

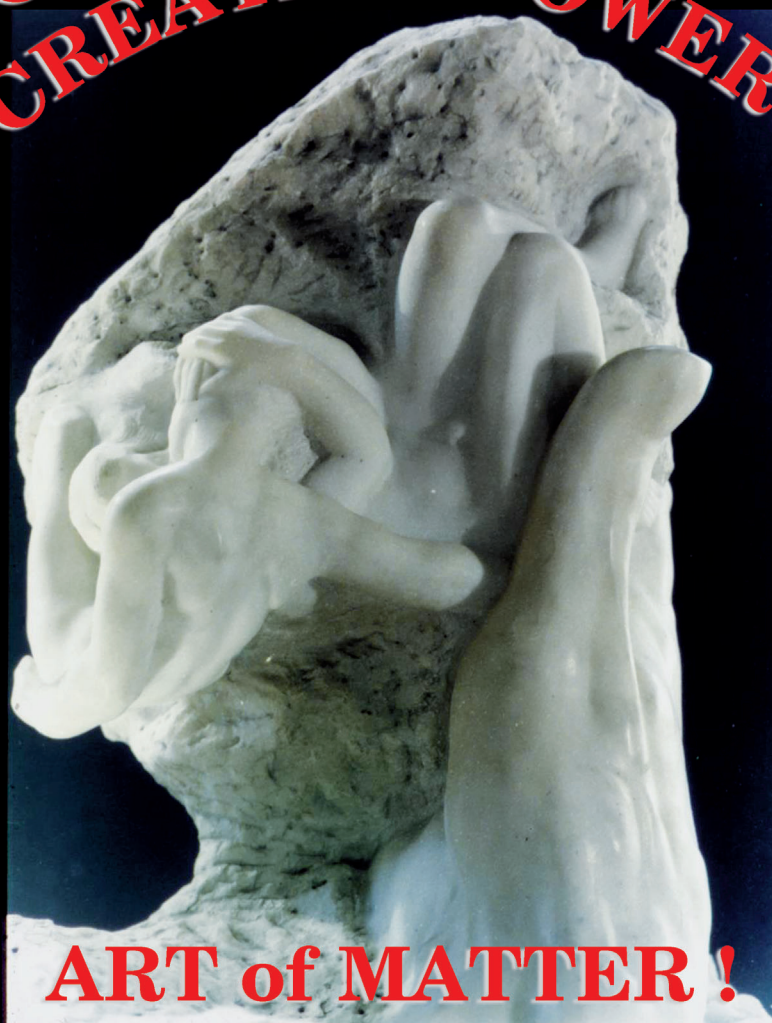
Perspectives in Chemistry—Aspects of Adaptive Chemistry and Materials**

Jean-Marie Lehn*

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**CHEMISTRY
CREATIVE POWER**



ART of MATTER!

Chemistry, pure and applied, is a science and an industry. By its power over the expressions of matter, it also displays the creativity of art. It has expanded from molecular to supramolecular chemistry and then, by way of constitutional dynamic chemistry, towards adaptive chemistry. Constitutional dynamics allow for adaptation, through component exchange and selection in response to physical stimuli (e.g. light, photoselection), to chemical effectors (e.g. metal ions, metal-loselection) or to environmental effects (e.g. phase change) in equilibrium or out-of-equilibrium conditions, towards the generation of the best-adapted/fittest constituent(s) in a dynamic set. Such dynamic systems can be represented by two-dimensional or three-dimensional dynamic networks that define the agonistic and antagonistic relationships between the different constituents linked through component exchange. The introduction of constitutional dynamics into materials science opens perspectives towards adaptive materials and technologies, presenting attractive behavioral features (such as self-healing). In particular, dynamic polymers may undergo modification of their properties (mechanical, optical, etc.) through component exchange and recombination in response to physical or chemical agents. Constitutional adaptive materials open towards a systems materials science and offer numerous opportunities for soft-matter technologies.

1. Introduction

This is indeed a very special occasion, the celebration of the 150th anniversary of the company which proudly (and courageously!) calls itself “The Chemical Company”, the Badische Anilin und Soda Fabrik, BASF! After its 125th Anniversary was recorded in print in 1990, a special issue of *Angewandte Chemie*, which just recently celebrated its own 125th Anniversary, again provides a particularly fitting occasion to sing the praises of the life and liveliness of our science, Chemistry, in the present context in an “*Angewandte*” to a “More-*Angewandte*”-than-Thou modulation.

