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Towards Complex Matter

Perspectives in Chemistry—Steps towards Complex Matter

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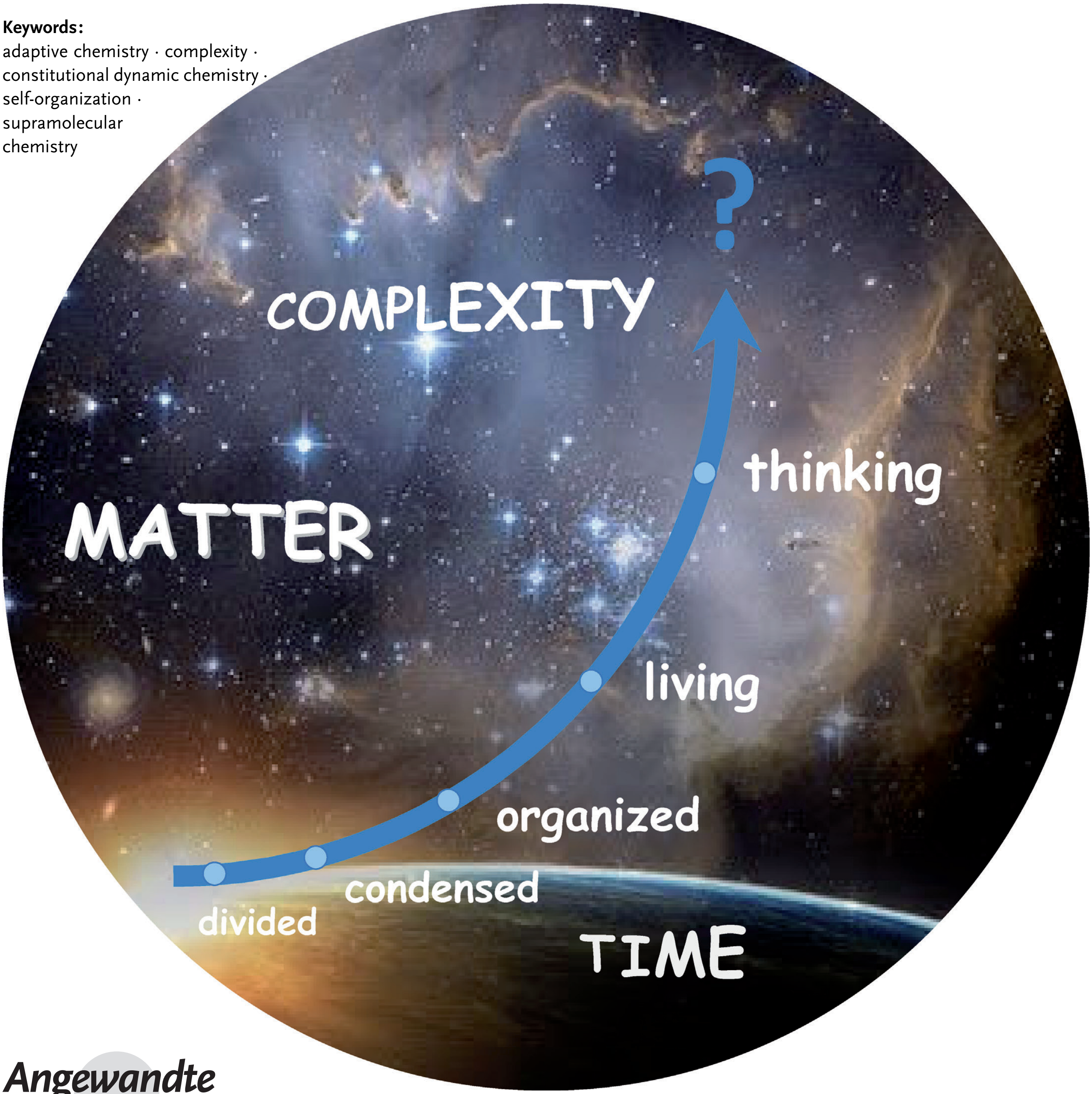

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Chemistry is progressively unraveling the processes that underlie the evolution of matter towards states of higher complexity and the generation of novel features along the way by self-organization under the pressure of information. Chemistry has evolved from molecular to supramolecular to become adaptive chemistry by way of constitutional dynamics, which allow for adaptation, through component selection in an equilibrating set. Dynamic systems can be represented by weighted dynamic networks that define the agonistic and antagonistic relationships between the different constituents linked through component exchange. Such networks can be switched through amplification/up-regulation of the best adapted/fittest constituent(s) in a dynamic set. Accessing higher level functions such as training, learning, and decision making represent future lines of development for adaptive chemical systems.

From the Contents

1. Introduction

125 years of *Angewandte Chemie* is not just an event to mark an anniversary, but an occasion to celebrate a science which it has so well served over all the years, chemistry! Chemistry is a major player in the general concert of the sciences and a key to the enterprise of understanding us and our universe. My intention is neither to look back, too much to say, nor to peer into the future, too risky, but to set a panorama and indicate a few of the perspectives that actual trends in chemistry open up. The present general exposition builds upon earlier ones,[1–5] starting 25 years ago with the year of the 100th anniversary.[1a] It also attempts some conjectures, suggestions, and projections. For the purpose at hand, it will not be an exhaustive review and the reader is referred to the literature cited in earlier publications[1–5] as well as to the vast array of reviews, monographs, and sets of volumes published on supramolecular chemistry and related topics.

It all started with a Big Bang, and chemistry came in when the universe had cooled down enough to allow for the formation of atoms and molecules, which constitute the 4% of visible matter, our matter, *the matter that matters!* Progressively climbing up the ladder of complexity led to the emergence of life and of thought (Figure 1). From divided,

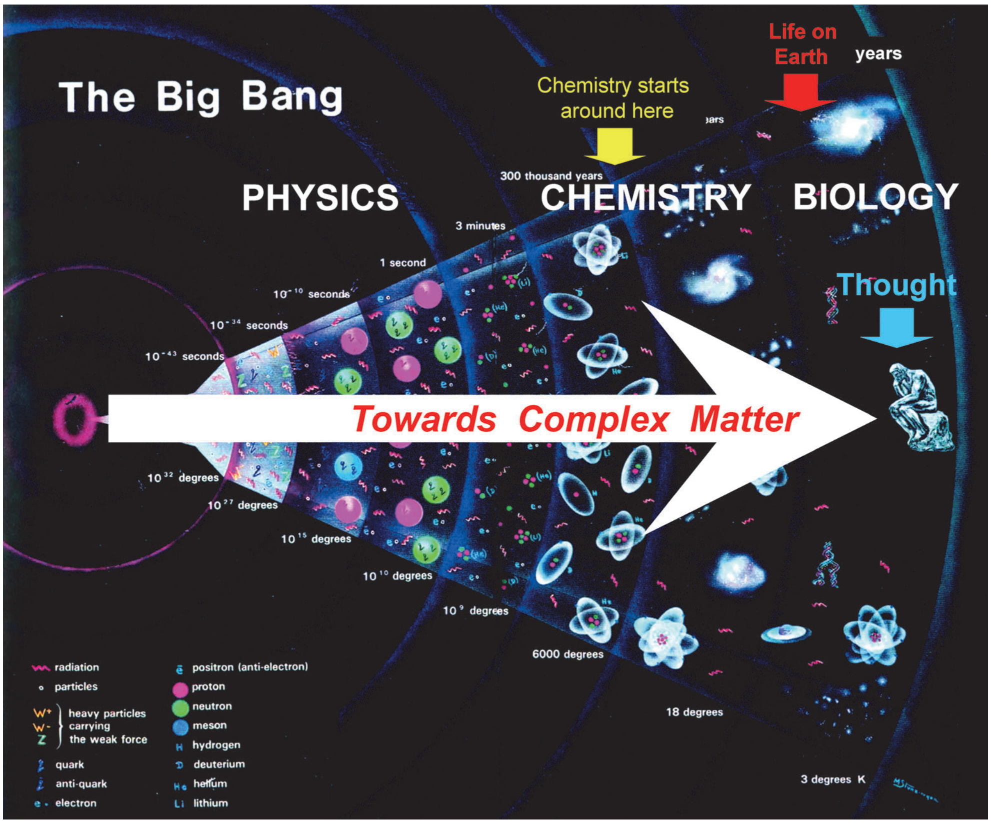

Figure 1. Evolution of the universe towards increasingly complex forms of matter: from particles to atoms, to molecules, to life, and on to the thinking organism.

