title already introduced us to the concept of *complexity* and further to that of *emergence*.

Since its first season, supramolecular chemistry is the chemistry *beyond the covalent bond*. Supramolecular chemistry develops molecular systems which are ensemble of chemical entities (for example molecules or molecules and ions) held together by *intermolecular interactions*. Covalent bonds are imposing certain rigidity to the atomic assemblages while molecular interactions are feeble implying a certain lability of molecular assemblies. These interactions are for instance: electrostatic bonds, Van der Waals forces, dipole-dipole interactions, hydrogen-bonding. New definitions and concepts, and language appear [13]: ligand, molecular receptor, substrate, host-guest, inclusion compound, complex, intermolecular interactions, feeble forces, macrocyclic effect, size effect, molecular recognition, complementarity, preorganisation, and molecular information. New names are given to series of molecules involved in: crown-ethers, cryptands, coronands, torands, spherands, speleands, calixarenes, and cryptophanes. According to the way they complex, the receptors are monotopic (one guest included) or polytopic (several guests included) receptors. Multiple recognition gives rise to higher forms of molecular behaviour: cooperativity, allostery, regulation, exchange, communication or signal transfer. The role of a new language and concepts is important for the development of a new discipline such as supramolecular chemistry.<sup>9</sup> Similarly to the specific pairing observed in the DNA double helix and to enzyme-substrate recognition processes, when two or several chemical entities are interacting, a phenomenon of information-recognition is established that involves atoms interacting in the expected topological disposition. This implies that one species senses and recognizes another due to the spatial identity of the partners. This recognition becomes of importance when it is *selective*. *Selection* means here that the receptor is able to choose its partner among various substrates.

Since the second season, molecular information-selective recognition processes have been leading to the concepts

of molecular organisation and assembly as they are known in biological systems. Control of geometry and rigidity of artificial molecules allows the building of molecules which can *spontaneously* generate well define molecular structures. ‘*It is designed assembly into a discrete molecular species, as compared to the spontaneous formation of molecular layers, films, membranes, etc.*’ New words and concepts different from the previous ones are appearing at this level: molecular engineering, self-assembly, self-organisation, tectons, dissipative structures, instructed components, programmed molecules, automorphogenesis, modular synthesis, synthesis beyond the molecules, poly-molecular shapes, etc. All the above concepts open new perspectives in materials chemistry. They are becoming supramolecular materials able to be explained and exploited by supramolecular rules. For example, a Langmuir-Blodgett film is often due to Van der Waals interactions between long alkyl chains while the polar head of the molecule is maintained on the water by hydrogen bonding.

Chemical transformations of these materials can lead to novel roles that make use of the principles of *molecular recognition*. In short, a phenomenon which was first observed by physicists can be studied and used by supramolecular chemists to invent similar artificial systems with specific applications. Basically, supramolecular chemistry seems to further dissolve the barriers across disciplines. Similarly, biologists explain natural processes on the basis of the formation or the disruption of non-covalent bonds between molecules, such as hydrogen bonds between the two strands of the DNA double helix. Recent applications of these molecular recognition principles to assemble DNA nanomaterials and nanomachines offer an archetype of the cross-talk between biology and supramolecular chemistry [62–65]. These supramolecular assemblies could be employed within organisms as delivery vehicles for therapeutic agents [66]. Now in its third season, supramolecular chemistry also focuses on the preparation of artificial genetic systems [23]. A step in that direction is to prepare programmed chemical systems that can break or form non covalent-bonds as determined by exterior conditions. This period also brings new words and concepts, influenced by the vocabulary of biology, such as [59, 60, 67]: self-replication, chemical evolution, programmed matter, complex matter, dynamic-reversibility, adaptive-evolutive chemistry, chemical and species selection (in the Darwin sense), Darwinian molecules, from inanimate to animate matter etc.