The present Review will build onto earlier ones, in particular on that which was part of the 125th Anniversary celebrations of *Angewandte Chemie* in 2013. “Steps towards Complex Matter” was the theme then.^[1] The link is clear. Chemical companies transform matter to generate materials of a myriad of breeds from bulk and robust to refined and delicate, towards more and more exquisite control of their features. So, one may feel it justified to take this occasion to briefly evoke some features of chemistry, to reflect somewhat more over the steps towards complex matter (and materials), and to sow some new pebbles along the path delineated earlier.^[1] The intention here is to pursue to some extent a few lines considered in previous recent texts,^[1–3] where numerous relevant references can be found, borrowing here and there themes, discussions, and language.

In view of their tight links, one might set the stage by very briefly (and thus very partially), considering the role of chemistry in science and society.

From the Contents

1. Introduction	3277
2. Background	3278
3. Constitutional Dynamics—Response, Control, and Adaptation	3279
4. Out-of-Equilibrium States	3282
5. Constitutional Dynamic Networks—Constitutional Information Storage and Transfer	3284
6. Constitutional Dynamic Materials—Adaptive Materials and Technologies	3285
7. Conclusions	3286

It is the task of chemistry to build the bridge between physics and the general laws of the universe on one hand, and biology and the emergence of life and thought on the other hand. Indeed, chemistry plays a central role with its place among the sciences and in human knowledge as well as by its economic importance and its ubiquity in our everyday lives.

Being present everywhere, it tends to be forgotten and to go unnoticed. It does not advertise itself but, without it, those achievements we consider spectacular would not see the light of day: therapeutic exploits, feats in space, marvels of technology, and so forth. It contributes to meeting humanity's needs in food and medication, in clothing and shelter, in energy and materials, in transport and communications. It supplies materials for physics and industry, models and agents for biology and pharmacology, properties and processes for materials and technology.

But is chemistry just a mere utilitarian activity? It is great to be considered so resourceful, but is that really all chemistry is about?

[*] Prof. J.-M. Lehn
ISIS, Institut de Science et d'Ingénierie Supramoléculaires
8, allée Gaspard Monge 67000 Strasbourg (France)
E-mail: lehn@unistra.fr

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Chemistry has traced its path in the history of the universe. It came about after particles formed into atoms, which united to give more and more complex molecules; these in turn formed aggregates and membranes, defining primitive cells, out of which life emerged. How did this evolution happen? How did and does matter become complex, from divided, to condensed, to organized, to living, and on to thinking matter? The answer is: by self-organization! It happened by itself, on the basis of the laws of our universe. But how? 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, even to look beyond at what higher forms of complex matter are there to be evolved, to be created by the minds and hands of the scientists. The goal is to discover, understand, and implement the processes that govern the evolution of matter towards increasing complexity, from the particle to thought, and this is a chemical problem. Life is a cosmic imperative,^[4a] and life can be written in chemical language^[4b] as two great figures of biology stated. The underlying process, self-organization, is the cosmic imperative underlying the evolution of life itself and thought as well.^[1,5,6]

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

Chemistry is also a science of transfers, a communication center, 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 interaction, of transformation, and of modelization. In its object, the molecule and the material, chemistry expresses its creative faculty. Chemical synthesis has the power to produce novel expressions of matter, new molecules and new materials with new properties. New indeed, because they did not exist before being created by the recombination of atomic arrangements into novel and infinitely varied combinations and structures.



Jean-Marie Lehn was born in 1939 in Rosh-eim (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 Professor at the University of Strasbourg Institute for Advanced Study. He shared the Nobel Prize in Chemistry in 1987 for his studies on the chemical bases of "molecular recognition". He defined a new field of chemistry, for which he coined the term "supramolecular chemistry". He subsequently developed the field into new directions towards self-organization processes and adaptive chemistry.

By its capacity to continuously recreate the real, to invent and reinvent itself as it develops, by the plasticity of the shapes and functions of the molecule and the material, by its role as a relay, chemistry expresses its creative power and presents an analogy to art. But, it acts not just on the perceptible reality, the appearance (color, texture, odor, etc.), but more deeply on the intimate structure of matter, its essence.

Thus, chemistry is a science and an art, but most to the point in the present context, it is also an *industry*: each scientific component of the discipline has its industrial counterpart. It has for this reason a very marked impact on economic and social life. Chemical companies are thus major players in our societies and in our own lives.