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matter became condensed, organized, living, and thinking. What lies beyond, we do not (yet?) know.

The driving force behind this evolution towards more and more complex forms of matter is the most basic of all features, the most fundamental concept: self-organization.[2,3,6] It all happened by itself and science will allow us to understand how and why. Chemistry has a key role and a major task in achieving this goal. Physics unravels the laws of the universe, and biology scrutinizes the rules of life. It is the mission of chemistry to build the bridge between the general laws and the specific expressions of these laws that are life and thought on our planet, Earth (Figure 2).

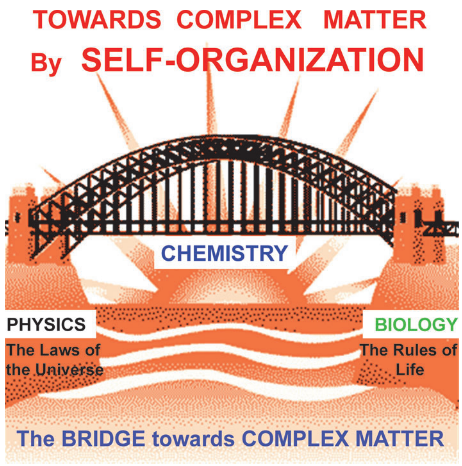


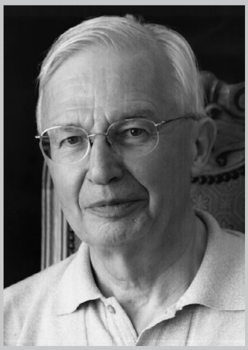
Figure 2. Chemistry, the bridge between the laws of the universe and their expression in a highly complex feature (life), thereby unraveling the generation of complex matter by self-organization, the driving force of the evolution of the universe.

2. Towards Complex Matter—Self-Organization

Self-organization drives towards systems of increasing complexity under the pressure of information, towards more and more complex forms of matter, up to the generation of life and thought (as we know it).[2,3,6]

Self-organization may be:

1) passive, equilibrium self-organization, involving the generation of organized molecular/covalent or supramolecular/noncovalent functional architectures by self-assembly from components under thermal equilibrium conditions; it allows for adaptation in response to external or internal stimuli/effectors under equilibrium conditions;
2) active, out-of-equilibrium self-organization, involving the generation of organized functional architectures driven by time-dependent, non-equilibrium, dissipative physical and chemical processes; it allows for adaptation and evolution under non-equilibrium conditions. Equilibrium self-organization could also be considered as self-assembly, a term which, however, does not express that it is not just the spontaneous generation of an assembly, but of an organized one.



Jean-Marie Lehn was born in 1939 in Rosheim (France). In 1970 he became Professor of Chemistry at the Université Louis Pasteur in Strasbourg and from 1979 to 2010 he was Professor at the Collège de France in Paris. He is currently an Emeritus Professor at the University of Strasbourg. In 1987 he shared the Nobel Prize in Chemistry for his studies on the chemical principles of "molecular recognition". He defined a new field of chemistry and coined the term "supramolecular chemistry". He subsequently developed the field in the direction of self-organization processes and adaptive chemistry. He is author of over 900 scientific publications and member of many academies and institutions. He has received numerous international honors and prizes.

Increasing complexity leads to the emergence of higher level features in chemistry and biology.[2,3,6] Such chemical evolution rests on selection, operating on structural and functional diversity generated by the action of intra- and intermolecular electromagnetic forces on the components of matter. It is clear that, before Darwinian evolution of living organisms, there must have been a purely chemical evolution that progressively led to the threshold of life.[6e] Indeed, prebiotic self-organization needs to be understood to establish the basis for biotic self-organization.

2.1. Complexity—Emergence

In general terms, complexity $\boldsymbol{C}$ may be considered to result from a combination of three features: Multiplicity, interconnection, and integration [Equation (1); see also Figure 3].[2b]

$$\boldsymbol{C} \propto \boldsymbol{M} \copyright \boldsymbol{I}_1 \copyright \boldsymbol{I}_2 \qquad (1)$$

The terms in Equation (1) may be exemplified with respect to recent developments, in particular in dynamic chemistry: the multiplicity $\boldsymbol{M}$ represents chemical diversity in constitution and function, $\boldsymbol{I}_1$ stands for the interconnections—interactional (noncovalent), reactional (covalent), as well as their dynamics—and the third term, $\boldsymbol{I}_2$, indicates the full integration of all features (constitutional, functional, motional) through networks with feedback and regulation; $\copyright$ expresses some type of combination between these three parameters.

The species and properties defining a given level of complexity result from those belonging to the level(s) below as well as their multibody interactions, going from molecules to supramolecular entities, from supramolecular entities to cells, from cells to tissues, from tissues to organisms, and so on, up to the behavior of societies and ecosystems along a hierarchy of levels defining the architecture of complexity. At each level of complexity novel properties emerge that 1) do not exist at lower level(s), 2) may be deduced from, but 3) not reduced to those of lower level(s) (Figure 3).

Self-organization of matter generates complexity in space, using molecular structural diversity and selection to drive the evolution of constitution. Self-organization in time performs

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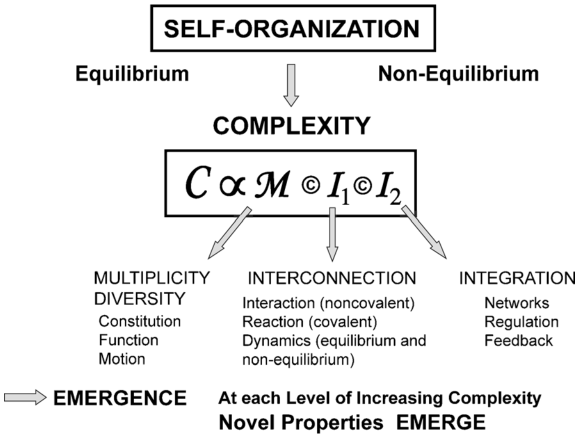

Figure 3. Self-organization (equilibrium and non-equilibrium) leading to complexity and emergence. Complexity C is given as a combination (©) of multiplicity M, interconnection I_1, and integration I_2. $\propto$ represents a proportionality/functional dependence. Increasing complexity induces the emergence of novel properties. Other specific features may be considered that would fall under these three types. For example, cooperativity, replication, and learning contribute to integration I_2.

selection of fluctuations, Brownian motions, to generate complex-oriented motion (Figure 4).

Control may act and be exerted on three levels: informational (designing programmed chemical systems), constitutional, and dynamic (motional). It may also be exerted through actions external to the system or by internal factors (self-control). External control and the response of the system to external physical stimuli or chemical effectors account for adaptation.

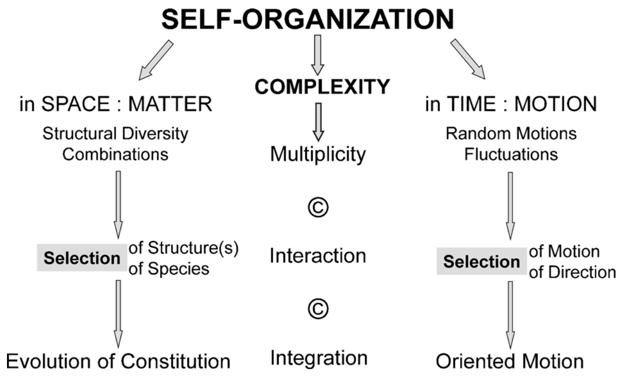

Figure 4. Self-organization of highly diverse forms of molecular matter in space drives the evolution of complex entities (left), and of random motion in time produces oriented motion (right). Complexity (center) is generated by the combination of multiplicity, interaction, and integration (see also Figure 3).

