

# Emergences of supramolecular chemistry: from supramolecular chemistry to supramolecular science

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**Abstract** We describe the field of supramolecular chemistry as a consequence of the progress of chemistry from its premises to recent achievements. Supramolecular chemistry has been claimed to be an emergent field of research taking its roots in chemistry. According to the definitions of emergences related to hierarchy or more recently to scope, supramolecular chemistry is shown to have bottom-up or top-down emergences. The bottom-up emergence, directly related to hierarchy by definition, opens up the world of nanochemistry and nanomaterials while the top-down one, attributable to scope due to the implication of supramolecular chemistry in other fields of research, open the world of supramolecular biochemistry. Both emergences lead supramolecular chemistry to become a supramolecular science. Combining supramolecular chemistry with biology opens new direction in the study of life and its origin.

**Keywords** Atoms · Supramolecular chemistry · Emergence · Living systems · Natural selection

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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 cross-checking, of contradictions and this, even, in the exceptional cases where it occurs with a lighting 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 on 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])

Your reading of ‘Plenty of room’ will show you that, if we treat this paper as the 1959 blueprint of nanotechnology, then nanotechnology failed Richard Feynman. I suggest a different way to appreciate it, namely, by seeing that this fine paper by a fine man

was more important to nanotechnology in 1992 than it was in 1959 [4].

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 [5].

The emergence of any novel field of science is linked to the past [6].

Often the seedlings of change are already planted in former times, yet they remain dormant within a community. So it was with what became known as supramolecular chemistry. It is impossible to dissociate language from science or science from language, because every natural science always involves three things: the sequence of phenomena on which the science is based; the abstract concepts which call these phenomena to mind; and the words in which the concepts are expressed. To call forth a concept a word is needed; to portray a phenomenon, a concept is needed. All three mirror one and the same reality. The text is taken from Antoine Laurent Lavoisier. *Traité Élémentaire de Chimie*. (1789) and translated by the authors of Ref. [7].

It is enough to create new names, estimations and probabilities in order to create in the long run new things.

Friedrich Nietzsche. *The Gay Science*

Supramolecular chemistry is now ~50-years old field of research in chemistry. During the past 50 years, the interdisciplinary nature of supramolecular chemistry has appeared encompassing origins, foundations, principles, applications, and philosophy. The present work reviews chosen examples illustrating how other scientific disciplines such as biology have informed chemistry, leading to the emergence of supramolecular chemistry in, 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* (1907) was a vigorous opening to the art of the 20th century. Likewise, the pioneering work of Charles Pedersen [8], Jean-Marie Lehn [9], and Donald J. Cram [10] in the 1960s was an energetic impetus to chemistry, and in particular to organic chemistry, which was about 200 years old at that time [11–13].

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* [9]. 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 or not, 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.<sup>1,2</sup>

A first and simple example can already be given: ethanol–water mixtures have less volume than the sum of their individual components at the given fractions. Mixing equal volumes of ethanol and water results in only 1.92 volumes of mixture. This is explained by intermolecular forces ordering the molecules of ethanol and water mixed in such a way their volume is lowered at the molecular level.

The field of supramolecular chemistry is among one of the most interesting and promising ones in modern chemistry. 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' [14]. 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 new applications [15].

Supramolecular chemistry dealing with *supermolecules* has historical roots in organic synthetic chemistry. In the present work, we will show how the accompanying concepts and ideas of atoms, molecules, chemical transformations, synthesis, and other tools of organic chemists

<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, 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 is given in Simonson and Schlosser [110].

<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. [111].

have been developed to reach our present view of super-molecules. 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 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. One has to note here that whatever was done, organisation of thoughts was the main driving force to reach our present knowledge 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 started. 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

Clayton and Davies declare [16]: ‘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’.

The concept of *atom* was first proposed by Leucippus (ca. 5th century BC). The divisibility of matter was then

<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’ [112].

considered to have limits which were defined by atoms; the term ‘atom’ comes from the Greek word ‘*ατομος*’ or ‘*atomos*’, 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 *vacuum*.

During the Middle Ages (roughly 5th to 15th 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*. Probably following the simple ideas of Plato that as for instance heating a liquid gives vapours which can liquefy back by cooling. 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 ideas became of paramount.<sup>4</sup> 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. This period of time was important showing that men can not only isolate but also transform matter, like the Nature, and act as the Nature does.

<sup>4</sup> A recent account deals with the matter symbolized by alchemists and the evolution of alchemy to chemistry: see L. Fabbri [113].

## Modernisation 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 in *The Sceptical Chymist*, in which he criticized previous researchers for believing that salt, sulfur, and mercury were the ‘true principles of things.’ He advanced the view that the basic elements of matter are ‘corpuscles,’ or particles, of various sorts and sizes. He believed that these corpuscles were capable of arranging themselves into groups, and that each group constituted a chemical substance. He successfully distinguished between mixtures (substances mixed together) and compounds (chemically bonded substances) and showed that a compound can have very different qualities from those of its constituents. 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*.<sup>5</sup>

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

<sup>5</sup> According to H. H. Kubbinga [114] two first ‘molecular’ theories have been conceived by Isaac Beeckman (1588–1637), a Dutch philosopher and scientist, and Sebastian Basso (1573–?), a French physician and natural philosopher, introducing the concept of ‘substantial individuals’ (Beeckman, 1620) and ‘substantial species’ (Basso, 1620). Beeckman and Basso are also credited by Kubbinga to have anticipated the concept of isomers. Their theories gave quite important consequent concepts such as the ‘minima sui generis’ of Daniel Sennert (1592–1637), a German physician, the ‘particles’ of René Descartes (1596–1650), a French philosopher, mathematician and physicist, and Christian Huygens (1629–1695), a Dutch mathematician, astronomer, and physicist, the ‘monads’ of Gottfried Leibniz (1649–1716), a German philosopher and mathematician, the ‘molecules’ of Georg Ernst Stahl (1659–1734), a German chemist and physician, and the ‘particulae ultimate compositionis’ of Isaac Newton (1643–1727) an English physicist, mathematician, astronomer and chemist. In the same paper, H. H. Kubbinga also gives a reference indicating that the word ‘molecule’ has been introduced by Gassendi.



responsible for oxidation processes.<sup>6</sup> 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 or have *affinities* with an infinite number of other elements, but rather would combine in a specific manner. This association or organization of elements 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’.<sup>7</sup>

