FROM MATTER TO LIFE: CHEMISTRY ?!

Jean-Marie LEHN

Collège de France, Paris and Université Louis Pasteur, Strasbourg, France

In the beginning was the Big Bang, and physics reigned. Then chemistry came along at milder temperatures; particles formed atoms; these united to give more and more complex molecules, which in turn associated into organized aggregates and membranes, defining primitive cells out of which life emerged.

CHEMISTRY is the science of matter and of its transformations, and *LIFE* is its highest expression. It provides structures endowed with properties and develops processes for the synthesis of structures. It plays a primordial role in our understanding of material phenomena, in our capability to act upon them, to modify them, to control them and to invent new expressions of them.

Chemistry is also a science of transfers, a communication centre and a relay between the simple and the complex, between the laws of physics and the rules of life, between the basic and the applied. If it is thus defined in its interdisciplinary relationships, it is also defined in itself, by its object and its method.

In its method, chemistry is a science of interactions, of transformations and of models. In its object, the molecule and the material, chemistry expresses its creativity. Chemical synthesis has the power to produce new molecules and new materials with new properties. New indeed, because they did not exist before being created by the recomposition of atomic arrangements into novel and infinitely varied combinations and structures[1].

Towards Molecular Chemistry

The first chemical manipulations were those profound and complex thermal transformations by which the Raw becomes the Cooked. Thus, before being understood, chemistry was practised in the cooking of food; in the fermentation of

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Text taken in large part from ref. 7.

dough and of drinks; in the metallurgy of trinkets, of tools and weapons; in the extraction of natural substances, perfumes, colours, philtres and drugs.

Chemistry was for a long time empirical and descriptive. In the days of alchemy, all matter resulted from the admixture of varying proportions of the four basic elements: fire, air, earth and water. Through more and more refined analysis, chemistry became the composition of subtances, then the combination and linkage of atoms to form molecules. When empirical formulae gave way to exact formulae, the problem of the geometry of arrangement of atoms in molecules arose, whence emerged the notion of structure. With Van't Hoff and Lebel, the planar chemical representations unfolded and left the plane. The molecule became architecture, and the elaboration of molecular structures became mastery of space. With the work of Pasteur, optical activity found its explanation in the asymmetry of structures; thus arose the body of molecular chirality.

The alchemists' dream of transmutation became reality in *chemical synthesis*. At first an empirical knowhow, this science of molecular manipulation etablished its power with Friedrich Wöhler's synthesis of urea in 1828: "Über Künstliche Herstellung des Harnstoffes"[2], (On the artificial preparation of urea), by which it was proved that natural substances were chemical compounds like any other, accessible in the laboratory without the intervention of a living organism. On 28 February 1828, Wöhler wrote to Berzelius 'I can make urea with no need of a kidney, or let alone an animal, be it a man or a dog'.

Organic synthesis grew rapidly, continually adding to its panoply of tools with each new reaction discovered, allowing access to innumerable new compounds, along with the refinement of strategies for obtaining more and more complex natural substances in the laboratory. A whole series of brilliant achievements, where elegance of strategy combined with feats of efficiency and selectivity, led to the great syntheses of the last 50 years - notably, to what is considered to be the epitome, the synthesis of vitamin B_{12}, due to the combined efforts of Robert Burns Woodward[3] and Albert Eschenmoser[4], assisted by a hundred or so collaborators. We are a long way from Wöhler's urea! On the one hand there is a planar molecule with 4 atoms (not counting hydrogens), and on the other, a set of 93 atoms and extremely difficult stereochemical problems; between the two lies a century and a half (see Figure 1).

INSERT FIGURE 1

From Molecular to Supramolecular Chemistry

MOLECULAR CHEMISTRY, thus, has established its power over the covalent bond. The time has come to do the same for non-covalent intermolecular forces. Beyond molecular chemistry based on the covalent bond there lies the field of *SUPRAMOLECULAR CHEMISTRY*, whose goal it is to gain control over the intermolecular bond[5-7].

It is concerned with the next step in increasing complexity beyond the molecule towards the supermolecule and organized polymolecular systems, held together by non-covalent interactions.