2.2. From Molecular and Supramolecular towards Adaptive Chemistry

On the way towards more and more complex forms of matter, chemistry has taken steps that, although having occurred in sequence, develop in parallel, continuously reinforcing each other and transferring features to mutually enrich.

Thus, molecular chemistry has built the basis on which supramolecular chemistry has grown. The cross-fertilization of molecular chemistry by the constitutional dynamics inherent to supramolecular chemistry has opened the route towards adaptive chemistry by way of constitutional dynamic chemistry (CDC),[4,5,7] which brings together both molecular and supramolecular levels, that is, dynamic covalent (DCC) and dynamic noncovalent (DNCC) chemistry, respectively (see also Sections 3.1 and 3.3).[4,5,7–9] Thus, in a sort of back to the future movement, supramolecular chemistry has introduced into molecular chemistry the notions of 1) molecular information which is stored at the molecular level and processed at the supramolecular level,[2,5,10] 2) molecular recognition, interactional and functional, at the supramolecular and molecular levels, respectively, and 3) constitutional dynamics,[4,5,7] as expressed in DCC and DNCC (Figure 5).[4,5,7–9]

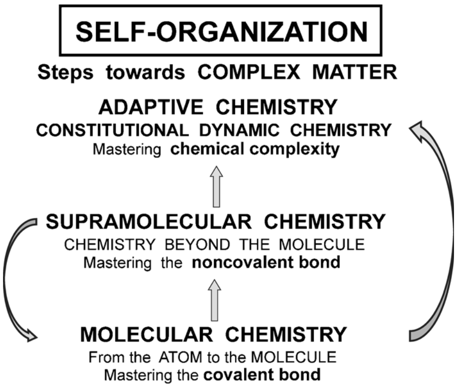

Figure 5. The evolution from molecular to supramolecular to adaptive chemistry as steps towards increasingly complex levels of matter. The introduction of the dynamic features of supramolecular chemistry into molecular chemistry leads to constitutional dynamic chemistry that opens towards adaptive chemistry.

Developments in nonbiological self-assembly, equilibrium self-organization processes, have made use of the whole range of noncovalent interactions: hydrogen bonding, donor–acceptor, van der Waals … Particularly successful has been the designed generation of highly complex metallosupramolecular architectures by combining the richness of molecular ligand structures with the coordination features of metal ions.[11] A major goal is to be able to program, control, and predict the outcome of such processes.[10,12]

2.3. Self-Organization and Information

Self-organization implements information[2,3,6] and involves the operation of programmed chemical systems, whereby molecular information stored in the molecular structural features is processed at the supramolecular level through interaction algorithms.[2,3,10]

A basic conceptual question is that of expressing the notion of molecular information in physicochemical terms. It was suggested earlier[13] that kT could be taken as the recognition bit to define the amount of recognition, related to the strength of an association, that is, the recognition between entities measured by the association free energy ΔG, so that a measure of recognition would be considered as $\Delta G/kT$.[14] Landauer's principle[15,16] relates information to energy through temperature as a single parameter.

One may conjecture about an informational equation of state (see also Ref. [16]). Following the classical van der Waals equation of state,[17] which relates pressure, volume, and temperature as $PV = nRT$, or in terms of number of particles as $PV = Nk_B T$, and transcribing pressure into energy E (high pressure⇔high energy) and volume into entropy S (high volume⇔high entropy), one may write $ES = Nk_B T$. Considering that (high) interaction energy results in (high) recognition and thus implies (high) information $\mathbf{I}$, the equation may be translated into Equation (2).

$$\mathbf{I}S = Nk_B T \tag{2}$$

By introducing Boltzmann's equation $S = k_B \log W$, one may write $\mathbf{I}k_B \log W = Nk_B T$, which results in an *information equation of state* [Equation (3)].

$$\mathbf{I}\log W = NT \tag{3}$$

Herein, when information content $\mathbf{I}$ increases, the number of states decreases at a fixed temperature. Higher recognition is associated with larger differences in the binding free energy ΔG between receptor–substrate associations, and thus with higher information content in the recognition process and lower entropy.

3. Dynamic Chemistry

3.1. Self-Organization, Constitutional Dynamics, and Adaptation

Adaptation and self-organization are intimately linked. Adaptation implements the ability of a system to undergo self-organization towards another direction in response to external stimuli and environmental pressure. One may say that it consists of the reorientation of self-organization towards the expression of adapted features.

As self-organization takes place following a multistep pathway towards the progressive build-up of the final entities from their components, it has to explore the hypersurface of the available constitution/structure/energy combinations. Consequently, self-organization processes are, in principle, able to select the correct molecular components for the generation of a supramolecular entity of given constitution from a collection of building blocks. Thus, beyond self-organization *by design*, which relies on programming, self-organization may take place *with selection*, by virtue of a basic feature inherent in supramolecular chemistry, the *dynamic character* residing in its ability to undergo *constitutional dynamics*. The latter defines CDC, whereby a chemical entity, be it molecular or supramolecular, may undergo continuous change in its constitution through dissociation into various components and reconstitution into the same entity or into different ones. CDC takes advantage of its dynamic character for the generation of molecular and supramolecular constitutional diversity to allow for *variation* and *selection*. It operates selection on dynamic constitutional diversity in response to the pressure of chemical, physical, internal, or external factors to achieve adaptation, thereby enabling *adaptive chemistry* (Figure 5).

Thus, in addition to *reactional dynamics* and *motional dynamics*, there is a third type of dynamic processes to be considered: *constitutional dynamics*.

Interactional and reactional dynamics are a prerequisite for CDC and adaptive chemistry. Whereas interactional dynamics are embedded in supramolecular chemistry, DCC requires the exploration of the reactional dynamics of reversible covalent bond formation and dissociation. These aspects have been extensively studied in recent years[8,9] and will not be considered here.

3.2. Motional Dynamic Chemistry

Living species implement a wide variety of molecular motions, motors, and machines to sustain the processes of life.[18] High interest and activity has been shown towards the understanding of biological systems, the development of analogues and mimics, as well as the design of fully artificial devices displaying motional dynamics. These investigations have been the subject of many reports and reviews.[19] Some aspects of molecular motional processes of special significance, related more directly to our studies, will be discussed here.

3.2.1. Molecular Motions in Liquids

Molecular motions in biological entities occur in a viscous medium, that is, at low Reynolds number R, which represents the ratio of inertial momentum to viscous forces. Thus, life occurs at low Reynolds number.[20]

Investigating molecular motions in terms of the controlling forces is of great interest for both gaseous and condensed molecular matter. A particularly intriguing case would be that of a molecule crossing over from low to high R behavior as a function of a given parameter. In fact, one may consider that such behavior is presented by the motion of flat molecules, such as benzene and pyridine, as a function of temperature. These considerations suggest to revisit a much earlier study of the physics of molecular motions in liquids.[21]

A detailed analysis of the motions of pyridine molecules, as represented by the rotational correlation times obtained from measurements of nuclear quadrupolar relaxation times, has been performed as a function of temperature (Figure 6).[21] It showed that in the liquid phase, where viscosity is expected to control the dynamic behavior, the motion around the axis perpendicular to the plane (***c***) of the molecule is faster than those around the in-plane axes. In the gas phase, where inertia controls the motions, the opposite holds, because for an oblate molecular rotor, such as pyridine, the moment of inertia is smaller and rotation is easier around