<sup>6</sup> The existence of the ‘phlogiston’ (Greek *φλογιστόν* *phlōgiston* = burning up, from *φλόξ* *phlōx* = fire) as the fifth element with air, earth, fire and water, was first proposed in 1667 by German physician and chemist Johann Joachim Becher (1635–1682) to explain processes such as combustion and the rusting of metals. He published his *Physical Education*, which was the first mention of what would become the phlogiston theory. In his book, Becher eliminated fire and air from the classical element model and replaced them with three forms of earth: *terra lapidea*, *terra fluida*, and *terra pinguis*. *Terra pinguis* was the element which imparted oily, sulfurous, or combustible properties. *Terra pinguis* was a key feature of combustion and was released when combustible substances were burned. In 1703, Georg Ernst Stahl (1659–1734), a German physician and chemist, proposed a variant of the theory in which he renamed Becher’s *terra pinguis* to *phlogiston*, and it was in this form that the theory probably had its greatest influence. Lavoisier and before him Mikhail Lomonosov (1711–1765) a Russian chemist who had expressed his ideas during 1748 and proved them by experiments, showed that in fact phlogiston does not exist and that combustion consumes the oxygen of the air. The German philosopher Immanuel Kant (1724–1804) was first in favor of the phlogiston theory of Stahl but later supported the Lavoisier’s proposal of oxygen consuming. The no-need of phlogiston was expressed in the *Méthode de Nomenclature Chimique* of de Morveau, Lavoisier, Bertholet and de Fourcroy in 1787 and in the *Traité Élémentaire de Chimie* of Lavoisier in 1789.

<sup>7</sup> The *Méthode de Nomenclature Chimique* and the proposal made by Berzelius of designating the elements by the one or two first letters were not only useful for the communication between scientists but also they provide the memory with what is named a *double mediation*: tools and organs. This is mentioned in the preface of the books by Lavoisier who noted that due to the simplification of new naming of substances will provide the chemists with a new common language with no possible misinterpretation. This new naming is necessary to learn and give a mathematic-like logic to chemical science in such a way that names or words—directly based on experiments—are giving birth to ideas. That means at the same time that memory is organised and organising. And this leads Lavoisier to write 2 years later the *Traité Élémentaire de Chimie* in which he developed the concepts of modern chemistry. Examples can be found in other fields than chemistry. For example, it has been shown that the effect of the appearing of script was not to memorise oral culture but to introduce a graphic rationality (<http://www.mediologie.org>). See also Merzeau [115] and Goody [116].

## Classification of atoms

Throughout the 19th 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.<sup>8</sup> 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 (see footnote 8).

<sup>8</sup> By the middle of the 19th century chemists generally understood that chemical elements can be grouped together in separate classes according to similarities and dissimilarities in their properties. For example alkali metals are flammable and form cations while halogens are poisonous and form anions. A recent article has appeared on the subject of atoms and molecules, and periodicity: Babaev and Hefferlin [117].

Archibald Scott Couper (1831–1892), a Scottish chemist, proposed an early theory of chemical structure and bonding. He developed the concepts of tetravalent carbon atoms linking together to form large molecules, and that the bonding order of the atoms in a molecule can be determined from chemical evidence. He published his *New Chemical Theory* in French in 1858. Johan Josef Loschmidt (1821–1895), an Austrian chemist and physicist, published in 1861 the *Chemische Studien I, Constitutionsformeln der organischen Chemie in graphischer Darstellung* in which he drew 241 molecular formulae very similar to the one in use nowadays. He was the first to propose the cyclic structure of benzene and aromatics pioneering, 4 years before, the ideas of Friedrich August Kekule (1829–1896). 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 20th 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 Böhr (1885–1962), a Danish 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.<sup>9</sup> 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 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 (‘The more precisely the position is determined, the less precisely the momentum is known in this instant, and vice versa’ said Heisenberg, uncertainty paper, 1927).<sup>10</sup> Linus Carl Pauling (1901–1994), an American chemist (Nobel Prize of Chemistry in 1954 and Nobel Prize of Peace in 1962), 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 two German physicists, Ernst Ruska and Gerd Binnig, and Heinrich Rohrer, a Swiss physicist 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

Footnote 9 continued

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. [118].

<sup>10</sup> Attempts to rationalize the periodic table have included reduction to quantum mechanics as well as approaches from mathematical chemistry. However quantum mechanics does not provide a conclusive means of classifying certain elements like hydrogen and helium into their appropriate groups. An alternative approach using atomic number triads is proposed and the validity of this approach is defended in the light of some prediction made via the information theoretical approach that suggests a connection between nuclear structure and electronic structure of atoms [119].

<sup>9</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

(<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’.<sup>11</sup>

<sup>11</sup> The molecular structure hypothesis—that a molecule is a collection of atoms linked by a network of bonds—was forged through experiments during the nineteenth century. It has continued to serve as the principal means of ordering and classifying the observations of chemistry. However, this hypothesis was not related directly to quantum mechanics which governs the motions of the nuclei and electrons that make up the atoms and the bonds. Indeed there was, and with some there still is, a prevailing opinion that these fundamental concepts, while unquestionably useful, were beyond theoretical definition. Chemists have an understanding based on a classification scheme that is both powerful and at the same time, because of its empirical nature, limited. Richard Feynman and Julian Schwinger have given a reformulation of physics that enables one to pose and answer the questions ‘what is an atom in a molecule and how does one predict its properties?’ It was demonstrated that this new formulation of physics, when applied to the topology of the distribution of electronic charge in real space, yields a unique partitioning of some total system into a set of bounded spatial regions. The form and properties of the groups so defined faithfully recover the characteristics ascribed to the atoms and functional groups of chemistry. By establishing this association, the molecular structure hypothesis is freed from its empirical constraints and the full predictive power of quantum mechanics can be incorporated into the resulting theory—a theory of atoms in molecules (AIM) and crystals.

AIM recovers the central operational concepts of the molecular structure hypothesis, that of a functional grouping of atoms with an additive and characteristic set of properties, together with a definition of the bonds that link atoms and impart the structure. Not only does the theory thereby quantify and provide the physical understanding of the existing concepts of chemistry, it makes possible new applications of theory as for example enabling one to perform on a computer, in parallel to experiment, everything that can now be done in the laboratory thus linking together the functional groups of theory. AIM enables one to take advantage of the single most important observation of chemistry, that of a *functional group* with a characteristic set of properties. This outlines and illustrates the topological basis of the theory and its relation to the quantum mechanics of an open system. However AIM cannot be directly observed by experiment, nor can one measure enough properties of an atom in a molecule to define it unambiguously. They are multiple ways to partition molecules into atoms that are consistent with various observed chemical trends and experimental data. And some authors emphasized that because of this ambiguity atoms in molecules remains a *noumenon* in the sense given to this word by Immanuel Kant [120]. Similarly, ‘Few people seriously argue that atoms and molecules are fictitious, but there is no picture or model of an atom that is equivalent to a photograph of an object at the human scale’. These words are taken from a publication of Chris Toumey dealing with the relation between an object and an image of the object [121]. He asks the questions about representations of atoms and molecules by STM and AFM techniques which are seen as indirect techniques: What is a faithful reproduction? How do technical processes affect the image? Nanoscale images evoke these issues. To enhance our visual knowledge of nanoscale objects he revisits earlier cubist theory. This lead to suggestions in a neo-cubist spirit for making and seeing nanoscale structures [121, 122].