### Emergence of complex properties from simple elements: bottom-up and top-down approaches

Systems evolution, organisation and self-organisation, programmed and complex systems, complexity and

<sup>9</sup> According to J.-M. Lehn: ‘Definitions have a clear, precise core but often fuzzy borders, where interpenetration between areas takes place. These fuzzy regions in fact play a positive role since it is often there that mutual fertilization between areas may occur. This certainly also true for the case at hand, the case of supramolecular chemistry and its language’ and language seems to be one of the driving forces that allows ideas to come. For the evolution and need of concepts and new names for chemistry to advance see also: Shaik [89] and Childs [90].

emergence of systems, dynamic assemblies, adaption capacity, evolution, selection, and so on are concepts currently under investigations in several disciplines, including supramolecular chemistry. Before coming to the subject of the emergence of supramolecular chemistry, we shall give some definitions and concepts of *emergence* and *complexity*, which are intimately connected to supramolecular chemistry.

John Stuart Mill (1806–1873), a British philosopher and political economist, is credited to be at the origin of the concept of some logical organization or emergence connected with life with the following words found in *A System of Logic*: ‘All organized bodies are composed of parts, similar to those composing inorganic nature, and which have even themselves existed in an inorganic state; but the phenomena of life, which result from the juxtaposition of those parts in a certain manner, bear no analogy to any of the effects which would be produced by the action of the component substances considered as mere physical agents. To whatever degree we might imagine our knowledge of the properties of the several ingredients of a living body to be extended and perfected, it is certain that no mere summing up of the separate actions of those elements will ever amount to the action of the living body itself.’

The word ‘emergent’ was first used in 1875 to describe the concept by George Henry Lewes (1817–1878), a British philosopher in *Problems of Life and Mind*: ‘Every resultant is either a sum or a difference of the cooperant forces; their sum, when their directions are the same – their difference, when their directions are contrary. Further, every resultant is clearly traceable in its components, because these are homogeneous and commensurable. It is otherwise with emergents, when, instead of adding measurable motion to measurable motion, or things of one kind to other individuals of their kind, there is a co-operation of things of unlike kinds. The emergent is unlike its components in so far as these are incommensurable, and it cannot be reduced to their sum or their difference.’

Nevertheless, emergence is a difficult concept to describe with a single definition [68]. According to Halley and Winkler [69], this may come from the fact that emergence is ‘a phenomenon that can exist across many scales of organization, ranging from the microscopic (atoms and molecules) to macroscopic (organisms, species, and ecosystems)’. Similarly, Corning says [70]: ‘Among other things, emergence has been used by physicists to explain Bénard (convection) cells, by psychologists to explain consciousness, by economists and investment advisors to explain stock markets behaviour, and by organization theorists to explain informal ‘networks’ in large companies.’

In spite of these difficulties, a simple definition of emergence can be implied from Aristotle’s famous saying:

‘the whole is bigger than the sum of the components’. Indeed, molecules are a system of atoms. Due to covalent bonds they are individual entities not only depending on the property of the constituent atoms but also on their arrangement in a particular molecular framework. A large number of molecules that differ in size, shape and structure are known, ranging from small molecules like methane, to synthetic polymers and biological macromolecules. Molecules are thus able to form molecular assemblies or systems of individual molecules assembled together to give supramolecular systems. The structural and functional properties of molecular assemblies are not depending on the individual property of the molecules they are formed with. They are better explained as a result of the particular organization of individual molecules rather than the knowledge of the individual properties. For example, the first crown-ethers were able to dissolve metal-salts in organic solvents in which they were insoluble [6]. Submitted to a complexation-dissolution process the metallic-salt acquired a different property (here the solubility in organic solvents) than when single [6]. Similarly, the presence of ethers crowns is able to activate anionic polymerisation due to the complexation of the counter-ion [71]. In this sense, supramolecular systems offer emergent properties due to host-guest and recognition [6].