“Just as there is a field of molecular chemistry based on the covalent bond, there is a field of supramolecular chemistry, the chemistry of molecular assemblies and of the intermolecular bond”. It is “chemistry beyond the molecule”, whose objects are “supramolecular entities, supermolecules possessing features as well defined as those of molecules themselves”[5-7].

It is a sort of molecular sociology! Non-covalent interactions define the intercomponent bond, the action and reaction, in brief, the behaviour of the molecular individuals and populations: their social structure as an ensemble of individuals having its own organisation; their stability and their fragility; their tendency to associate or to isolate themselves; their selectivity, their “elective affinities” and class structure, their ability to recognize each other; their dynamics, fluidity or rigidity of arrangements and of castes, tensions, motions and reorientations; their mutual action and their transformations by each other.

When a substrate binds to an enzyme or a drug to its target, when signals propagate between cells, highly selective interactions occur between the partners and control the process. Supramolecular chemistry is concerned with the study of the basic features of these interactions and with their implementation in specially designed non-natural systems.

Molecular interactions form the basis of the highly specific recognition, reaction, transport, regulation, etc. processes that occur in biology, such as substrate binding to a receptor protein, enzymatic reactions, assembling of multiprotein complexes, immunological antigen-antibody association, intermolecular reading, translation and transcription of the genetic code, regulation of gene expression by DNA binding proteins, entry of a virus into a cell, signal induction by neurotransmitters, cellular recognition, and so on. The design of artificial, abiotic systems capable of displaying processes of highest efficiency and selectivity requires the correct manipulation of the energetic and stereochemical features of the non-covalent, intermolecular forces (electrostatic interactions, hydrogen bonding, van der Waals forces, etc.) within a defined molecular architecture. In doing so, the chemist finds inspiration in the ingenuity of biological events and encouragement in the demonstration that such high efficiencies, selectivities, and rates can indeed be attained. However, chemistry is not limited to systems similar to those found in biology, but is free to create unknown species and to invent novel processes.

Supramolecular chemistry is a highly interdisciplinary field of science covering the chemical, physical, and biological features of the chemical species of greater complexity than molecules themselves, that are held together and organized by means of intermolecular (non-covalent) binding interactions. This relatively young area has been defined, conceptualized, and structured into a coherent system. Its roots extend into organic chemistry and the synthetic procedures for molecular construction, into coordination chemistry and metal ion-ligand complexes, into physical chemistry and the experimental and theoretical studies of interactions, into biochemistry and the biological processes that all start with substrate binding and recognition, into materials science and the mechanical properties of solids. A major feature is the range of perspectives offered by the cross-fertilization of supramolecular chemical research due to its location at the intersection of chemistry, biology, and physics. Drawing on the physics of organized condensed matter and expanding over the biology of large molecular assemblies, supramolecular chemistry expands into a *supramolecular science*. Such wide horizons are a challenge and a stimulus to the creative imagination of the chemist. Thus, supramolecular chemistry has been rapidly expanding at the interfaces of chemical science with physical and biological phenomena.

The emergence of any novel field of science is linked to the past. Where would the roots of supramolecular chemistry reach? It is *Paul Ehrlich* who recognized that molecules do not act if they do not bind ("Corpora non agunt nisi fixata") thus introducing the concept of *receptor*[8]. But binding must be selective, a notion that was enunciated by *Emil Fischer* in 1894 [9] and very expressively presented in his celebrated "lock and key" image of steric fit, implying geometrical complementarity, that lays the basis of molecular recognition. Finally, selective fixation requires interaction, affinity between the partners, that may be related to the idea of *coordination* introduced by *Alfred Werner*[10], supramolecular chemistry being in this respect a generalization of coordination chemistry.

With these three concepts, fixation, recognition and coordination, the foundations of supramolecular chemistry are laid.

Molecular Recognition, Catalysis and Transport

Supramolecular chemistry started with the selective binding of alkali metal cations by natural[11] as well as by synthetic macrocyclic and macropolycyclic ligands, the crown ethers and cryptands[5,12]. This led to the emergence of *molecular recognition* as a new domain of chemical research that expanded over other areas and became supramolecular chemistry[5-7]. It underwent explosive growth with the development of synthetic receptor molecules of numerous types for the strong and selective binding of cationic, anionic or neutral complementary substrates of organic, inorganic or biological nature, by means of various interactions (electrostatic, hydrogen binding, Van der Waals, donor-acceptor). Molecular recognition implies the (molecular) storage and (supramolecular) retrieval of molecular structural information.