## Organic chemistry and supramolecular chemistry share similar roots

Supramolecular chemistry and organic synthetic chemistry, which itself derives from studying the chemistry of living systems share similar roots. And, in some part, supramolecular chemistry is reliant on inorganic chemistry given the prevalence of inorganic systems in biology (this point will be not discussed in this essay). 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 [17, 18]. Until the end of the 18th century, chemists were working without differentiating mineral and organic bodies. When publishing his *Cours de Chymie* in 1690, Nicolas Lémery (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. Mineral and organic chemistries were two distinct fields with no possible communication in experiments. 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.<sup>12</sup>

#### Organic synthesis during the 20th century: creation and invention

During the 20th century, organic chemistry grew up, affording a large number of organic reactions and products for industry, companies and fundamental research. Mainly organic syntheses were devoted to the preparation of *natural substances*. In 1965, the American Robert Burns Woodward (1917–1979) was awarded the Nobel Prize of Chemistry for the total synthesis of vitamin B12 [19]. This achievement demonstrated that organic chemists were able to synthesize complex molecules by forming *covalent* chemical bonds. In parallel, the synthesis of *unnatural* organic 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 [20]. These ideas were reflected in the words of Nicolaou [17]: ‘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’. The words of Nicolaou are reminiscent of the words of Picasso: ‘One has to use Nature and even to be stronger than Nature’. 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’ [21].<sup>13</sup> And he gave as one example, the first preparation of interlocking molecules<sup>14</sup> thanks to the concept of

chemical topology and topological isomerism [22–24]. Importance of topology was also invoked as early as 1941 by Paul John Flory (1910–1985)<sup>15</sup> who recognised in theory that the branched structures of three-dimensional polymers should engender unique physical and chemical properties [25–27]. The topological importance of branched structures is now developed by chemists dealing with dendrimers and their very unique properties.<sup>16</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’ [28].<sup>17</sup> It is in this context of a healthy development of organic synthesis, that about 40 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* [29]. Twenty years later, in 1987, Charles Pedersen (1902–1979) [8], Jean-Marie Lehn (born, 1939) [9], and Donald J. Cram (1919–2001) [10] were awarded the Nobel Prize in chemistry in recognition of their pioneering work in supramolecular chemistry. The scheme below gives the different dates of publications with the complexing receptor molecules of Pedersen, Lehn and Cram with their own principle and the evolution in the gain of selectivity of complexation of cations.

Footnote 14 continued

review on these molecular systems has been published by Kay et al. [124].

<sup>15</sup> Paul John Flory (1910–1985) is an American chemist who was known for his prodigious volume of work in the field of polymers and macromolecules. He was a leading pioneer in understanding the behavior of polymers in solution, and won the Nobel Prize in Chemistry in 1974 ‘for his fundamental achievements, both theoretical and experimental, in the physical chemistry of macromolecules.’

<sup>16</sup> Dendrimers (greek *dendron* = tree) are macromolecules with a tree-like structure. They are synthetically built from a core with repeating units as molecular branches and terminated by end groups. The preparation of such branched structures demands the use of particular building blocks with appropriate stereochemistry and multiple, equivalent reaction centres. See for example Newkome et al. [125].

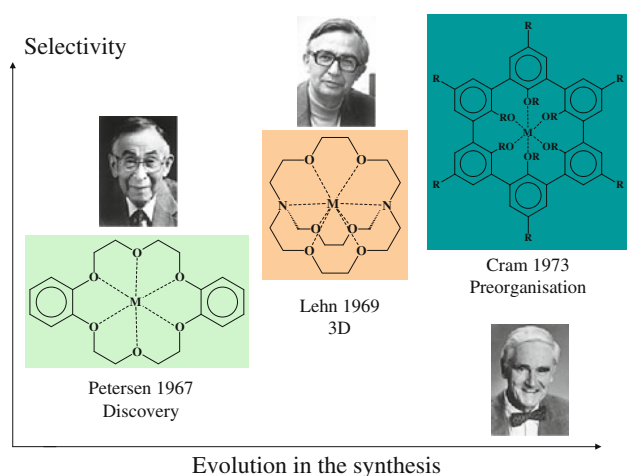
<sup>17</sup> This sentence of Sismour and Benner is reminiscent of the concept of double mediation that is memory is organised, organising and in the same run involved in the creation processes of synthesis of molecules. Another very important concept used by the memory of organic chemists is the use of curly arrows to represent the movement of electrons. Curly arrows are currently used for both explaining reaction mechanisms and to anticipate reactions. Robert Robinson (1886–1975), Nobel Prize for Chemistry in 1947 is credited for the invention of this useful tool [126]. The atomic theory developed during the first half of the twentieth century was not readily accepted by all organic chemists and its acceptance has been made difficult by French organic chemist [127].

<sup>12</sup> Marcellin Berthelot noted that ‘chemistry creates its own objects’. These words are important in the sense that due to the possibility given to chemists to develop reactions for synthesis from simple elements—and one can say now from the table of elements of Mendeleiev—the work of chemists has been the reverse to the achievement of alchemists and chemists until the beginning of the 20th century. In other words chemists have analysed and separated chemical substances into simple elements that have been used further to prepare molecules with higher structures, successively going from complex to simple and from simple to complex.

<sup>13</sup> For further reading on ‘molecular beauty and chemists’ imagination see also: Spector and Schummer [123].

<sup>14</sup> The study of interlocked molecules is now an emerging field of research dealing with catenanes and rotaxanes. Catenanes are chemical structures in which two or more molecules are interlocked while in rotaxanes one or more macrocycles are mechanically prevented from dethreading from a liner unit by bulky ‘stoppers’. Such interlocked systems that at the beginning were curiosity or challenge of chemists are now related to molecular machines and present applications in molecular devices. A wide and important





### 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* [30]: ‘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’ [14].