In short, the term of ‘emergence’ becomes characteristic of a system of individuals which exhibits properties that *emerge* from the interactions between its constituent elements and which are not in evidence in any of its constituent components. This means that components can be simple as long as their interaction potential is rich. Synergies due to interactions between molecules are also a good example of such emergence. A supermolecule is built and defined as an ensemble of interacting molecules. A supermolecule is at a *higher* level than a molecule, which itself is at a higher level than an atom, which itself is at a higher level than its protons, neutrons, and electrons constituents, and so on. Every level is a system of preceding systems. This approach of seeing supramolecular chemistry from the low level to higher is *bottom-up*. This bottom-up emergence of supramolecular chemistry appears as a *hierarchy of levels*. Jones defines and generalizes this emergence as: ‘Each level cannot come into being until the previous level is fully established and we see this epigenetic sequencing as the history of the universe. Since the Big Bang, nothing that exists can have been made from something other than what previously existed. Each level of object in the universe is emergent upon its constituents’ [68]. This comes from the organization of the constituents. Let us call this emergence the ‘original’ emergence of supramolecular chemistry simply due to its definition, since the prefix ‘super’ means above or beyond. This emergence by hierarchy level is also applicable to synthetic molecular

assemblies which are designed and programmed by chemists. This emergence is directed by interactions, signal-information, and recognition-selection corresponding to the first two overlapping phases in the description given by Lehn. We could refer to this emergence as the *bottom-up emergence*.

In a recent paper [72], Ryan defends the idea that emergence is coupled to scope and not to hierarchy level. He explains that *'since its application, emergence has been explained in terms of levels of observation'*. He shows that this approach—the use of emergence hierarchy—has led to confusion, contradiction, and incoherence. *'When the concept of level is replaced by a framework of scope, resolution and state, the confusion is dissolved'*. If one looks at the development of supramolecular chemistry and the use made of the accompanying concepts, a second type of emergence appears. Now, the supramolecular chemistry concepts are applied to molecular ensembles that have not been built in a specific manner by step-by-step organic and supramolecular syntheses. This approach may correspond to a *top-down* approach. This top-down emergence is coupled to the scope of the chemistry of condensed matter (for instance), living systems and life, where it is rather a diffusion and application of supramolecular concepts across different disciplines such as physics, biology, biochemistry, pharmaceuticals, and medicine. This has been termed by Lehn as a *'supramolecular science'*.

### Emergence(s) of supramolecular chemistry in literature

Emergence of supramolecular chemistry has been first suggested by Lehn [11]: *'Since macropolycycles contains intramolecular cavities delineated by molecular segments which may bear various sites for binding and reaction, the most fascinating aspects of their chemistry lie in their ability to form inclusion complexes, to bind selectively substrates, and eventually to perform transport or reactions on the bound substrate? Thus a field of supramolecular chemistry emerges which, based on intermolecular binding forces, and expands over molecular recognition processes, receptor chemistry, carrier design, and molecular catalysis.'*

More recent papers deal with supramolecular chemistry and complexity. *'We believe that the time has come for chemists to firmly embrace complexity and we make a case of systems chemistry as a new discipline that looks at complex mixtures can give rise to interesting and desirable emergent properties—properties that result from the interactions between components acting in isolation'* [73]. This emergence corresponds to the bottom-up emergence.

In some papers, emergence is accompanied by self-organization and complexity. 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 the living matter and thinking matter, up the ladder of complexity.

Complexity implies and results from multiplicity of components, interaction between them and integration, correlation, coupling and feedback. The species and properties defining a given level of complexity results and may be explained on the basis of 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 term of cells, organisms in terms of tissues and so on, up to the behaviour 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 reducible to those of lower levels.

Supramolecular chemistry provides ways and means for progressively unravelling the complexification of matter through self-organisation....

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' [5].

Desiraju G. R. also adds [74]: *'Supramolecular chemistry is intrinsically a dynamic chemistry, in view of the lability of interactions connecting the molecular components of a supramolecular entity and the resulting ability of supramolecular species to exchange their constituents. The same holds for molecular chemistry when a molecule entity contains covalent bonds that may form and break reversibly, so as to make possible a continuous change in constitution and structure by reorganization and exchange of building blocks. This behaviour defines a constitutional dynamic chemistry that allows self-organization by selection as well as by design at both molecular and supramolecular levels. Whereas self-organization by design strives to achieve full control over the output molecular or supramolecular entity by explicit programming, self-organization by selection operates on dynamic constitutional diversity in response to either internal or external factors to achieve adaptation in a Darwinistic fashion.'*