It is therefore not surprising that chemistry is permanently called upon to face a number of new, or increasingly important, socioeconomic questions associated with geopolitical phenomena. Some result from new economic conditions in the industry—costs and availability of raw materials and energy—others from the reorientation of the chemical industry (to deliver products that possess new properties and have high added value), and still others from social concerns about environment and quality of life, such as improvements in working conditions, safe use of products, protection of the community, fighting against pollution. Each aspect of human activity therefore depends upon a better knowledge of chemistry and on its progress, and can be improved by it.

2. Background

2.1. From Molecular to Supramolecular Chemistry

Over about two centuries, molecular chemistry has developed a very powerful arsenal of procedures for making or breaking covalent bonds between atoms in a controlled and precise fashion. Furthermore, it has implemented them in efficient and exquisitely designed strategies for constructing ever more sophisticated novel molecules and materials, presenting a wide range of original properties of broad interest for both basic and applied sciences. Molecular chemistry, thus, has progressively and most impressively established its power over the covalent bond and the world of the molecule.^[7]

Then, in a first change in paradigm, came the time to tame and harness noncovalent intermolecular forces, the time of supramolecular chemistry, the chemistry beyond the molecule, whose goal it is to gain control over the intermolecular bond.^[8] It aims at generating highly complex, functional architectures from designed positioning of molecular components interacting through noncovalent interactions. It has over the last almost 50 years by now, grown into a major field of investigation and has fuelled numerous developments at its interfaces with biology, physics, and materials science, leading to the emergence and progressive establishment of supramolecular science and technology.^[8] The appropriate manipulation of intermolecular noncovalent interactions involved the design and investigation of more or less strictly preor-

ganized molecular receptors of numerous types, capable of performing molecular recognition processes, that is, of binding specific substrates with high efficiency and selectivity. Such processes define an *instructed chemistry*, that implements the storage of information at the molecular level in the structural (geometrical and electronic) features of the molecular components and its processing at the supramolecular level through specific molecular recognition events based on well-defined interaction patterns.

2.2. Programmed Chemical Systems and Self-Organization

These developments led to a second change in paradigm, as supramolecular chemistry paved the way to comprehending chemistry not only as the science of the structure and transformation of matter, but also as an information science, the *science of informed matter*, bringing forward in chemistry the third component of the basic trilogy matter–energy–information.

On the basis of the knowledge gained through the investigation of design and preorganization, supramolecular chemistry has been actively exploring systems undergoing self-organization, that is, systems capable of generating, spontaneously, but in a controlled manner, well-defined, organized, and functional supramolecular architectures by self-assembly from their molecular components, on the basis of the molecular information stored in the covalent framework of the components and processed at the supramolecular level through specific noncovalent interactional algorithms, thus behaving as programmed chemical systems.

The design of such molecular information controlled, “programmed” self-organizing systems also provides an original approach to engineering and processing of functional nanostructures. It offers a powerful alternative or complement to nanofabrication and to nanomanipulation for the development of nanoscience and nanotechnology.

2.3. Constitutional Dynamic Chemistry—Adaptive Chemistry

The third change in paradigm arose from the recognition and implementation of an intrinsic feature of supramolecular chemistry, that it is *dynamic chemistry*, in view of the lability of the interactions connecting the molecular components of a supramolecular entity and the resulting ability of supramolecular species to exchange their components. The extension of such dynamicity to molecular chemistry may be achieved by introducing into the molecular framework covalent bonds that are able to form and break reversibly, so as to allow a continuous change in constitution by reorganization and exchange of building blocks. Bringing together both the molecular and supramolecular levels under a unifying concept led to the definition of *constitutional dynamic chemistry* (CDC),^[1–3,9] residing in the plasticity of the very constitution of the chemical object. CDC generates chemical diversity at both levels within constitutional dynamic libraries (CDLs) of interconverting constituents formed from reversibly connected components. A rapid

development of dynamic covalent chemistry (DCC) to produce dynamic covalent libraries (DCLs) was witnessed in the last fifteen years.^[10,11]

Whereas constitutionally static chemistry relies on designed synthesis for the generation of a target entity, CDC takes advantage of dynamic diversity to allow for variation and selection. The implementation of selection in chemistry introduces a fundamental change in outlook. Thus, *self-organization by design* strives to achieve full control over the output molecular or supramolecular entity by explicit programming, while *self-organization with selection* operates on dynamic constitutional diversity in response to either internal or external factors to achieve adaptation and opens the road towards *adaptive chemistry*.