This statement reflects the development of supramolecular chemistry and its relationship to the stereochemistry and topology of molecules, which dates back to the 19th 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 comes from the fact that chemistry was written on paper and chemists could not figure out that molecules actually had three dimensions. Probably chemists were focussing on chemical formulas (by analysis of matter) rather than their structure representation. In 1865, German chemist August 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 tetra-valent 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 and isomerism 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>18</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. That cyclohexane is not flat but having a 3D structure was first proposed as early as 1890 (in *Berichte*) by Hermann Sachse (1862–1893), a German scientist, based upon trigonometric proofs deriving from the tetrahedral angle of 109.47° at carbon, and producing what he termed stainless rings. To explain, he published instructions for folding a piece of paper (similarly to the cardboards of van’t Hoff) to represent two forms of cyclohexane he called symmetrical and unsymmetrical (now called chair and boat conformations). One can propose that was as the birth of *molecular architecture* in chemistry and the comparison of atoms with bricks became real.<sup>19</sup> The

<sup>18</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 [128].

<sup>19</sup> One can ask the question that if matter is made of atoms and molecules why the three dimensions of crystals has not been taken into account to figure out that molecules being the smallest part of them have three dimensions too. Crystals have long been collected, sold, manufactured, and admired for their regularity, but they were not investigated scientifically until the 17th century. Johannes Kepler (1571–1630), a German mathematician, described in *Strena seu de Nive Sexangula* (1611) the hexagonal symmetry of snowflake crystals as a regular packing of spherical water particles. Nicolas Steno (1638–1686), a Danish anatomist and geologist, showed in *De solido intra solidum naturaliter contento dissertationis prodromus* (1669) that the angles between the faces are the same in every sample of a particular type of crystal opening the road to crystal geometry or

event of the third dimension was important for example to describe and synthesize sugars by Emil Fischer.

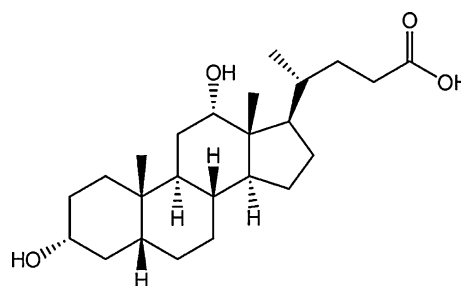
It took a while for chemists to comprehend the implications of these 3-dimensional molecular models, and Pierre Laszlo has stressed that chemists were playing as children with them [31]. The use of molecular models proved to be so practical that many calculations-based molecular modelling softwares were programmed to allow many kinds of representations of various types of molecules, as well as to calculate distances between atoms, to determine the thickness of molecules, 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 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 [32], Hoffman and Laszlo [33], and Goodwin [34]. Significantly, chemists ‘make visual imagery for problem-solving, in order to sort out and organise information to find analogies, to think’ [33].

Nowadays, 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 [35]<sup>20</sup> and read a formula like an ideogram [36, 37]. They have developed a *visual thinking* [38].<sup>21</sup> A direct consequence of visual thinking is that organisation and creation are connected [38].

Thus, organic chemists enhance their ability to think and create visually, and communicate ideas in visual ways. For example, the following formula:



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’

Footnote 19 continued

crystallography. Later on, René Just Haüy (1743–1822), a French mineralogist, reported in *Essai d'une théorie sur des cristaux* (1784) that every face of a crystal can be described by simple stacking patterns of blocks he named ‘molécules intégrantes’ of the same shape and size: crystals are a regular three-dimensional array of atoms and molecules in which a single unit cell is repeated indefinitely along three principal directions. As a consequence in 1839, William Hallowes Miller (1801–1880), a British mineralogist and crystallographer, was able to give each face a unique label of three small integers, the Miller indices which are still used today for identifying crystal faces. In the 19th century, a complete catalogue of the space groups of a crystal was elaborated by J. Hessel, A. Bravais, Y. Fyodorov, and A. Schönflies. In 1880, William Barlow (1845–1934), an English crystallographer, proposed structural models of NaCl and CsCl that were later confirmed using X-ray crystallography. All these studies were made on mineral crystals. One can assume that no link was made at that time between three dimensions of mineral matter and organic molecules. The studies on crystals were mainly based on mathematics and reasoning while studies on the matter was mainly based on obtaining a chemical structure by analysis. The first structures of organic molecules were lately published by William Lawrence Bragg (1890–1971), an English physicist in 1921 thanks to X-ray techniques [129].

<sup>20</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 Caley [35, 130, 131].

<sup>21</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 [38]. A recent book has appeared in which A. J. Rocke emits the thesis that chemists have been progressing in defining molecular structures because ‘human minds work far more visually, and less purely linguistically than we realize’ [132].

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 (<http://www.nzp.co.nz/products.php?cid=2&pid=2>). Then, a different (supramolecular) use of DOCA is as a biological detergent to lyse cells and to 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 centres* 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’ [39].

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

Supramolecular chemistry, its concepts and vocabulary were developed since the 1960s [15]. 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. [40].), 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 [41–45]. 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) [46]. 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. But it stems also on the presence of hydrogen bonds to maintained the pairs: two for A:T and three for G:C. This observation was the opening of the world of *digital-like information* in molecules and important was the fact that the molecular information allowing the molecules or parts of molecules to communicate was *inherent* information. 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 [47, 48].

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 19th century, Emil Fischer (1852–1919), a German chemist, coined his famous *lock-and-key* analogy to picture the specificity of enzyme reactions, which are a molecular premise of life [49, 50]. The enzyme was considered to be a rigid catalyst to which the substrate had to fit as a key into a lock.<sup>22</sup> Over the years, however, it became apparent that a rigid fit between preformed molecular structures could not explain all aspects of enzyme catalysis [49, 50]. 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

<sup>22</sup> The use of ‘key and lock’ complementarity was also often used by German physiologist Paul Ehrlich (1854–1915; Nobel Prize in 1908). This is mentioned in 1946 by Pauling [133] in an article showing how many basic problems of biology—nature of growth, mechanism of duplication of viruses and genes, action of enzymes, mechanism of physiological activity of drugs, hormones, and vitamins, structure and action of nerve and brain tissue—find answers in the knowledge of molecular structure and intermolecular reactions. Many examples are given which are explained by the underlying concept of molecular recognition involving ‘shape and size and the detailed nature of intermolecular forces.’ And in his paper dated of 1946, Pauling uses words and expressions that will be used later on to describe in some parts contemporary chemistry, as exemplified: molecular architecture, size and shape, intermolecular forces, duplication, storage battery, machinery, ring gear, brake pedal, hydrogen bonds, Van der Waals forces, surface regions, complementary in structure, fit into the molecule of the recipient combination, specificity, and, fit into the cavity [133].

molecules? In 1958, Daniel E. Koshland (1920–2007) formulated the theory of the *induced fit* to account for these observations [51, 52]. 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 [53]. 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 complementarities of shapes and functions was introduced by Donald Cram (1919–2001) [9]. The fact that a receptor has to rearrange itself to reach the best fit is often translated in terms of entropy. Recently, Julius Rebek (born, 1944), an American chemist, identified new types of molecular stress encountered by includes molecules: bending, straightening, squeezing, grinding and compression. He declared that for some flexible alkanes in reversibly formed capsules a fluid model of recognition can be proposed that is neither lock-and-key nor induced fit. Instead, the guest assumes the shape that best fills the available space, even if conformations to higher energy are required [54, 55].