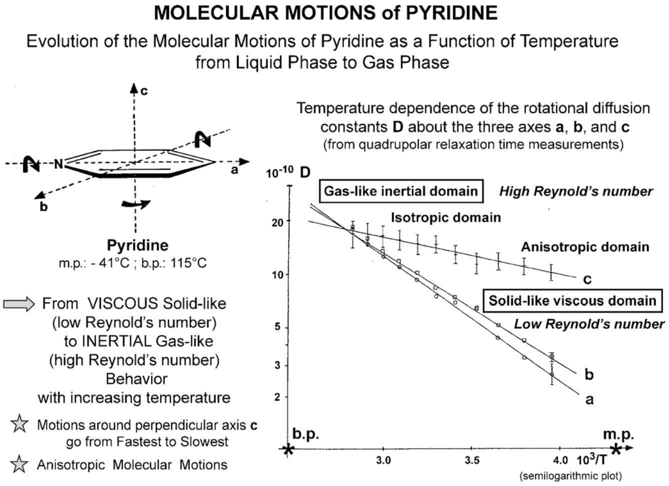

Figure 6. Molecular motions of the pyridine molecule.[21] Evolution of the molecular dynamics of pyridine molecules from viscous type (low Reynolds number motions in the liquid) to inertia-determined motion in the gas phase. The anisotropy switching from the liquid to the gas phase involves a change from the fastest to the slowest motion about the axis *c* perpendicular to the molecular plane.

the in-plane axes than around the perpendicular axis.[22a] The temperature dependence of the motions indicates that the slopes (activation energies) of the graphs in the liquid are different, so that, by extrapolation, the rates of the two types of motions cross in the region of the boiling point. Thus, the pyridine molecules undergo a *motional transition* from a low *R*, viscous (or solid-like) behavior, to a high *R* (gas-like) behavior as a function of temperature (Figure 6). As in benzene[22b] and 1,3,5-triazine,[22c] the motions are anisotropic, both in the liquid and in the gas phase, but with opposite anisotropy. One may note that the title of the PhD thesis of Johannes Diderik van der Waals reads "T*he continuity of the gaseous and liquid states*".[17,23] It is clear that, with respect to the dynamics of molecular motions, there may be a discontinuity from the condensed to the gaseous phase.

3.2.2. Extension–Contraction Molecular Motions

Molecular shape changes of various types and amplitudes, induced by a physical stimulus (such as light) or a chemical effector, are well documented.[19] Particularly large changes in amplitude are provided by the extension–contraction processes undergone by chains of linked heterocyclic groups on the binding of metal ions and on protonation. Suitably designed polyheterocyclic strands, which contain specific folding-inducing sequences of heterocyclic groups (folding codons or foldons), wrap into enforced helical conformations.[24a,b] The binding of metal ions such as lead(II) or zinc(II) to the coordination subunits contained in the strand leads to complete uncoiling and yields a polymetallic complex presenting a fully extended shape.

The addition of a competing complexing agent (such as a cryptand), which strongly binds the metal ions and releases them under protonation, allows for a reversible pH modulation of the coiling/uncoiling process. Thus, extension/contraction is realized by a coupled ion/pH-induced structural switching as a controlled periodic motion. It amounts to a two-stroke, linear motor-type action with a very large stroke amplitude associated, for example, with a change from 11 Å to 60–70 Å (Figure 7). This mechanochemical process is fueled by protonation/deprotonation, that is, by acid/base neutralization energy.[24c,d] The reverse process, coupled ion/pH-modulated reversible coiling of a linear polyheterocyclic strand can also be performed, thereby leading to a helical complex that also represents an induced cation channel (Figure 7).[24e] Combining the two types of processes in a suitably designed ligand yields a device that reversibly contracts in one part while extending in the other (Figure 8).[24f]

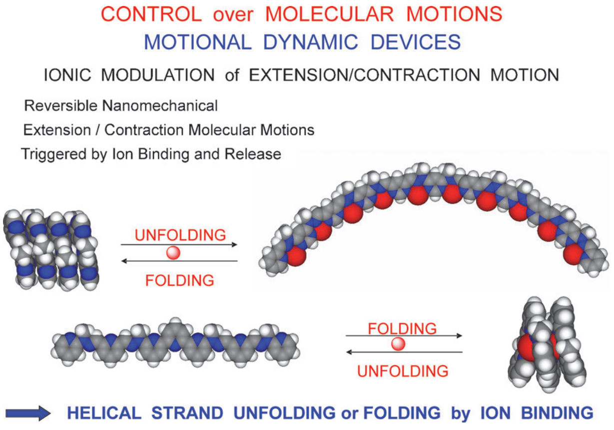

Figure 7. Reversible extension–contraction molecular motions of a molecular strand induced by metal cation binding and release: helical to linear strand (top) and linear to helical strand (bottom) conversion upon ion binding.

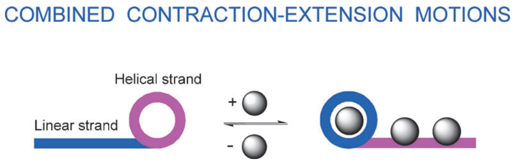

Figure 8. Combination within the same molecule of extension–contraction motions induced by metal-ion binding (see Figure 7).

Similar reversible large-amplitude extension/contraction processes may also be induced in polypyridine-carboxamide strands on protonation/deprotonation.[25]

Shape switching induced by ion binding may be coupled to constitutional dynamics, thus allowing for constitutional adaptation to the morphological state of a component, for example by interconversion between macrocycles and a polymer.[26]

3.3. Constitutional Dynamic Chemistry—Dynamics, Diversity, Selection

Constitutional dynamic chemistry (CDC), briefly introduced above, has been the subject of a number of recent

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general reviews.[4,5,7] Its covalent subdivision has been extensively reviewed.[8,9] CDC processes allow for the generation of diversity and thus are a major factor in the emergence of complexity (see Figure 5). The dynamic combinatorial recombination of compounds gives access to all possible constituents resulting from all possible combinations of the available components, whether they are already formed or potentially available. The full set of constituents of such a constitutional dynamic library (CDL) may thus be considered as virtual, accessible, but not necessarily preformed, that is, as a virtual dynamic library.[8a,27]

CDC thus introduces the concept of *virtuality* into chemical systems, along with the notions of *virtual complexity* and *dynamic complexity*, through both parameters of multiplicity and dynamics (Figure 3). It brings forward another facet of complexity: complexity through the realization/reification of virtuality.

The generation of diversity and the operation of selection by CDC systems have been implemented in a great number of cases involving the search for receptors, substrates, and biologically active substances,[4,8,9,28,29] the self-assembly of dynamic nanostructures,[30] as well as the development of constitutional dynamic aggregates and materials.[4,5,31] In the last case, constitutional response to different stimuli or effectors opens the way towards adaptive functional materials presenting different functions, as for example in a library of dynamic molecular and supramolecular polymers (dynamers)[31] growing out of a rich set of monomer components (Figure 9). Dynamers are able to undergo marked changes in their physical and chemical properties (such as mechanical, optical, substrate binding etc.) through constitutional changes involving monomer incorporation and bond recombination between components; the latter also confers self-healing features (see Refs. [5,31i] and references therein).

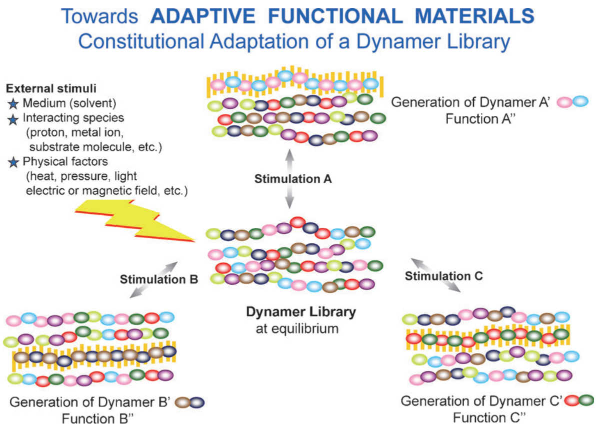

Figure 9. Adaptation of a constitutional dynamic library of dynamic polymers (dynamers; center) to the application of different stimuli **A**, **B**, and **C** by generation of a specific dynamer and a specific function depending on the stimulus.