Many types of receptor molecules have already been explored (crown ethers, cryptands, spherands, cavitands, calixarenes, cyclophanes, cryptophanes, etc.)[5-13]. Still many others may be imagined for the binding of complementary substrates of chemical or biological significance, for instance for the development of substrate specific sensors or for the recognition of structural features in biomolecules (nucleic acid probes, affinity cleavage reagents, enzyme inhibitors, etc.).

The combination of recognition features with reactive functions generates *supramolecular reagents and catalysts* that operate in processes involving two main steps: substrate recognition followed by its transformation into products. Because of their relationship with enzymatic catalysis, they present protoenzymatic and biomimetic features. By nature they are abiotic reagents, that may perform the same overall processes as enzymes without following the same mechanistic pathways. More importantly, they may also effect highly efficient and selective reactions that enzymes do not perform. This represents a very important area for further development, that may lead to a range of reactive receptor molecules combining substrate specificity with high reactional efficiency and selectivity. Much work remains to be done that should contribute very significantly to the understanding of chemical reactivity and to its application in industrial processes.

Suitably modified receptors act as *carriers* for the selective *transport* of various types of substrates through artificial or biological membranes. Again, many further developments may be envisaged, concerning for instance the construction of selective membrane sensors or the transport of drugs through biological barriers which may include targeting if suitable target-selective recognition groups are introduced.

Recognition, reactivity and transport represent the three basic functional features of supramolecular species. (Figure 2).

INSERT FIGURE 2

Molecular and Supramolecular Devices

A further important line of development concerns the design of *supramolecular devices* built on photoactive, electroactive or ionoactive components, operating respectively with photons, electrons and ions. Thus, a variety of photonic devices based on photoinduced energy and electron transfer may be imagined[6,7,14]. Molecular wires, ion carriers and channels facilitate the flow of electrons and ions through membranes. Such functional entities represent entries into molecular photonics, electronics and ionics, that deal with the storage, the processing and transfer of materials, signals and information at the molecular and supramolecular levels.

A whole field, at the interface with physics, microelectronics and microoptics lies here, which has barely been explored and remains wide open, presenting such intriguing goals as storage (battery), amplification, switching, rectification, etc., devices. The chemistry of molecular signal generation, processing, transfer, conversion and detection, *semiochemistry*, touches upon both physical and biological signalization processes.

Self-Processes. Programmed Chemical Systems

The most recent developments concern the implementation of *molecular information* and recognition as a means of controlling the evolution of supramolecular species as they build up from their components. Thus, beyond the preorganization used in the construction of molecular receptors, lies self-organization. It involves the design of systems capable of spontaneously generating well-defined supramolecular entities by self-assembling from their components in a given set of conditions[6,7,15].

The information necessary for the process to take place and the programme that it follows must be stored in the components and operate via an algorithm based on molecular recognition events. Thus, these systems may be termed *programmed supramolecular systems*[6,7].

Self-assembly and self-organization have recently been achieved in several types of organic and inorganic systems[6,7,15,16]. By clever use of metal coordination, hydrogen bonding or donor-acceptor interactions, researchers have achieved the spontaneous formation of a variety of novel and intriguing species such as inorganic double and triple helices, termed helicates, catenanes, threaded entities (rotaxanes), cage compounds, etc...

The self-assembly of inorganic structures of several types has been effected, based on ligand design and on the use of suitable coordination geometries that act as the assembling algorithm. It may serve here to describe the present state of the art.

Double-stranded and triple-stranded helicates, metal complexes of double helical and triple helical architectures, are formed by the spontaneous assembly of two or three linear oligobipyridine ligands of suitable structure into a double or a triple helix by binding of specific metal ions displaying respectively tetrahedral (Cu^I) and octahedral (Ni^{II}) coordination geometry. These species are illustrated by the trinuclear double and triple helicates **1**[17] and **2**[18] respectively.