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 [56, 57]. The words of the original publication are as follows [56, 57]: ‘indirect interactions exist 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’. 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 and release a ligand), only after an effector molecule would bind [58].

In parallel to these advances in biology, organic reactions in the solid state were widely investigated 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 is explained by the crystal structure of and the mutual disposition of molecules in the starting material [59]. 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. This means that in some cases molecular crystals are organizing themselves to react. This was rather in contradiction with the fact that molecules need kinetic energy to react. 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’<sup>23</sup> for creating absolute asymmetric syntheses and obtaining highly selective reactions [60]. The transition state is no longer an abstraction associated with an energy diagram but a geometrical reality in which a portion of the pathway of atoms from the starting compound to the product can be drawn. Important was the observation that the crystal is building itself by inherent forces to give rise to a selective reaction. The example of cooperativity in a reaction within a crystal is similar to that observed for a crystal which has piezoelectric properties described by the French philosopher Gaston Bachelard (1884–1962) in *Le Rationalisme Appliqué*. The author notes: ‘The crystal obtained by techniques so carefully designed is not only matter endowed with a geometrical character. It is an apparatus where an operation is performed.’ Further, he states: ‘The physics eliminates the quantity which was used to establish relations to focus upon the concept of the relations themselves.’

In the 1960s, French theoretical physicist, Pierre-Gilles de Gennes (1932–2007; Nobel Prize in Physics 1991), who was working on magnetic and superconductive materials, became interested in liquid crystals and found analogies between liquid crystals<sup>24</sup> and superconductors as well as

<sup>23</sup> Molecular engineering was first introduced by A. I. Kitaigorodskii as the concept of close packing for molecular crystals giving to molecules shape and volume [134, 135]. Molecular recognition in organic crystals is nowadays in various subjects of research [136].

<sup>24</sup> In 1888, the Austrian chemist Friedrich Reinitzer (1857–1927), working in the Institute of Plant Physiology at the University of Prague, discovered a strange phenomenon. He was determining the melting point of a derivative of cholesterol and he noticed two melting points. At 145.5 °C the solid melted into a cloudy liquid which existed until 178.5 °C where the cloudiness disappeared, giving way to a clear transparent liquid. He turned for help to the German physicist Otto Lehmann (1855–1922) who realized that the cloudy liquid is *new state of matter* (three states were known: solid, liquid, and gas) and coined the name ‘liquid crystal’, illustrating that it was something between a liquid and a solid. In liquids the properties are isotropic, i.e. the same in all directions. In liquid crystals they are not. Liquid crystals were already submitted to supramolecular concepts.



magnetic materials. Important was the finding that liquid crystals present anisotropic phases with ordered arrays of components [61].

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 (born, 1927), a German biophysicist, 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’ [62]. 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-organising chemical processes in generating complex molecular arrangements in relationship to selection and evolution of RNA or DNA molecules. Following his work, Hans Kuhn (1919-born), a Swiss chemist described in a report a possible pathways leading to self-organisation and evolution of genetic apparatus already noting that molecules with reassumed tertiary structure matching molecules will form aggregates in which replication and reproduction may occur [63]. In parallel, in the beginning of the 1960s, Hans Kuhn thought about a new paradigm in chemistry: the synthesis of different molecules which fit structurally into each other in such a way that they form planned functional units (supramolecular machines) [64]. His theoretical approach of evolution of genetic apparatus and the unifying paradigm of constructing supramolecular machines lead him to assume that the skill of chemists who prepared molecular machines is replaced in origin of life by very particular conditions given by chance in a very particular location on the prebiotic earth and elsewhere in the universe driving process.

A new structure resulting from self-organisation was called a ‘dissipative structure’ because it occurs spontaneously and is directed or controlled by a 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 Belgian 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* [65]. In a quite different field of research, some topological

behaviours and dynamic systems are also investigated by the French mathematician René Thom (1923–2002) [66]. The catastrophe theory [66–69] 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 equilibriums, 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 [66–69]. Although these few last examples are not directly related to ‘pure’ chemistry they may have some influence in the thinking of pionniers in supramolecular chemistry.

Besides these important events that can be considered as a deep and common knowledge surrounding the scientific community at that time, some works were *dans l’air du temps* with a flavour of supramolecular chemistry. During the 1950s–1960s, a German chemist, Friedrich Cramer (1923–2003), developed the chemistry of natural doughnut-shaped molecules named cyclodextrins (CD’s) as matrices for inclusion in solution and solid state by interactions of the substrate with their hydrophobic pocket and/or by hydrogen-bonding. In a paper of 1967 he reviewed inclusion compounds of CD’s [70]. Inclusion occurs because the CD’s can combine to form cylinders which accommodate the ‘guest’ molecules forming ‘channel inclusion complexes’. Mimicking enzymes pocket with the formation of E(nzyme)–S(ubstrate) complex, CD’s were also used to catalyse some reactions in a similar way as living systems. Cramer also introduced in this paper the word ‘machinery’ to describe the whole molecular process [70].

Another very close example of a supramolecular behaviour, dated from 1968, is probably the encapsulation of halide ions by macrobicyclic amines in their ammonium forms. During the studies of the conformation and prototropy in diazabicycloalkaneammonium ions, Park and Simmons show evidence of the encapsulation of an anion in a macrobicyclic structure [71–73]. They named the halide complex ‘katapinate’ from katapinosis (Greek, *καταπινω* = swallow up, engulf) to describe the ‘diffusion of molecules into a larger molecule with a sensible cavity to give a discrete molecular species’ [73]. This work gave probably rise to the supramolecular chemistry dealing with anion complexation.