The features of CDC provide novel opportunities in a number of areas of chemical sciences. They have been implemented in particular in three main areas: 1) the dynamic generation of receptors or substrates driven by molecular recognition processes; 2) the exploration of methodologies for the dynamic search for bioactive substances; 3) the development of dynamic materials.

Of special importance is to optimize the recovery of the fittest constituent(s) from a CDC system under thermodynamic control. It may be achieved by a dynamic resolution methodology, whereby application of an irreversible transformation (e.g. an enzymatic reaction) to the optimal constituent(s) of an equilibrating CDL generates a selection pressure enforcing the exhaustive re-equilibration and up-regulation of this (these) constituent(s) until completion of the selection process.^[12]

In view of a number of recent essays and overviews, (see references [9–11] and references therein) the present report will be limited to the consideration of some specific themes and only with respect to their relevance for CDC and adaptive chemistry. It will elaborate further on three main topics extending along the lines of development of earlier work and discuss how some recent investigations from our group and their implications relate to these perspectives: constitutional dynamics and response, out-of-equilibrium states, constitutional networks, and constitutional dynamic materials.

3. Constitutional Dynamics—Response, Control, and Adaptation

Constitutional dynamics allow for the adaptation of a set of constituents in response to either internal factors or to external physical stimuli and chemical effectors, through up-regulation or down-regulation of given members of the set by component redistribution under thermodynamic (or eventually kinetic) control.

3.1. Self-recognition/Self-sorting.

Self-sorting and self-recognition are features of dynamic systems on both the molecular and supramolecular levels. They rely on dynamic component exchange through reversible covalent or noncovalent connections. They are a feature

of “instructed mixtures”^[13] One may consider that sorting is a separation of objects (entities) into different categories (categorization). On the other hand, self-recognition emphasizes the informational content of the process, as a dynamic selection in response to an agent is an “informed” sorting.

In this context, the recombination of components occurs in response to factors intrinsic to the system, without the intervention of any external agent, and leads to the preferential generation of given entities in the thermodynamically favored state. Such is the case when CDLs undergo a redistribution of their components under the effect of interactions between components of the dynamic library to generate a final distribution of the constituents, as occurs in metallosupramolecular dynamic libraries comprising ligands and metal ions undergoing self-recognition^[13] or self-sorting^[14] processes.

Thus, self-recognition displayed in the binding of different ligand strands to several identical metal cations, as well as of different ligands to several different metal cations leads to the selective formation of double and triple helicates from the mixture of ligands and metal ions.^[13] Particularly intriguing is the generation of highly intertwined architectures resulting from a combination of metallodynamics and covalent dynamics, whereby the ligands within a metallosupramolecular architecture are connected by reversible imine formation.^[15] An impressive recent illustration relates to the formation of metallosupramolecular knots and links derived from circular helicates from functionalized ligands connected through bisimine bridges.^[16] It is based upon the formation of open pentagonal and hexagonal^[17] as well as square^[17b] circular helicates, which also display self-sorting features, as illustrated in Figure S1.^[18] Similar behavior is found for other types of interactions and directing effects. Such processes are now well-documented and the reader is referred to the extensive citations listed for instance in reference [16]. Furthermore, it is worth pointing out that within the framework of dynamic networks (see Section 6), self-recognition and self-sorting processes implement agonistic relationships between the members of the set.

While usually under thermodynamic control, the dynamic build up of metallosupramolecular architectures may reveal kinetically trapped intermediates, as in the case of the successive formation of a triple helicate followed by the conversion of the assembly into a circular helicate (Figure S2).^[19] Such kinetic control involves an out-of-equilibrium step, an important feature of self-organizing systems (see also Section 4).

One may note that, by analogy with reactional, regio- and stereoselectivities, the self-sorting processes may be considered as agent-enforced constitutional selectivity.

3.2. Adaptation in Response to External Agents and to Switching Processes

Molecular devices and materials incorporating stimuli-responsive components have been extensively studied.^[20,21] In combination with constitutional dynamics, they give access to stimuli-responsive constitutional dynamic systems. In this

respect, light is a particularly attractive stimulus as it is orthogonal to chemical effectors and does not introduce any foreign species into the system. It has been extensively used in photoresponsive devices and materials.^[20–22]

Multiple dynamics and the resulting ability of multiple adaptation are of special interest as they may in principle allow for separate manipulation of the dynamic system by different physical or chemical agents. Thus, triple dynamics operate in pyridylhydrazones and pyridylacylhydrazones, which are able to undergo: 1) *conformational dynamics* by shape switching on cation coordination to the triple coordination site;^[23] 2) *configurational dynamics* on photoisomerization from *E* to *Z* configuration stabilized by internal hydrogen bonding to the pyridine group; 3) *constitutional dynamics*, by component exchange through the reversible C=N bond.^[24]