*The merging of the features, information and programmability, dynamics and reversibility,*

constitution and structural diversity, point towards the emergence of adaptive and evolutionary chemistry. Together with the corresponding fields of physics and biology, it constitutes a science of informed matter, of organized, adaptive complex matter.' 'Closely allied to the notion of complexity is the idea of emergence. Emergent phenomena are structures, behaviours, events or patterns that arise only when a large number of individual agents (molecules, cells, water droplets, musical notes, ants, birds, people, and stars) somehow aggregate. Unless a critical number of agents act together, the phenomenon does not occur. An emergent property is created when something becomes more than the sum of its parts. The whole is difficult to predict from the properties of individual parts and it is no surprise then that supramolecular chemistry.... ...In supramolecular chemistry, one makes higher level aggregates (supermolecules) from lower level entities (molecules) using weak intermolecular interactions as a glue.'

Whitesides and Ismagilov write as well [75]: 'Additional understanding of complexity in chemical systems may also be developed by examining the behaviour of very simple systems—single molecules. Chemistry has relied heavily on the ability of ensemble of properties that are obtained through thermodynamics and statistical mechanics to make it unnecessary to consider the behaviour of individual molecules.... Understanding how properties of single molecules aggregate into the familiar average properties of macroscopic samples of chemicals will help to tease apart the threads of complexity in chemical systems.'

These quotes highlight an emergence that shifts from bottom-up to top-down, and from hierarchy to scope. In this case, emergence is coming from the primal concepts developed by supramolecular chemistry: complexation, molecular interactions, molecular recognition leading to the concepts of self-assembling, and self-organization and which are applied, verified, and magnified in different disciplines. These concepts are becoming active in other fields.

### Back to living systems

Lestel and Tkatchenko notice [11]: 'Nature, while being based on the multiplicity of ion-ion, ion-molecule, and molecule-molecule interaction modes, exploits this concept with increasing complexity, leading finally to living organisms capable of self-replication. Supramolecular chemistry suggests that if these interactions can be broken in the same way as they are made, a genuine constitutional

dynamic chemistry would be in operation, providing original structures capable of auto-repair, another property related to all living things'.

In another article, Graham Cairns-Smith declares [76]: 'Well, "life" is not a well-defined term. As implied at start of this piece it can be said to describe a sort of natural engineering that is a typical long-term product of natural selection'. In a sense, life has already figured out that a supramolecular strategy relying on attractive forces is the most efficient way to build and maintain every organism [77]. Supramolecular self-assembly enters the world of living systems because their elements are molecular. Supramolecular science is not explaining the origin of life but rather explaining the selectivity for life that could be expressed by its own concepts.

Ultimately, if one wants to apply supramolecular concepts and molecular selection to promote the evolution of living systems, one has to find ways to fill the gap between inanimate and living matters. This gap may be filled by an interplay between bottom-up and top-down approaches of supramolecular chemistry. For example, our deeper understanding of the supramolecular properties at play in Nature makes it tantalizing to create life from components able to self-associate, self-dissociate and self-replicate [78]. A major advance in that direction is the spontaneous condensation of activated monomers into DNA, RNA or alternative genetic systems, with hints toward non-enzymatic replication of genomes [79]. In addition, artificial vesicles made of fatty acids and containing nucleic acids were shown to be able to grow when fed with micelles, before dividing when subjected to gentle shearing, without releasing into the environment the genomic mimic that they contain [80]. Together, these examples draft a scenario of how life within cells could have arisen from inert materials.

The bottom-up emerging of the features of supramolecular systems (e.g., *information and programmability, dynamics and reversibility*) from the preliminary simple systems with subsequent *self-organizing and self-assembling systems* leads to *combinatory and structural diversity*. Points towards the top-down emergence of an *adaptive chemistry with molecular selection* can be applied to any existing systems not created by man. As noticed by Lehn, a 'further development will concern the inclusion of the arrow of time, i.e. of non-equilibrium, irreversible processes and the exploration of the frontiers of chemical evolution towards the establishment of *evolutive chemistry*, where the features acquired by adaptation are conserved and transmitted. In combination with the corresponding fields of physics and biology, chemistry thus plays a major role in the progressive elaboration of a science of informed, organized, evolutive matter, a *science of complex matter*'.

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