As has been noted,[5] the full CDL may be considered as the *combinome*, that is, the full set of all combinations of the components, of the dynamic system under consideration, the set of components forms its *genotype* and the sets of constituents generated from these components constitute its *phenotypes*. It may modify its composition, that is, the relative amounts of its constituents, and be characterized by three main parameters: *conversion*, *composition*, and *expression*.[32]

The simultaneous modulation of these three parameters results in the expression of different constituents through component selection driven by chemical effectors or physical stimuli, such as, for example, changes in protonation and/or temperature.[32] The ability of a CDL to respond to stimuli or effectors depends on the dynamic process inducing component exchange and may be activated by different means, for example, through changes in temperature or the addition of additives or catalysis, including organocatalysts.[33] Variations in the expression of the different constituents in response to external agents represent an adaptation of the system to environmental conditions, such as the medium (solvent), to the action of interacting species (protons, metal ions, substrate molecules, etc.), or to physical stimuli (temperature, pressure, electric or magnetic fields, etc.). A case in point is that of adaptation to a phase change, as will be considered in Section 4.2.

CDC has been operational in the implementation of selection in chemistry. Selection in a DCL is performed by interaction of its constituents with a target or an effector. It depends on the information stored in the constituents and its processing through the interaction patterns. Thus, DCLs and their behavior lead to a paradigm shift from the notion of "pure compounds" towards an "instructed mixture", which involves the spontaneous but controlled build-up of structurally organized supramolecular entities from a mixture of instructed components, following well-defined programs and interactional algorithms.[2c,10,34] Such considerations are pushed to their most forceful expression in the extremely large sets of molecules that constitute DNA-encoded libraries; these are the subject of very active development, particularly because of their role in novel routes to drug discovery.[35]

3.4. Multiple Dynamics

The three basic types of dynamic chemistry processes—reactional/interactional, motional, and constitutional dynamics—may be combined in an orthogonal fashion to provide features of higher complexity to the system.

Reactional/interactional dynamics concern the making and breaking of chemical bonds on the molecular level and of intermolecular interactions on the supramolecular level, respectively. Multiple dynamics implement several covalent reactions and noncovalent interactions, especially orthogonal ones.[36a] A case in point is represented by the combination of coordination dynamics (ligand exchange on a metal cation center) with amine exchange on imines formed with lateral carbonyl groups borne by the ligand.[36b]

Motional dynamics cover molecular motions, reversible changes in shape (morphological exchange, including conformational and configurational changes), molecular motors, and "machines".[19]

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Constitutional dynamics involve reversible changes in the constitution of molecular and supramolecular entities by component exchange. Concomitant conformational, configurational, and constitutional changes have been shown to occur during the formation of a receptor for a hydrogen-bonded substrate in an induced-fit process (see Figure 4 in Ref. [5]).[37]

Imines have been described as double dynamic devices, with both motional and constitutional functionality. On the one hand, they show genuine molecular motor-type motion as they are capable of undergoing a full interconversion cycle along a pathway following two different forward and backward steps of configurational isomerization: a photoinduced E-to-Z conversion through out-of-plane rotation about the C=N bond and an in-plane thermally activated nitrogen inversion returning from the Z to the E isomer. On the other hand, imines may also undergo constitutional change by component exchange.[38] These features may be implemented for information processing,[39] as described for a system presenting triple dynamics, in an approach to triple "action" devices, whereby the fast dynamics of photo- or thermo-induced configurational change, the comparatively slow constitutional exchange, and the ability to bind metal ions allow for short term, long term, and locked information storage, respectively (Figure 10; see Figure 17 in Ref. [5]).[39a] Such entities offer three levels of control and generate different physical properties in a switchable fashion.

A particularly intriguing case of merging motional and constitutional covalent dynamics is that of imines of oligoamine chains, whereby the alkylidene residue shifts from an amine site to a neighboring one and also undergo constitutional variation by component exchange, namely of the amine partner (Figure 11).[40] Nondirectional displacement occurs with symmetrical linear oligoamines, whereby the alkylidene residue "walks" along the molecular track. Imines thus behave as very simple but highly versatile prototypes of systems that display relative motions of molecular moieties, which may become motor-like through the introduction of directionality. The unveiled behavior also characterizes a category of motional processes: dynamic covalent motions, which take place through covalent dynamics but without a change in constitution. Numerous extensions may be imagined that give access to a wide range of both motional and constitutional processes.[41] One may note that molecular motions in biological systems as well as in most artificial ones are based on supramolecular dynamics involving noncovalent interactions between molecular partners.[18,19]

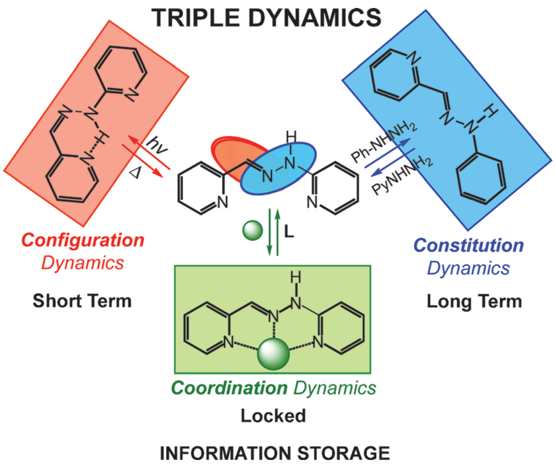

Figure 10. Three types of reversible dynamic processes operating in a bispyridyl hydrazone molecule: configurational, photochemical, and thermal isomerization (top left); constitutional interconversion by component exchange (top right); and lock-in by metal-ion coordination (bottom center). These processes correspond to short-term, long-term, and locked information storage processes, respectively.

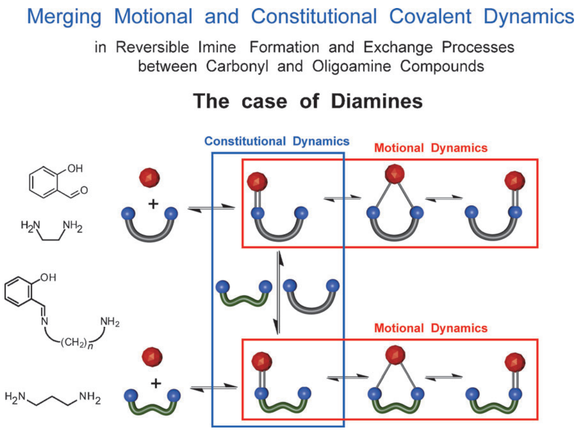

Figure 11. The merging of constitutional and motional dynamic covalent processes, involving: the reversible formation of imines from a carbonyl compound and a terminal diamine (left), the exchange of diamines through transimination (blue frame), and the back and forth motion of the alkylidene moiety between the terminal amine sites (red frames). The structures on the left show specific examples of molecules involved in the processes.

4. Adaptive Chemistry

The various dynamic processes discussed above allow for the advent of adaptive chemistry, rooted in CDC, which allows for constitutional variation by component selection, and relying on motional dynamics for morphological change and nanochemical action. The merging of the features—information and programmability, dynamics, and reversibility as well as constitution and structural diversity—opens up vast perspectives and points towards the emergence of *adaptive and evolutive chemistry.*

Adaptive chemistry explores the response of a system to physical or chemical agents, such as environmental/medium influences, phase exchange, physical stimuli (temperature, light, pressure), chemical effectors (protons, ions), morphological switching.