A CDL of pyridylhydrazones and pyridylacylhydrazones may undergo *double adaptation* in response to two orthogonal agents: a chemical effector (for example, a metal cation) and a physical stimulus (for example, light irradiation). Such CDLs display selection and adaptation when subjected either to interaction with metal cations or to light irradiation under conditions allowing for component exchange, thus leading to adaptation under two orthogonal selection processes, respectively *metalloselection* or *photosselection* (Figure 1).^[25a] A related CDL has been shown to form photo- and thermoresponsive supramolecular assemblies on photorelease of potassium cations and under constitutional exchange.^[25b]

3.3. Adaptation to Morphological Changes—Shape Switching.

When a given physical or chemical agent induces a conformational and/or configurational switching of the shape of a component, in addition to interacting with specific constituents of the dynamic library, redistribution of components leads to the up-regulation of given constituents. Shape switching of a component from an extended W form to a compacted U form induced by metal ion coordination, causes a reversible interconversion between a oligomeric/polymeric and a macrocyclic constitutional state, respectively.^[23a,b] A morphological change may also result from light-triggered *E*-to-*Z* configurational isomerization of a photoresponsive component in the DCL. Such is the case for pyridylhydrazones and pyridylacylhydrazones which combine responsiveness to metal ions as well as to light, thus allowing for the operation of reversible adaptation to both metallo- and photoinduced shape switching by oligomer–macrocycle interconversion with component selection in a three-state constitutional dynamic system. The system presents a triple selectivity behavior, being nonselective in the oligomeric state and displaying metalloselectivity and photoselectivity respectively in the two other states (Figure 2).^[26]

3.4. Adaptation in Response to Phase Change

CDLs may be expected to respond to phase changes (liquid/liquid, liquid/solid) by recombination of their compo-

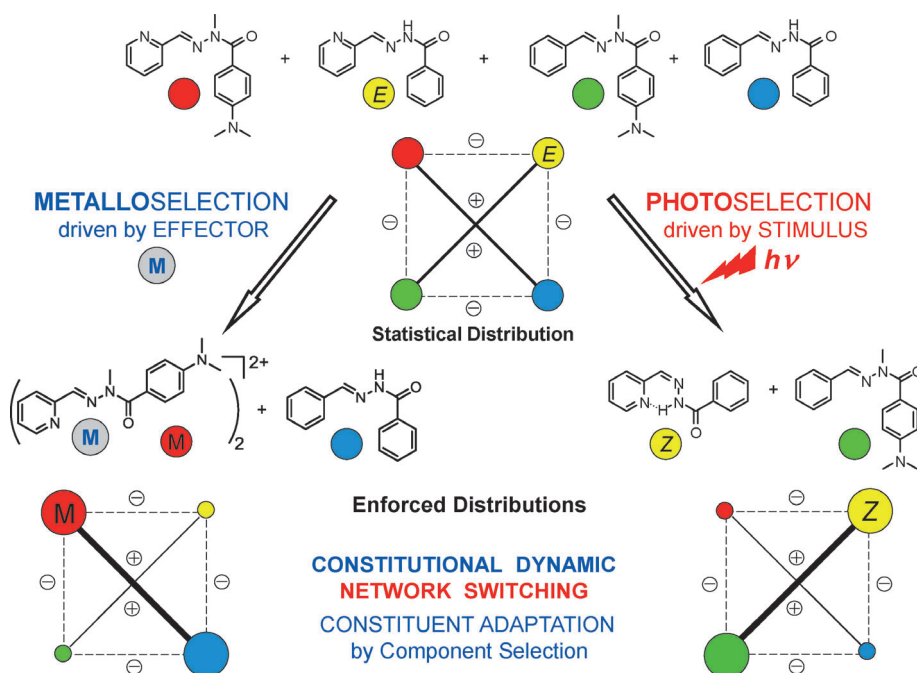


Figure 1. Adaptation of a CDL of four pyridylacylhydrazone constituents by component exchange under (left) *metalloselection* on addition of metal cations and (right) *photoselection* by photoisomerization upon light irradiation. The square CDNs formed by the four constituents may be represented as weighted graphs which display selection and amplification of the ligand constituent forming a cation complex under metalloselection (bottom left) and of the constituent giving a hydrogen bonded Z-form under photoselection (bottom right). The distributions undergo constitutional dynamic network switching on application of the two selection processes. The diagonals and edges of the square link respectively agonistic (+) and antagonistic (−) constituents (for more details see reference [25a]).