### The three seasons of supramolecular chemistry

According to Lehn [74]: ‘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 preorganisation 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.<sup>25</sup> 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 [5, 6, 75] and are reflected by the words of the title of an important review article of Gale [76]: 'Supramolecular chemistry: from complexes to complexity'. 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. But, the larger are the molecules the stronger are interactions between them. These interactions are for instance: electrostatic bonds, Van der Waals forces, dipole–dipole interactions, hydrogen-bonds.<sup>26</sup> To these bonds we shall add coordination metal bonding. New definitions and concepts, and language<sup>27</sup> appear [15]: 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, cryptophanes, and cucurbiturils. 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>28</sup> Similarly to the specific pairing observed in the DNA double helix and to enzyme–substrate recognition processes [77], 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.' [74]. 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, polymolecular shapes, molecular self-assembly etc. All the above concepts open new perspectives in materials chemistry as for example nanoparticles. They are becoming supramolecular materials able to be explained and exploited by supramolecular rules. For

<sup>25</sup> Self-organisation is manifested in any *complex* system, which is in any system rich in interactions between its elements. Such systems are found in the physics of condensed matter, chemistry, biology, economics, social sciences, computer sciences etc. It is the complexity that is essential for the emergence of new phenomena, and self-organisation is the most striking but not the only example. The word 'complexity' comes from the Latin roots: 'com' meaning 'together', and 'plectere' meaning 'to plait'. Like most of the concepts in chemistry, the concept of complexity seems rather fuzzy and even subjective. Complexity is so wide-ranging that nobody knows quite how to define it, or even where its boundaries lie. In fact there are different kinds of complexity and no single concept could embrace all the aspects of complexity. Scientists generally agree that the more complex the system, the less predictable it is. A typical complex system is one for which at least some of its global behaviors 'that result cannot be predicted simply with the rules of the underlying interactions': see the excellent and informative chapter of Bonchev and Seitz [137].

<sup>26</sup> Some molecular interactions were known from earlier 20th century and hydrogen bonding was termed as a weak bond in the case of water and ammonium hydroxide [138, 139].

<sup>27</sup> 'It is impossible to dissociate language from science or science from language, because every natural science always involves three things: the sequence of phenomena on which the science is based; the abstract concepts which call these phenomena to mind; and the words in which the concepts are expressed. To call forth a concept a word is needed; to portray a phenomenon, a concept is needed. All three

Footnote 27 continued

mirror one and the same reality'. Antoine Laurent Lavoisier, *Traité Élémentaire de Chimie*.

<sup>28</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 is 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 [140] and Childs [141].

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. Many examples are known of a provoked building of molecular architectures by hydrogen bonding (the simplest is molecules of water maintained in ice) or by the steering of metal coordination such as metal–organic frameworks (MOFs).<sup>29</sup> Chemical transformations of these materials can lead to novel materials that use the principles of molecular recognition. In short, a phenomenon which was first observed by physicists or biologists 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 [78, 79]. These supramolecular assemblies could be employed within organisms as delivery vehicles for therapeutic agents [80].

Now in its third season, supramolecular chemistry also focuses on the preparation of artificial genetic systems. 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 [74, 81, 82]: 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

emergence of systems, dynamic assemblies, adaption capacity, evolution, selection, and so on are concepts currently under investigations in several disciplines, including supramolecular chemistry.<sup>30</sup> Before coming to the subject of

<sup>30</sup> Supramolecular chemistry has a vocabulary borrowed from other disciplines, mostly in human sciences. For example the word *entropy* is as much a part of the language of the physical sciences as it is of the human sciences. Fortunately or unfortunately, physicists, chemists, and sociologists use indiscriminately a number of terms that they take to be synonymous with entropy, such as disorder, probability, noise, random mixture, heat. And all use terms such as information, complexity, organisation, order, selection, etc. But they are used in different sense. For example a ‘supramolecular complex system’ is different from the concept of ‘complex system’. One can make a short glossary of the words in use and see that the confusion and mixing of the words have lead in parts to the ideas and concepts of supramolecular chemistry, the experimental evidence of the concepts being obviously given by chemists:

- *Self-organisation* is a process where the organisation of a system spontaneously increases without the control by the environment or an external system.
- *Selection* is the quantity of variety: some of the possibilities or alternatives are eliminated, others are retained. The result is a constraint: a limitation of a number of possibilities.
- *Systems Theory* is the transdisciplinary study of the abstract organisation of phenomena, independent of their substance, type, or spatial or temporal scale of existence. It investigates both the principles common to all complex entities, and the (usually mathematical) models which can be used to describe them.
- *Constraint* is a measure of the reduction of variety or reduction of freedom.
- *Complexity* (not a supramolecular complex!) has many definitions all falling short in one respect or another, classifying something as complex which we intuitively would see as simple, or denying an obviously complex phenomenon the label of complexity. These definitions are either only applicable to a very restricted domain, such as computer algorithms or genomes, or so vague as to be almost meaningless. Complexity comes from the Latin word *complexus*, which means ‘twisted together’. A complex is made of two or more objects, joined in such a way that it is difficult to separate them. Here is found the basic duality between parts which are at the same time distinct and connected. A system would be more complex if more parts could be distinguished, and if more connections between them existed.
- *Statistical entropy* is a probabilistic measure of uncertainty or ignorance and *information* is a measure of a reduction in that uncertainty.
- *Fit* is an assumed property of a system that determines the probability that that system will be selected, i.e. that it will survive, reproduce or be produced.
- *Dissipative structures* characterizes a system that exits far from thermodynamic equilibrium, hence efficiently dissipates the heat generated to sustain it, and has the capacity of changing to higher levels of borderlines. Many definitions and useful explanations can be found on the site: <http://pespmc1.vub.ac.be>.

At this level of such very simple glossary it would be to emphase that supramolecular chemists and cybernetics elaborate similar new concepts to improve their ability to communicate. For, example, L. M. Rocha introduced the concept of ‘Selected self-organization’ [146]. Self-organization is the spontaneous formation of well organized structures. They possess a large number of elements and variables and thus very large state spaces. But starting from some

<sup>29</sup> Metal–Organic Frameworks (MOF’s) are crystalline compounds consisting of metal ions or clusters coordinated to often rigid organic molecules to form one-, two-, or three-dimensional structures that can be porous. In some cases, the pores are stable to elimination of the guest molecules (often solvents) and can be used for the storage of gases such as hydrogen and carbon dioxide. Other possible applications of MOFs are gas purification, gas separation, catalysis and sensors. This field of research is in full development. Several names are associated to this research which can be found in review articles [142–144]. We would like to take the opportunity of this special issue dedicate to Pr Leonard F. Lindoy to mention one of his papers dealing with this chemistry [145].

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 [83]. According to Halley and Winkler [84], 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 [85]: ‘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 [8]. Submitted to a complexation–dissolution process the metallic-salt acquired a different property (here the solubility in organic solvents) than when single [8]. This property is reminiscent of the observation made in 1951 by Harned et al. [86] that nigericine, an antibiotic extracted from streptomycin’s, is a natural ionophore able to dissolve alkali metal cations in hexane. Also, the presence of ethers crowns is able to activate anionic polymerisation due to the complexation of the counter-ion [87]. In this sense, supramolecular systems offer emergent properties due to host–guest behaviour and recognition process.