4.1. Adaptation to Phase Change/Transition

Constitutional dynamic entities may undergo variation in their molecular and/or supramolecular constitution when subjected to a change in phase. Thus, equilibrating metallosupramolecular aggregates in solution adapt to the solid state by transformation into a single entity on crystallization,[5,42a,b] as well as to solvent change, by the generation of different architectures.[5,42c] Dynamic polymers have been shown to select specific components in response to changes in the composition of the medium under the pressure of hydrophobic effects (see Figure 13 in Ref. [5]).[43]

4.2. Adaptation to Medium Switching: Reversible Phase Separation

The passage from a hydrophilic to a hydrophobic environment or the reverse is of great importance, as it takes place in membrane transport processes that may involve liquid membranes, artificial bilayer membranes, or transfer through cell membranes. One may expect that CDLs adapt to such a phase change and that this adaptation would be reversible if the system can be switched back and forth between homogeneous/single phase and phase-separated states.[44]

Indeed, a dynamic covalent library of interconverting imine constituents, dissolved in an acetonitrile–water mixture, has been shown to undergo constitutional reorganization upon liquid–liquid phase separation induced by a physical stimulus (heat) or a chemical effector (inorganic salt, hydrophilic or hydrophobic additive; Figure 12).[44a] The process operates reversibly, regenerating the initial library upon phase reunification. It represents the behavior of a dynamic covalent library upon reversible phase separation and its adaptation to a phase change, with amplification of the best-suited/fittest constituents for each phase and down-regulation of the amphiphilic ones through medium-induced component selection. It may also be considered as self-sorting,[34,45] modulated by reversible phase change. Such processes are of wide interest for the study of adaptive behavior in abiotic as well as biological membrane transport systems,[46] including the potential dynamic delivery of active agents. Furthermore, they allow, in principle, to subject a CDL to non-equilibrium conditions by coupling it to a phase change. They also touch upon the interesting question of the behavior of a dynamic covalent library at an interface, where dynamic redistribution of the components could take place and facilitate phase transfer.

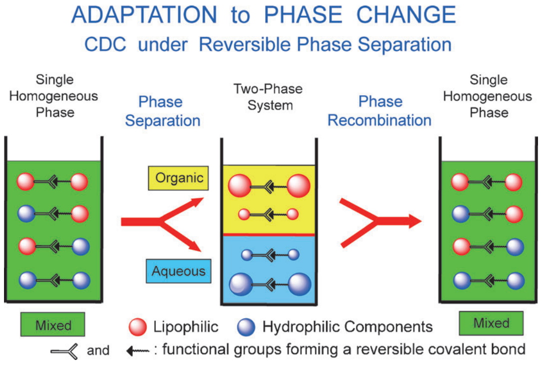

Figure 12. Component redistribution occurring in a dynamic covalent library on phase separation and recombination of a binary organo-aqueous solvent mixture. Left: Library constituents in the single homogeneous phase (green). Center: Phase distribution and redistribution of constituents after phase separation and equilibration, with up-regulation of the homophilic constituents and down-regulation of the amphiphilic ones in the organic phase (yellow) and aqueous phase (blue). Right: Regeneration of the initial library after phase reunification. Red and blue spheres: lipophilic and hydrophilic components, respectively; their size represents their relative abundance.

4.3. Simultaneous Adaptation: Co-Evolution

Multiple dynamics provide the opportunity to perform multiple adaptation by the optimization of several features: constitutional, motional, and structural. Multiple constitutional adaptation represents a *co-evolution* process, whereby two or more species engaged in an agonistic relationship operate synergistically and reinforce the formation of each other by their simultaneous optimization. It involves the constitutional amplification of the best adapted partners.

This is the case for the enforced parallel formation of given dynamic receptors under the effect of those substrates that are bound the best. Thus, simultaneous formation of a bis(imine) macrocyclic ligand and complexation of a metal ion cause the synergistic generation of the most stable complexes with component selection: each metal ion selects for the diamine that gives the best adapted macrocyclic ligand (i.e. the best binder) and conversely (Figure 13, top).[47] In other words, the substrates (metal ions) generate their own receptors by parallel selection of the "best" components.

The ability of metal ions to rearrange a dynamic covalent polymer to generate a new polymer and to reveal the very presence of those cations by an optical signal offers a case of self-sensing.[48] DCLs of metal–dye complexes provide a platform for sensing.[49] Co-evolution processes allow for fast optimization and provide a strong driving force in adaptive chemical systems through simultaneous selection of the mutually "fittest" partners.

5. Constitutional Dynamic Networks

Along the path towards systems presenting higher levels of complexity (Figure 3), multiple dynamics generate complex networks that connect multiple constituents presenting multiple functional and motional behaviors. As stated earlier,[5] CDC gives access to the generation of networks of dynamically interconverting constituents connected structurally (molecular and supramolecular arrays) and eventually also reactionally (sets of connected reactions). They define *constitutional dynamic networks* (CDNs) that may in particular couple to reversible or irreversible thermodynamic processes and present a specific stability/robustness with respect to external perturbations. Connectivities between the constituents of a dynamic library define agonistic and antagonistic relationships, depending on whether the increased expression of a given constituent increases or decreases the expression of one or more of the others. Thus, feedback between two (or more) species (e.g. a substrate and its receptor) may lead to their simultaneous optimization.

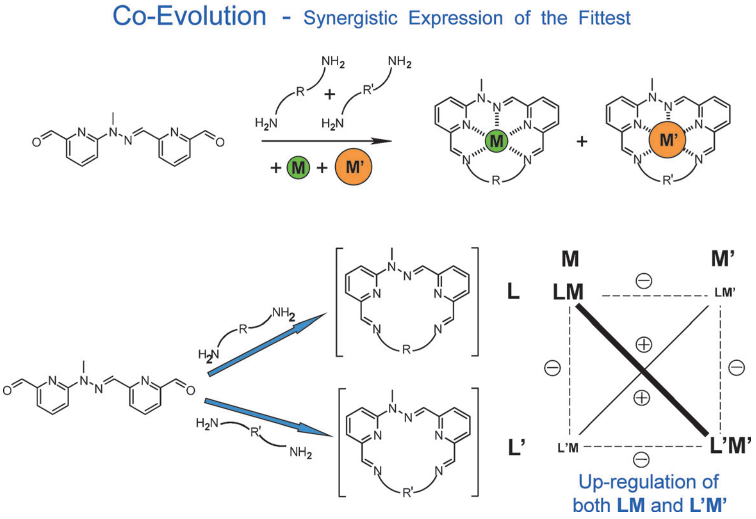

Figure 13. Co-evolution: Two agonists are simultaneously amplified by synergistic expression of the mutually fittest members of a receptor (ligand)–substrate (metal ion) pair (top). An illustration of a co-evolution process whereby the assembly of two macrocyclic ligands **L** and **L′** from their acyclic components is driven by the binding of the preferred metal ion **M** and **M′**, respectively. Note that: 1) the assembly involves selection of the diamine component; 2) it occurs with shape switching of one of the components; 3) cation binding drives shape switching and formation of the ligands, which only exist as such when the complex is formed.[47] Bottom: Representation of the process above within the framework of square networks; left: formal representation of the formation of ligands **L** and **L′** from their components; right: square network representation of the process; it involves the simultaneous amplification of the best/mutually fittest partners **L**-**M** and **L′**-**M′**. The substrates (metal ions) generate their own receptors by parallel selection of the "best" components.

The structures of the constituents[50a] and the network in which they participate may be analyzed within the framework of graph theory[50b] and complex networks.[51] Such dynamic sets of interconnected compounds (in the present case, by constitutional interconversion) may be represented by weighted networks,[52] where vertices, edges, and diagonals describe the connections between the members of a set, their agonistic or antagonistic relationships, and are characterized by their relative weights. Figure 14 illustrates the simplest case, that of four components **A**, **A′**, **B**, and **B′** which generate four constituents **AB**, **A′B**, **AB′**, and **A′B′** by reversible connection of **A** and **A′** with **B** and **B′**. Such networks are adaptive, as the weights of their vertices/nodes and of their connections/links/ties respond to the application of a stimulus or an effector. Thus, subjecting such a system to interaction with an effector **E** that acts on constituent **AB** drives the up-regulation of **AB** (and therefore of its agonist **A′B′** as well) and the down-regulation of the antagonists **AB′** and **A′B**.