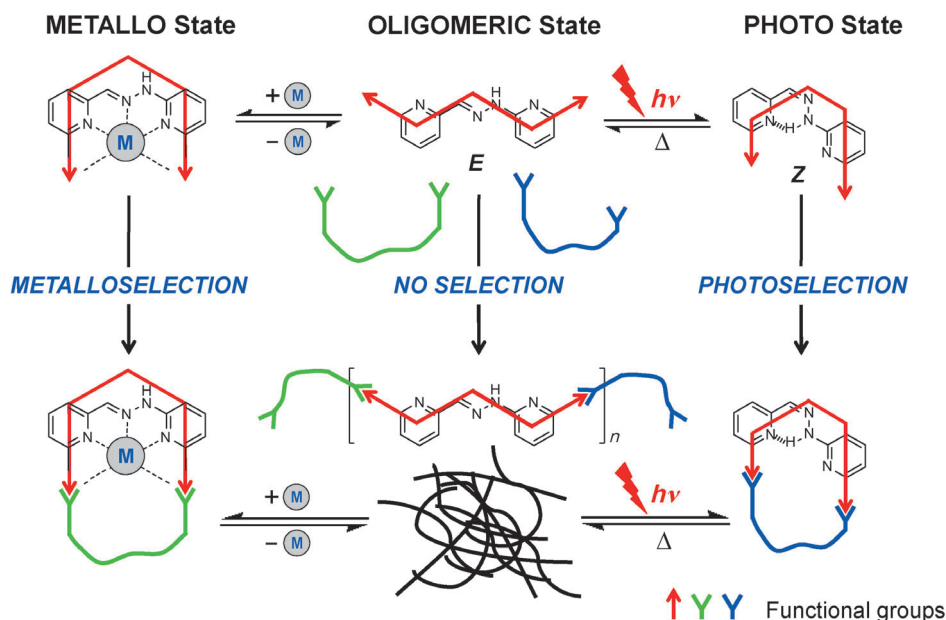


Figure 2. Constitutional adaptation in a triple-state covalent dynamic system: whereas the initial form with W type shape (top, center) yields oligomers by nonselective condensation with partner components, selective reaction with a specific partner takes place under metalloselection, where the ligand adopts a U shape in the complex, (left) and photoselection (right) response (for more details see reference [26]). Note: the metallo and oligomeric states are at thermodynamic equilibrium, whereas the photo state is a light-induced out-of-equilibrium state.

nents so as to generate the constituents best-adapted/fittest for distribution into each phase. Such is indeed the case for separation of a mixed solvent phase into a separated aqueous/organic two-phase system by various chemical agents.^[27a] Similar behavior is achieved when light-induced phase separation caused by photorelease of metal cations from a photoresponsive complex is coupled to a dynamic library of imines.^[27b] The latter process involves a photothermal cycle with reversible interconversion between monophasic and biphasic states. In the presence of a dynamic library of imines generated from hydrophilic and hydrophobic aldehyde and amine components, a coupling to the phase interconversion processes is achieved, leading to a dynamic redistribution of the imine constituents, with amplification, by component selection, of the most lipophilic and the most hydrophilic constituents, respectively, in the organic and in the aqueous phases. The system thus undergoes an adaptation to liquid/liquid phase separation by up-regulation of the fittest constituent for its specific phase. The process is reversible, regenerating the initial distribution of constituents upon phase reunification. It also represents the coupling of a dynamic covalent library to out-of-equilibrium conditions resulting from the photogeneration of a kinetically trapped entity (see also Section 4).

3.5. Dynamic Covalent Chemistry at the Solid/Liquid Interface—Adaptation to a Surface

With respect to DCC in solution or in liquid/liquid two-phase conditions, novel features may emerge when it is conducted in a two-phase setup involving a solid/liquid interface. The occurrence of DCC at the solid/liquid interface has been demon-