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

Footnote 30 continued

initial conditions they tend to converge in small areas of this space. It seems that when supramolecular chemists directed the synthesis of a system towards a desire self-organisation they are describing experimentally the concept of selected self organization. Such a selected self-organization concept has been named by Lehn in one of his papers ‘Self-organization by selection’ [147]. Self-organization by selection occurs through a two-level self-assembly with components selection driven by the formation of a specific product in a ‘self-design’ fashion [147].



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' [83]. This comes from the organization of the constituents. Let us call this emergence the 'original' or 'natural' 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*. This emergence has to give rise in the future to a new field of research with a new emergence if research in supramolecular chemistry is maintained.

In a recent paper [88], 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 [9]: '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.' [89]. This emergence corresponds to the bottom-up emergence.

In some papers, emergence is accompanied by self-organization and complexity. According to Lehn [5]: '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' [6].

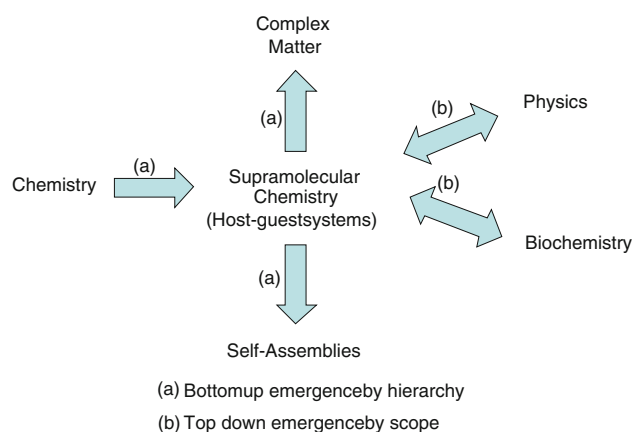
Desiraju also adds [90]: 'Supramolecular chemistry is intrinsically a dynamic chemistry, in view of the lability of interactions connecting the molecular components of a supramolecular entity and the resulting ability of supramolecular species to exchange their constituents. The same holds for molecular 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.' [90].

Whitesides and Ismagilov write as well [91]: '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 showing that chemistry, and more particularly supramolecular chemistry is a key component in all the scientific disciplines (see scheme below) [92].



### ‘All life is chemistry’

Before presenting the emergence of supramolecular chemistry in living systems it is to be mentioned that the thesis that ‘all life is chemistry’ has been written long time ago by the Belgian physician Jan Baptist van Helmont (1579–1644) in his *Ortus medicinae* (1648).<sup>31</sup> This statement is credited to Helmont in a paper of Wächterhäuser [93] who gives at the same time the experiment used to prove it. Helmont grew a willow tree and measured the amount of soil, the weight of the tree and the water he added. After 5 years the plant had gained about 164 lb. Since the amount of soil was basically the same as it had been when he started his experiment and he deduced that weight gain of the tree had come from water. Since it had received nothing but water and the soil weighed practically the same as at the beginning, he argued that the increased weight of wood, bark and roots had been formed from water alone. Of course we are very far away from what is known today on the growing of plants or any living system. But let us just comment that at anytime in the development of scientific knowledge, scientists, including chemists, have always drawn connections between science and life (for scientists) and between chemistry and living products (for chemists). Depending on time, the search for reproducing life is different. ‘Inanimate to animate’, a nowadays expression, was ‘mineral to organic’ in old times. As mentioned before, in 1828 Wöhler was the first to transform mineral matter into an organic compound. In 1913, the German chemist, Walther Löb (1872–1916) produced artificial glycine the simplest amino acid in natural proteins by reaction of a mixture of carbon dioxide, ammonia and water by means of a silent discharge [94]. Landmarks can be found on the search of the origin of life and the theory of biological evolution as seen by chemists. These are very well collected in the Wächtershäuser’s paper [93].

<sup>31</sup> van Helmont, J. B.: *Ortus Medicinae*, Amsterdam, 108–109 (1648). The exact reference is given by Pross [97].

The emergence of chemistry in biology is somewhat amazing. For the little history, looking at the development of chemistry and biology, one can note from the date of publications that Johannes Friedrich Miescher (1844–1895) a Swiss physician and biologist isolated in 1869 phosphate-rich chemicals he called ‘nuclein’ (now nucleic acids) from white blood cells<sup>32</sup> paving the way for the identification of DNA as the carrier of inheritance. He also proposed that nuclein is a polymer composed of repeating units as words are composed of letters to form sentences and he is credited to have anticipated heredity in DNA. His work was first published in 1871 [95] approximatively the same year as the Table of Elements was proposed by Mendeleiev [96]. Nowadays, these two quite different works at that time, are converging by knowing that DNA is simply an organic molecule you can synthesize. Emergence of chemistry in the field of nucleic acids was achieved by Albrecht Kossel (1853–1927), a German biochemist who was awarded the Nobel Prize for Physiology or Medicine in 1910 and who elucidated the chemical structure of nucleic acids allowing to understand their chemistry. Chemistry has shown that cells are composed of molecules containing carbon, hydrogen, oxygen, nitrogen, phosphorus, and sulfur, and, from the 1950s, cell studies have focused on DNA or RNA’s as molecular entities and their informational features. The emergence of molecular chemistry in biological processes also convinced chemists of a possible bridging between chemistry and biology and to seek the ‘Chemical Roots of Darwinism’ [97]. Recently biochemical evolution and adaptation of RNA has been demonstrated in vitro. Mixed populations of two different ‘species’ of RNA enzymes were made to compete for limited amount of one or more substrates, with utilization of the substrate being necessary for amplification of the RNA. Evolution in the

presence of a single substrate led to the extinction of one or the other enzyme whereas evolution in the presence of five alternative substrates led to accumulation of mutations that allowed each enzyme to exploit different preferred resource. The work demonstrates how, when given a variety of resources, the different species will evolve to become increasingly specialized, each filling different niches within their common ecosystem [98]. To go further in the reasoning, species of living systems are submitted to ‘perpetual’ changes occurring by chance without any intention and these changes are selected or not by the environment.

### Supramolecular chemistry of living systems

One of the first meeting between supramolecular chemistry and living systems is probably the structural studies concerning macrocyclic antibiotics. Macrocyclic antibiotics, such as nonactine, enniatine, valinomycin etc. exhibit a high cation-specificity in metabolic behaviour. Nonactin and monactin possess highly specific potassium and rubidium transport properties through cells membranes. They were shown to enhance the transport of potassium ion to a significant greater extent than sodium ion. These features were understood at the molecular level, at the end of the 1960s, by studying the complexation of these cations by proton magnetic resonance and by X-ray techniques [99, 100]. This allowed to assume that nonactine is acting as a mobile transporter. The selectivity of nonactine was explained by the flexibility of its framework able to adapt its structure by reorientation of the chelating residues to accommodate an ion. The gathering of details at the molecular level of antibiotics used as tools for metabolic studies showed that one can apply concepts of supramolecular chemistry to living systems. The train of thought of studying living systems from the use of biochemical tools to the use of supramolecular principles has lead to link more and more deeply supramolecular chemistry and biochemistry. Examples can be found tracing the way of this link due to the elucidation of biological process by supramolecular tools. Detailed examples are found in the excellent book of Steed and Atwood [101]: ‘Porphyrins are tightly bounds to metal due to their rigid preorganization of the donor-atoms and are key-components in electron and energy transfer processes; vital oxygen is reversibly bounded to haemoglobin and can be released with high selectivity.’