A specific case is that of a CDN undergoing co-evolution (see Section 4.3), a process of connected evolution, whereby two different effectors act simultaneously on the two members of a pair of agonists, thus up-regulating both of them in a synergistic fashion (Figure 13, bottom). The feedback between two (or more) species leads to simultaneous optimization of both (some) through a sort of double (multiple) parallel adaptation. Thus, the generation of a potential receptor may induce the expression of the corresponding substrate and conversely, or two receptors and two substrates may drive synergistically their respective formation in a co-evolution manner (see Figure 13).

Of particular significance is the case where the selection of components in a CDL network is driven by self-organization, specifically by the expression of the constituent leading to the formation of an organized structure, such as a crystalline solid or a gel (as compared to a solution; see also Figure 5 in Ref. [4]).[53]

A network may undergo constitutional dynamic switching from one distribution of constituents to another one when subjected to two different effectors **X** or **Y** that act on a given constituent or on one of its antagonists, respectively, for example, **AB** or **AB′**, as shown in Figure 15 (top) for the simplest case of four constituents. Each state may be characterized by the generation of different properties, such as optical effects and/or substrate binding induced by the constitutional changes.

Figure 15 shows a system illustrating both of the attractive features of a CDN: 1) *dynamic network switching* by adaptation to the application of two different effectors **X** or **Y**; 2) *agonist amplification*, whereby amplification of one constituent drives the amplification of its agonist. This simultaneous up-regulation of agonists may be put to work for the generation of a property displayed by one of the partners by acting on its agonist. This feature is illustrated in Figure 15 (bottom, right-

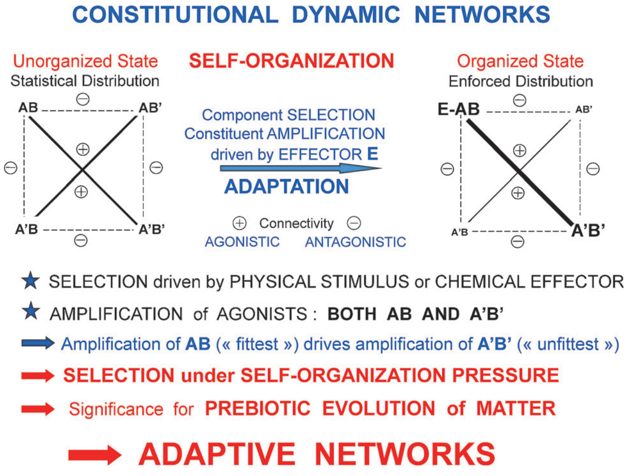

Figure 14. Adaptive networks. Left: 2D representation of a [2×2] constitutional dynamic network as a weighted square graph of four interconnected and interconverting constituents **AB**, **AB′**, **A′B**, and **A′B′** generated by recombination of four components **A**, **A′**, **B**, and **B′** in the combination of **A** and **A′** with **B** and **B′**. Diagonals and edges connect constituents presenting agonistic (+) and antagonistic (−) relationships, respectively. Center and right: Adaptation of the dynamic network in response to the effector **E** acting on **AB** by component selection and leading to an enforced distribution with simultaneous up-regulation/amplification of both agonistic constituents **AB** and **A′B′** (large, bold letters) and down-regulation/repression of their antagonists **A′B** and **AB′** (small letters).

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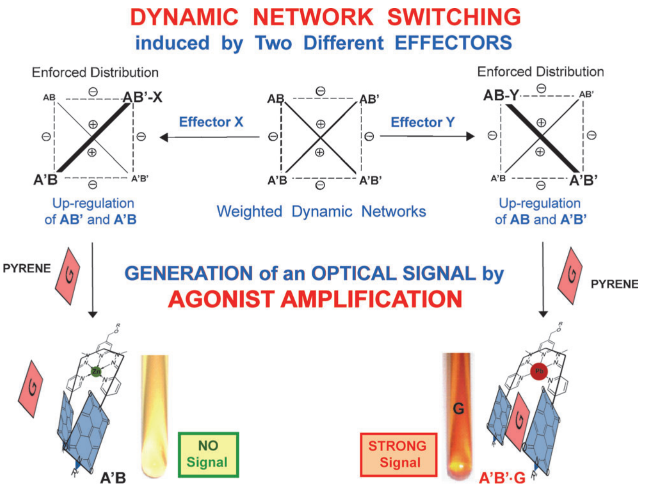

Figure 15. Switching of a constitutional dynamic network (CDN) and implementation of agonist amplification. Top: Graphical representation of the CDN switching occurring on adaptation of a constitutional dynamic network in response to two different effectors **X** and **Y** that act on constituents **AB′** and **AB**, respectively, with generation of two opposite enforced distributions and simultaneous up-regulation of the two agonists **AB′** and **A′B** by **X** (top left) and **AB** and **A′B′** by **Y** (top right) through component selection and constituent expression. Addition of the effectors induces amplification/up-regulation of the agonist constituents (in bold) and repression/down-regulation of the other two (antagonist) constituents, connected by a heavy and a light diagonal axis, respectively. Bottom right: Generation of an optical signal by an indirect process involving the agonistically enforced amplification of the optical sensor **A′B′** (capable of binding a pyrene guest molecule by insertion)[54] through up-regulation of its agonist **AB** by the effector **Y**. Bottom left: Repression of signal generation by up-regulation of the inactive **A′B** through up-regulation of its agonist **AB′** (unable to bind a guest molecule) by the effector **X**.

hand side), where the up-regulation of the constituent **AB** responding to effector **Y** (a metal complex) up-regulates its agonist **A′B′**, which is able to bind a guest, and thus generate an optical signal (e.g. a color change) in this indirect fashion.[54]

A consequence of the fact that agonistically related constituents are simultaneously amplified is that enhancement of the "fittest", with respect to application of/interaction with a given effector, also induces promotion—survival of the "unfittest"! In a more general view, one could consider that evolution towards the "fittest" also provides a niche (environmental, "ecological" or something else) for the "unfittest". It represents an amplification of the constituents that display the least competition for the same resources and occupy different ecological/medium/environmental niches. Along the same lines, antagonistic relationships lead to the repression or extinction of partial competitors that thrive for some of the same resources (components).

5.1. From 2D to 3D Constitutional Dynamic Networks

The great majority of analyses and applications concern two-dimensional networks. Three-dimensional networks are rather uncommon.[55] Nevertheless, an experimental realization is embodied in a CDC system subjected to distribution between two phases, as a single homogeneous liquid phase is separated into two phases (see Section 4).[44a] The process undergone by the system can be represented within the framework of constitutional dynamic networks. The four constituents in the single homogeneous phase define a square, which splits, for the separated two-phase system, into two squares whose corners are connected through the interface, thus defining a cube (Figure 16). The system exemplifies the splitting of a 2D (square) into a 3D (cube) constitutional dynamic network. The trans-phase edges of the cube connect identical constituents distributed in the two phases. The trans-phase diagonals connect the agonists between the two phases, in particular those two agonists that are amplified on phase separation and represent the *fittest constituent in each phase.* Thus, the generation of the fittest in one phase is linked to that of the fittest in the other phase, each of them occupying their environmental "ecological" niche. Such phase change induced modulation of chemical constitution may bear relation to the selective evolution of biologically significant molecules, whereby they adapt their constitution to specific interconnected environmental niches in prebiotic conditions. On the large scale, it also relates, for example, to the parallel evolution of organisms on the ground or in the aqueous phase of the sea.