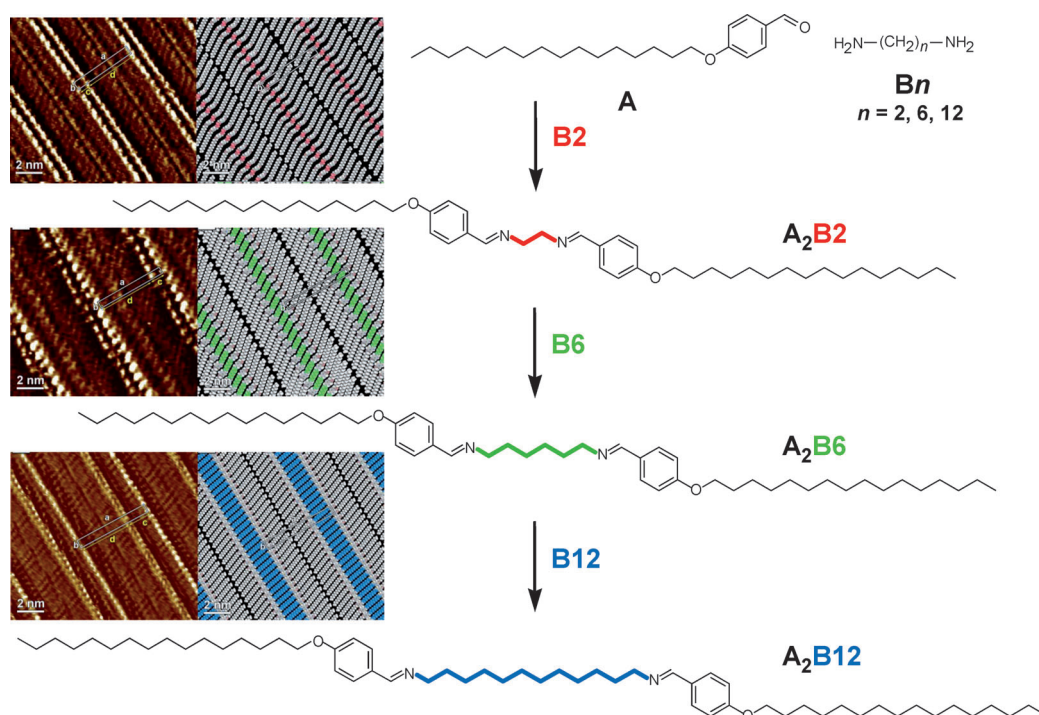


Figure 3. Dynamic covalent chemistry at the solid/liquid interface monitored by STM: Formation of the bisimine A_2B_2 and bis-transimination exchange processes by reaction with the diamines **B6** and **B12** (right); STM images of self-assembled 2D nanopatterns of the molecules A_2B_2 , A_2B_6 , and A_2B_{12} (left, from top to bottom) at the liquid/graphite interface. For clarity, the bisimine chains have been highlighted in different colors (for more details, see reference [28]).

strated on the submolecular scale by in situ scanning tunneling microscopy (STM) imaging.^[28] Thus, the formation of A_2B bisimines was found to occur at the HOPG–solution interface upon double condensation of the aldehyde **A** with different aliphatic α,ω -diamines (**B**; Figure 3). The process displays adaptation to the formation of the 2D array under surface-controlled product formation and chemoselectivity, whereby, in contrast to the solution, adsorption drives the reaction to completion and induces constituent selection for the bisimine with the longest chain. The reversible bis-transimination reactions between A_2B and different diamines **B_n** to give different bisimines A_2B_n was monitored in situ by STM (Figure 3). The surface-mediated bis-transimination reactions and their visualization at the solid/liquid interface open new avenues for the understanding of the parameters, such as packing and adsorption, affecting thermodynamic and kinetic features of covalent dynamic processes at a surface, and leading in particular to constituent selection and selective pattern formation.

Of particular significance is the ability of adsorption free energy to act as physical agent driving the completion of a reaction and the selection of a given constituent of a dynamic covalent library. The incorporation of specific functionalities at predefined positions also paves the way towards the bottom-up construction of multicomponent dynamic molecular nanostructures as key element in novel responsive 2D molecular materials and devices, opening up a field of *constitutional dynamic nanotechnology*.

Furthermore, in a broad perspective, the specific behavior observed represents a step in linking CDC with surface science, whereby the fate of a CDL is driven by the thermodynamics, and possibly kinetics, of the interaction of its constituents with a given surface, in a surface-material-dependent manner. Extending to three dimensions, one may consider component recombination and adaptation of a CDL to constituent inclusion into porous materials.

4. Out-of-Equilibrium States

CDC processes are usually performed in equilibrium conditions, resulting in the ther-

modynamically controlled distribution of constituents in a given set of conditions. It amounts to the adaptation of the dynamic system to thermodynamic equilibrium. An important step in the further exploration of CDC, notably within systems chemistry,^[29] is to apply out-of-equilibrium or far-from-equilibrium conditions to the system and examine its behavior under kinetic control.