As a mirror image, the merging of both disciplines has led supramolecular chemistry to invent, by mimicking, new techniques such as the selective transport of species through artificial membranes, the fabrication of molecular tunnels to include in natural membranes, the preparation of chiral structures, opening the way to biomimetic chemistry.

<sup>32</sup> In 1665, Robert Hooke (1635–1703), an English scientist, mathematician and architect published an important work titled *Micrographia: Physiological Descriptions of Minute Bodies made by Magnifying Glasses* and described an observation that changed basic biological theory and research. While examining a dried section of cork tree with a microscope, he observed small ‘monk’s chambers’ and coined the term ‘cell’ (from the Latin ‘cellula’ which means small compartment). Over the next 175 years, research led to the formation of the Cell Theory first proposed by Theodore Schwann (1810–1882) and Matthias Jacob Schleiden (1804–1881) both German physiologists by explicit claim that ‘there is only universal principle of development for the elementary parts, of organisms, however different, and this principle is the formation of cells’ [148]. Around 1833 Robert Brown (1773–1858) a Scottish botanist reported the discovery of nucleus (or areola as he called it) as ‘an opaque spot’ in the course of microscopic studies of epidermis of orchids. German doctor, Rudolph Ludwig Karl Virchow (1821–1902) was one of the first to give credit and plagiarise the work of Robert Remak (1815–1865), a Polish/German physiologist who showed that origins of cells was division of pre-existing cells.

## Back to living systems: chemistry and origins of life

Concerning supramolecular chemistry and its implication in living systems and origin of life,<sup>33</sup> publications from supramolecular chemists can be found. Lestel and Tkatchenko notice [13]: ‘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 [102]: ‘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 [103]. 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. And in this case the term emergence is used in the sense of describing the process by which material one would classify as, intimate (molecules, molecular aggregates, etc.) was transformed into a simple living system, say, bacterial cell. Once that simple life emerged then the continuation of that process is, termed Darwinian evolution. But in fact when speaking of evolution of species Darwin was not speaking of bacteria even though he was agreeing with the possible involvement of chemistry [93].

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 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 [104]. 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 [105]. 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 [106]. 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 *evolutionary 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*’.

## The birthday of an idea

In a paper dealing with the advent of nanotechnologies in the social and political worlds, McCray [107] made this remark: ‘Historians of science and technology have long been recognized the existence of ‘creation stories,’ myth-like narratives for research communities that trace the development of a particular idea or invention back to singularity—lone inventor or small teams who create a revolutionary breakthrough. For geneticists, there is Watson, Crick, and the double helix; for electrical engineers, Shockley, Brattain, and Bardeen’s invention of the transistor looms large’.

Nanotechnologists’ creation story can be traced to a precise point in space and time—the evening of 29 December 1959 when American physicist Richard P. Feynman (1918–1988; Nobel Prize in Physics 1965) gave an after-dinner speech in Pasadena to members of the American Physical Society. Feynman, gave his address, whimsically entitled ‘There’s Plenty of Room at the Bottom’ at a time when the mass production of microelectronics was just beginning and computers still occupied entire rooms [107]. Nanotechnology was a prophecy of Feynman and indeed the term ‘nanotechnology’ appeared in 1974 in a Japanese industrial conference [108]. The 1959 lecture has become

<sup>33</sup> Origin of life has been the subject of wide research since the philosophers asked first the question. Origin of life can find some explanation in chemistry from two points of view. The first is the synthesis of the molecules the second is how the molecules could survive and evolve to life. In a publication entitled: ‘Chemistry and Selection’, Christian de Duve has reported how chemists have given rise to these two points of view [149].



an important document in the history of nanotechnology but, as Chris Toumey [4] reports, there are disagreements about when it became important, and why. Real life of nanotechnology effectively started in the 1990s. On the contrary, supramolecular chemistry can be given a real birthday based on experimentation when the first publication of Petersen on synthesis and complexing properties of crown-ethers appeared. Like nanotechnology the development was rapid and worldwide. This is probably due to a latent state triggered by the work of Petersen because organic chemistry reached *une masse critique* in favor for its development. As shown in this paper the development of supramolecular chemistry presents three stages and we have shown the two facets of its emergence. One emergence is the bottom up one which may correspond to the development of molecular objects and systems, nanotechnology and complex matter by a bottom up approach which is in fact due to the ability of chemists to handle in an ‘atom by atom’ construction way and takes advantages of molecular interactions. The second emergence rather corresponds to the involvement of the concepts of supramolecular chemistry in fields such as physics or biology, and to use and evaluate these concepts in different fields other than chemistry. According to Bronowski [109] supramolecular is becoming a science since ‘Science is a collection of concepts and their explorations in the facts’.

In the quest of knowledge, scientists divided the world and Nature into various fields of research such as physics, chemistry, biology etc., and they generally think that such partial conceptual knowledges put together will be able to explain the whole. However if scientists can explain many of the observations of our world they cannot still explain the origin of life and generate life. It seems that the addition of the concepts created up to now is not enough for this and that new concepts have to be found for achieving evolution from inert to living matter.<sup>34</sup>

To end this article one can say that whatever the means used to learn matter, entering the world of matter or entering the matter itself is always a way of entering a world of ecstasy of matter in which the scientist likes to be lost. Being lost and organizing to better understand matter is a never ending story giving birth to ideas and realities of the future. ‘Everything brings in itself its infinite. But this infinite is a substance, it is not an idea.’ says Jean-Marie

Gustave Le Clézio (born, 1940; Nobel Prize in Literature 2008) in *Extase matérielle*.

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<sup>34</sup> Recently a new step has been made by chemists to reproduce as near as possible natural molecules with desired functions. They started from the challenge of chemists in learning from Nature which combines four themes: chemical structure, function, size, and molecular shape. While structure and function are better understood, as can be seen in this work, size and shape remain challenging in synthesis. Thus, they prepared, by precise construction, a dendronized polymer that approximates the size and cylindrical shape of the tobacco mosaic virus pushing the chemical frontiers [150].

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