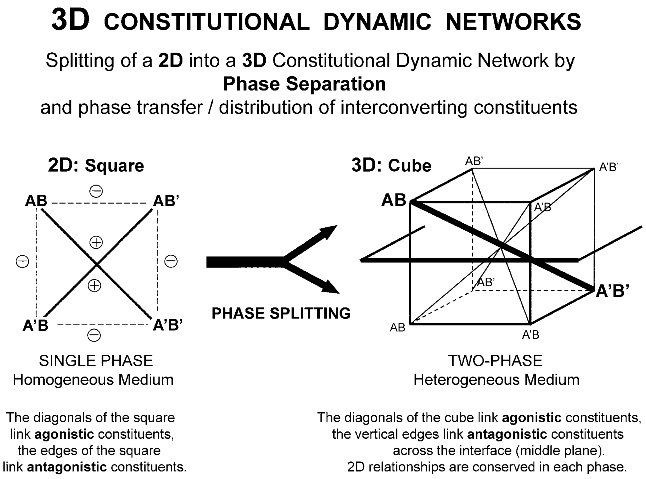

Figure 16. Splitting of a 2D (square) into a 3D (cube, or more generally, a square prism) constitutional dynamic network by liquid/liquid phase separation. Phase transfer of the interconverting constituents **AB**, **A′B′**, **A′B**, and **AB′** across the interface (horizontal plane) occurs with adaptation to each phase through component exchange. The diagonals of the cube link agonistic constituents and the vertical edges link antagonistic constituents across the interface. The larger size and bold letters of **AB** and **A′B′** as well as the thicker diagonal line linking them indicate simultaneous up-regulation of these two agonistic constituents across the interface. The interface plane makes a given constituent antagonistic to itself from one phase to the other.

Developments towards systems of higher complexity concern the generalization towards sets of multiple constituents (beyond four). These can result from the combinatorics of multiple components,[56] their analysis in terms of associated multinodal networks, and the consideration of networks

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of higher dimensionality than the 2D square network. Furthermore, they also concern the implementation of various network topologies that define the arrangements of the nodes and ties (links) describing such more complex CDLs that have preferential connections and circuits. Analysis of weighted networks defines the states of complex systems at multiple scales.[57] The full set of vertices/nodes, edges/links, diagonals, and their respective relative weights (and eventually directionality) together with their dimensionality may be considered to define the *connectome* of the system.

One may note that when the members/nodes of a network are formed by association between components involving molecular recognition processes, then constitutional networks become dynamic *recognition networks*. Similarly, when the links represent chemical transformations between constituents, one may speak of *reaction networks*.[58]

6. Chemistry of Complex Systems—Systems Chemistry

In the long-range perspective, the development of chemical science is toward complex systems, spanning the broadest outlook from divided to condensed matter then to organized and adaptive matter, on to living matter[59] and thinking matter, up the ladder of complexity.

The chemistry of complex systems rests on the implementation in chemistry of the features of complexity (Figure 3) and opens up to a chemistry of systems.[60,61] It leads from species to systems, from property to function, from structure to information. It represents a step forward in unraveling the ways and means that progressively drive the increase in complexity of matter through self-organization. It involves highly interconnected networks (reactionally as well as constitutionally) that present features such as feedback, regulation, and adaptation, or conversely robustness[62] in the presence of perturbations.

Entities presenting multiple levels of control (such as the three-way device shown in Figure 10)[39a] are able to generate different physical (e.g. spectroscopic) properties or chemical states (protonated, free or bound, reactive, etc.) in a switchable fashion. They thus represent components for the design of systems that display a high level of functional complexity.

Evolution is concerned with function rather than structure. In this respect, CDC may allow for two different, opposite, behaviors: *plasticity*, for achieving adaptation and generation of a novel function, and *robustness*, whereby a function is conserved, with functional stability resulting from the expression of the same or a similar function in different constitutions.

Cooperativity[63a–g] and nonlinearity[63h] are aspects relating to the integration term $\boldsymbol{I_2}$ of the complexity relationship [see Eq. (1)]. They participate in the functional features of the self-organization processes. Complex systems are characterized by a higher integration $\boldsymbol{I_2}$ with respect to complex processes.

Complex adaptive systems and networks present the characteristics that define complexity (Figure 3) with coupling to the environment and responding to it. They offer developments towards high-level functions, such as training, learning,[64] and decision-making[65] capabilities. Training and learning involve progressive adaptation of a system subjected to repetitive application of a stimulus or an effector, thus building up an adapted state and retaining it. Decision making represents a reaction of the "educated" system to multiple inputs. Training and learning thus involve progressive modification/adaptation of the connectome, and decision making rests in the response of the connectome to multiple inputs/solicitations. Further on, towards higher complexity, the introduction of compartmentalization and boundary conditions allows for different systems to be coupled and complex networks to be set up.[51,65–67]

The dynamic features of CDC allow for structural and functional variation in response to internal or external factors and for integration into dynamic systems, thus leading to adaptive chemistry and further to evolutive chemistry when the acquired features are conserved (Figure 17).[3a] Together with the corresponding areas in physics and biology, chemistry builds up a science of complex, self-organized, evolutive matter. The already remarkable achievements point to the even greater challenges that lie ahead. The goal is to progressively discover, understand, and implement the processes that govern the evolution from inanimate to animate matter and beyond, to ultimately acquire the ability to create new forms of complex matter.

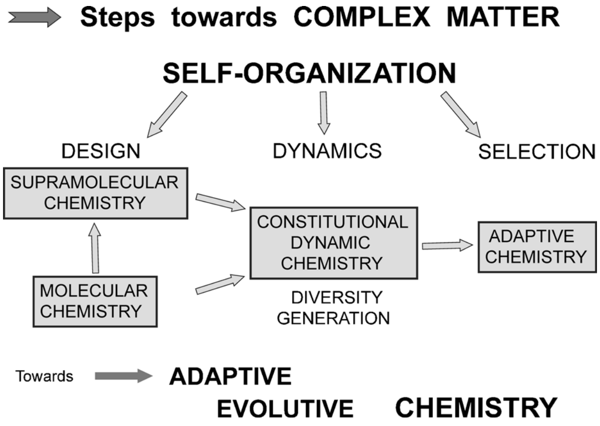

Figure 17. Self-organization of complex matter—Chemistry taking steps.

7. Conclusion

Angewandte Chemie, Applied Chemistry! All too often is chemistry considered as a mere utilitarian activity, barely a science, when it is not despised … It must be "green", it must answer the questions raised by society, it must store the CO_2 that others have produced, it must provide the solutions to problems that others have generated, and so on … It is great to be considered so resourceful, but is that really all chemistry is about?

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Some time ago, a science writer from one of those so-called "high-impact" journals, told me that he was writing an essay on the big questions in science, noting, in words on which I am expanding: the physicists proclaim, we are trying to unravel the laws of the universe. A big question, indeed. The biologists say, we are unraveling the rules of life. A big question, too. What are the chemists doing? They are producing new molecules, novel materials, useful drugs; fine, very nice, and of much help, but, where is the big question? My answer was in substance: "Wait a minute, maybe chemistry is in charge of the biggest question of all, and that is: How does and did matter become complex? How is it, that from divided, to condensed, to organized, to living, and on to thinking matter, the universe produced an entity that is able to ask about the origin of the very universe from which it emerged and about its own coming about? An entity able, in a radical short cut, to interrogate the universe itself from which it is born? Relativity theory, quantum physics, fantastic advances of science, but how is it that an Albert Einstein, a Max Planck, and so many other great scientists (and artists, and others …) of all types could arise? And the answer to this BIG question is: by self-organization! It happened by itself, on the basis of the laws of the universe. But how? And here the answer to the how, also answers the why. It is the task of chemistry to decipher what lies behind this word, to fill in the steps that progressively led to matter of increasing complexity, to find out how new properties emerged at each level, to look beyond at what higher forms of complex matter are there to be evolved, to be created in the minds and hands of the scientists. Thus, chemistry builds the bridge between the laws of the universe and their specific expressions in life and thought (Figure 2). The goal is to discover, understand, and implement the processes that govern the evolution of matter towards increasing complexity, from particles to thoughts. Here we come back to the beginning (Figures 1–3)[2,3,68] to look into the future.

On the occasion of the International Year of Chemistry, 2011, the French Physical Society asked me for a brief general text for their magazine *Reflets de la Physique*. I concluded, somewhat provocatively, that Chemistry is to Physics what a Beethoven quartet is to the laws of acoustics![69] And so, forward to the next 125 years …

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[14] It may be argued that information is a feature that is independent of physical effects, in particular independent of temperature. One may argue to the contrary that information does not exist outside its physicochemical support, and information on any support can be lost/destroyed at a high enough temperature (see also Ref. [15]).

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