INSERT STRUCTURES **1**, **2**, **3**

Especially attractive was the possibility to connect nucleosides to the oligobipyridine backbone, leading for instance to oligothymidine strands, which represent artificial oligonucleosides and may interact with natural polynucleotides or nucleic acids. On treatment with Cu^I they gave double-helical complexes representing inside-out analogues of double-stranded nucleic acids such as, which were called deoxyribonucleo helicates (DNH)[19]. The DNH complexes are double-helical oligonucleosides formed spontaneously by self-assembly of two suitably designed ligand strands and copper(I) ions. In contrast to DNA they have positive charges located inside the strands whereas the information-bearing nucleobases are on the outer spine of the double helix, pointing away from its axis. They should be able to interact with other species both electrostatically and by hydrogen bonding through the thymidines. In particular they might bind to both single-stranded and double-stranded nucleic acids with formation of mixed natural-artificial triple- and quadruple-stranded species. Such interactions could present selectivities resulting both from the overall shape of the DNHs and from the attached recognition groups.

INSERT FIGURE 3

Multiple component self-assembly leads to the spontaneous generation of a cylindrical superstructure **4** (Figure 3) from five ligands of two different types and six Cu^I ions[20]. This process represents the remarkable self-organisation of a closed inorganic architecture from multiple components by the spontaneous and correct assembly in one stroke of altogether eleven particles belonging to two types of ligands and one type of metal ion. Analogous cylindrical architectures of even larger size presenting three and four layered features have been obtained using similar procedures[21].

Grid-like inorganic superstructures, such as the 3 x 3 grid **5**, have been shown to self-assemble from six ligands and nine Ag^{I} ions[22].

INSERT STRUCTURE 5

The operation of such instructed supramolecular systems fulfills the three levels of molecular programming and of information input, *recognition, orientation* and *termination*, that determine the generation of a discrete supramolecular architecture. The steric and binding information contained in the ligand is read out by the metal ions following a given coordination algorithm. These processes represent progresive steps in the control of the self-organisation of large and complex supramolecular architectures through molecular programming.

In a study of helicate self-assembly from a mixture of different ligands and different metal ions, it was found that only the “correct” helical complexes were formed through *self-recognition*[23]. In a broader perspective, this points to a *change in paradigm from pure compounds to instructed mixtures,* that is from seeking chemical purity to designing programmed systems composed of mixtures of instructed components capable of spontaneously forming well-defined superstructures. This may recall the side-by-side buildup of complex species (displaying highly integrated functions) that takes place in the self-assembly of the machinery of living cell.

One may venture to predict that this trend will represent a major line of development of chemistry in the years to come: the spontaneous but controlled built up of structurally organized and functionally integrated supramolecular systems from a preexisting “soup” of instructed components following well-defined programs and interactional algorithms.

Such an evolution might also be brought into parallel with the recent development, via procedures of both chemical synthesis and molecular biology, of *molecular diversity methods* that combine the generation of large repertoires of molecules with highly efficient selection procedures to obtain products presenting specific properties[24]; the techniques of amplification by replication used in these methods would bear relation to the spontaneous generation of the target superstructures by the operation of self-processes. In this respect one may also point out that the very active development of the chemistry of molecular recognition processes make the chemist able to design instructed artificial receptor molecules for the selective binding and retrieval of a well-defined substrate in a mixture of many different molecules.

A further major development along these lines, concerns the design of molecular species displaying the ability to form by *self-replication*. This has been realized using components containing suitable recognition groups and reactive functions[25]. Thus, the study of self-processes represents an area of rapidly increasing activity.

Supramolecular Assemblies and Materials

In addition to dealing with the oligomolecular supermolecules, well-defined species resulting from the specific intermolecular association of a few components, supramolecular chemistry deals also with polymolecular assemblies formed by the spontaneous association of a large number of components into a specific phase (films, layers, membranes, vesicles, micelles, mesophases, surfaces, solids, etc.)[26]. There lies here a vast and fertile domain of research. Molecular recognition between complementary components provides means for directing the architecture of polymolecular assemblies and for endowing them with novel properties, such as for instance the selective binding of substrate molecules to layers and surfaces. It allows the design and engineering of *supramolecular materials*, in particular of liquid crystalline and of polymeric nature. For instance, the recognition-induced self-assembly of complementary components generates liquid crystalline “polymers” of supramolecular nature[6,7]. A sort of supramolecular polymer chemistry is thus emerging and receiving more and more attention (Figure 4).

INSERT FIGURE 4

Molecular recognition-directed processes also provide a powerful entry into *supramolecular solid state chemistry* and crystal engineering[27]. The ability to control the way in which molecules associate may allow the designed generation of desired architectures in the solid state. Modification of surfaces with recognition units could lead to selective surface binding and to recognition-controlled adhesion.

The design of molecular information controlled, “programmed” systems represents new horizons in materials engineering and processing towards “smart”, functional supramolecular materials, such as self-assembling nanostructures, organized and functional species of nanometric dimensions that define a *supramolecular nanochemistry*.

The Information Paradigm

It has become clear that the keyword of supramolecular chemistry is not size but information. Supramolecular species spontaneously build up from their components and accomplish complex tasks on the basis of the encoded information and instructions. Thus, if sizewise “there's plenty of room at the bottom” as the celebrated aphorism of Richard Feynman goes, through supramolecular chemistry “there’s even more room at the top”!

In chemistry, like in other areas, the language of information is extending that of constitution and structure as the field develops towards more and more complex architectures and behaviour. And supramolecular chemistry is paving the way towards comprehending chemistry as an *information science*. In the one hundred years since 1894, molecular recognition has evolved from Emil Fischer’s “lock and key” image[9] of the age of mechanics towards the *information paradigm* of the age of electronics and communication. This change in paradigm will profoundly influence our perception of chemistry, how we think about it, how we perform it. Instructed chemistry extends from selectivity in the synthesis and reactivity of molecular structures to the organization and function of complex supramolecular entities. The latter rely on sets of instructed components capable of performing on mixtures specific operations that will lead to the desired substances and properties by the action of built-in self-processes.

Supramolecular chemistry has started and developed as defined by its basic object, the chemistry of the species generated by non-covalent interactions. Through recognition and self-processes it has led to the concepts of (passive and active) information and of programmed systems, becoming progressively the chemistry of molecular information, its storage at the molecular level, its retrieval, transfer and processing at the supramolecular level.

The outlook of supramolecular chemistry is toward a general *SCIENCE OF INFORMED MATTER*, bringing forward in chemistry the third component of the basic trilogy matter-energy-information.

Steps towards Complexity. Chemistry and Biology

The progression from elementary particles to the nucleus, the atom, the molecule, the supermolecule and the supramolecular assembly represents steps up the ladder of *complexity*. Particles interact to form atoms, atoms to form molecules, molecules to form supermolecules and supramolecular assemblies, etc. At each level novel features appear that did not exist at a lower one. Thus a major line of development of chemistry is towards complex systems and the emergence of complexity.

The highest level of complexity is that expressed in that highest form of matter, living matter, life, which itself culminates in the brain, the plasticity of the neural system, epigenesis, consciousness and thought.

Chemistry and notably supramolecular chemistry entertain a double relationship with biology. Numerous studies are concerned with substances and processes of biological or *biomimetic* nature. There has been a profound evolution by which the chemist appropriates and diverts the power of the natural chemical processes of biology to the goals of chemistry, for instance, in the use of enzymes as reagents, the generation of catalytic antibodies, the control of gene expression, the development of molecular diversity techniques, etc. Conversely, the scrutinization of biological processes by chemists has provided understanding on a precise molecular basis and ways for acting on them by means of suitably designed substances. Thus, the cultures of chemistry and biology are intimately linked and coming closer and closer together.

On the other hand, the challenge for chemistry lies in the development of *abiotic*, non-natural systems, figments of the imagination of the chemist, displaying desired structural features and carrying out functions *other* than those present in biology with (at least) comparable efficiency and selectivity. Subject only to the constraints one chooses to impose and not to those of the living organism, abiotic chemistry is free to invent new substances and processes. The field of chemistry is indeed broader than that of the systems actually realized in nature.

The future path of chemistry will be shaped by both inside and outside forces. Its evolution towards increasing diversity and towards increasing complexity also takes biological phenomena as points of reference. The specificity of chemistry may be stressed by comparing biology and chemistry with respect to these two basic parameters, *complexity* and *diversity*. As presented in Figure 5, biology is of extreme complexity, however the substances on which it is based belong to defined classes, and although tremendously rich are nevertheless limited in variety of types. Chemistry, on the other hand, is still of very low complexity compared to biology but its breadth, the diversity of its substances, is infinite, being limited only by the imagination of the chemist in endlessly combining and recomposing the basic bricks of chemical architectures, thus filling in the unlimited white area in the complexity-diversity diagram.

INSERT FIGURE 5

The chemist finds illustration, inspiration and stimulation in natural processes, as well as confidence and reassurance since they are proof that such highly complex systems can indeed be achieved on the basis of molecular components. One might say that science, notably chemistry, relies on the biological world through an existence axiom: the mere fact that biological systems and, in particular, we human beings exist, demonstrates the fantastic complexity of structure and function that the molecular world can present; it shows that such a complexity can indeed exist despite our *present* inability to understand how it operates and how it has come about. So to say, if we did not exist we would be unable to imagine ourselves! And the molecular world of biology is only one of all possible worlds of the universe of chemistry, that await to be created at the hands of the chemist.

With respect to the *frontiers of life* itself three basic questions may be asked: How? Where? Why?

The first concerns the origin of life on earth as we know it, of our biological world. The second considers the possibility of extraterrestrial life, within or beyond the solar system. The third question wonders why life has taken the form we know; it has as corollary the question whether other forms of life can (and do) exist: is there "artificial life"?; it also implies that one might try to set the stage and implement the steps that would allow, in a distant future, the creation of artificial forms of life.

Such an enterprise, which one cannot (and should not) at the present stage outline in detail except for initial steps, rests on the presupposition that there may be more than one, several expressions of the processes characterizing life. It thus invites to the exploration of the *"frontiers of other lifes"* and of the *chemical evolution* of living worlds.

Questions have been addressed about which one may speculate, let one's imagination wander, perhaps even set paths for future investigations. However, where the answers lie is not clear at present and future chemical research towards ever more complex systems will uncover new modes of thinking and new ways of acting that we at present do not know about and may even be unable to imagine.

The perspectives are definitely very (too?) wide and it will be necessary to distinguish the daring and visionary from the utopic and illusory! On the other hand, we may feel like progressing in a countryside of high mountains: the peaks, the goals are visible and identifiable or may become so as progress is made, but we do not yet know how to reach them. We may find landslides, rockfalls, deep crevices, tumultuous streams along the way, we may have to turn around and try again, but we must be confident that we will eventually get there. We will need the courage to match the risks, the persistence to fill in the abyss of our ignorances and the ambition to meet the challenges, remembering that *"Who sits at the bottom of a well to contemplate the sky, will find it small" (Han Yu,* 768-824).

But to chemistry, the skies are wide open, for if it is a science, it is also an art. By the beauty of its objects, of course, but also in its very essence, by its ability to invent the future and to endlessly recreate itself.

Chemistry and Creativity

Like the artist, the chemist engraves into matter the products of creative imagination. The stone, the sounds, the words do not contain the works that the sculptor, the composer, the writer express from them. Similarly, the chemist creates original molecules, new materials and novel properties from the elements provided by nature, indeed entire new worlds, that did not exist before they were shaped at the hands of the chemist, like matter is shaped by the hand of the artist.

Indeed chemistry possesses this creative power as stated by *Marcelin Berthelot "La chimie crée son objet". ("Chemistry creates its object").* It does not merely fabricate objects, but creates its own object. It does not preexist, but is invented as progress is made. It is not just waiting to be discovered, but it is to be created.

The essence of chemical science finds its full expression in the words of that epitome of the artist-scientist *Leonardo da Vinci*: *"... dove la natura finisce di produrre le sue spezie, l'uomo quivi comincia con le cose naturali, con l'aiutorio di essa natura, a creare infinite spezie…". ("Where nature finishes producing its own species, man begins, using natural things and with the help of this nature, to create an infinity of species…").*

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

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Figure captions

Figure 1	Two milestones in organic synthesis: Urea (left) and Vitamin B_{12} (right).
Figure 2	From molecular to supramolecular chemistry: molecules, supermolecules, molecular and supramolecular devices.
Figure 3	A cylindrical cage-like structure **4** is spontaneously generated from five ligands of two different types and six Cu(I) ions.
Figure 4	Mesophases and liquid crystalline polymers of supramolecular nature have been generated from complementary components, amounting to macroscopic expression of molecular recognition.
Figure 5	A comparison between chemistry and biology with respect to the two parameters: complexity and diversity/breadth.