Such conditions can be established by changing the characteristics of the environment (temperature, pressure, pH, aqueous/organic, etc.) or by imposing an external perturbation to drive a system out of equilibrium.^[30,31] For instance, application of an electric field to liquid-crystal-forming imines^[30a,b] or micelle formation from amphiphilic imines^[30c] drives the amplification of the fittest constituent(s), and coupling to a chemical pH oscillator leads to a rhythmic assembly system.^[31]

Light is a particularly convenient tool for creating out-of-equilibrium conditions, as photoisomers are not the thermodynamically stable forms. This is the case for *E*-to-*Z* configurational photoisomerizations such as those involving C=N bonds shown in Figures 1 and 2.

In this respect, one may consider the assembly, by the dynamic covalent chemistry approach, of substrates or inhibitors for biological^[32] or synthetic receptors^[2,10,11] (see Figure 9 in [2]) in the context of out-of-equilibrium systems. Thus, the photoinduced modification of the binding site of a photoresponsive receptor entity would result in the generation of a kinetically trapped out-of-equilibrium form

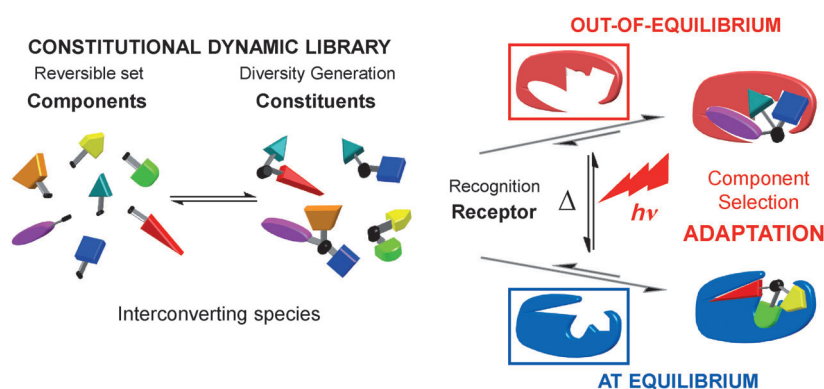


Figure 4. Photoresponsive constitutional dynamic system with photogeneration of an out-of-equilibrium state of a receptor entity. The system displays adaptation either to the equilibrium or to the out-of-equilibrium state of the receptor. It undergoes a dynamic search and up-regulation of the constituent that is the best partner for the receptor in each state by molecular recognition-driven component selection.

of the receptor, which then would be expected to amplify, by component selection in a dynamic library of constituents, the constituent that best fits the photomodified receptor. The process amounts to adaptation of a CDL to two different states, the thermodynamically stable state of the receptor on one hand, and on the other hand the out-of-equilibrium state of the photogenerated form of the receptor (Figure 4).

Imposing a *liquid/liquid phase separation* upon a solution of a CDL results in a perturbation of the system and provides a physicochemical tool for establishing nonequilibrium conditions to which the constituents adapt by recombination of their components with up-regulation of the fittest for each phase, organic or aqueous.^[27a]

If phase separation is induced by light, a sort of conditional doubly driven nonequilibrium state ensues, whereby the initial photochemical step generating the photoisomer causes the phase separation to occur. Thus, when phase separation is induced by photorelease of metal ions from their complex with a photoresponsive ligand, subsequent recombination of components takes place with amplification of the preferred constituents and redistribution between the two phases.^[27b]

In such coupled CDL phase-separation systems, whatever the separation-inducing agent, kinetically controlled out-of-equilibrium states are created upon phase separation and upon reunification as the CDL gradually returns to equilibrium (Figure 5). The rate of return to equilibrium is determined by the forward and backward rates of the reversible reaction providing for the exchange of the components and is expected to be different in each phase. Thus, exchange rates of components linked by C=N bonds usually decrease from imines, to acylhydrazones, to hydrazones, and to oximes under comparable conditions. Slow exchange reactions will thus maintain nonequilibrium conditions for a longer time and provide a means for coupling to other processes.

One may note that the simultaneous occurrence of reactions at different rates generates a *kinetic complex-*

ity while evolving towards equilibrium constitutional complexity.

Out-of-equilibrium conditions are instrumental in the operation of membrane transport processes,^[33,34] for instance in artificial three-phase liquid membrane systems.^[33a-e] Thus, beyond passive transport along a concentration gradient, pH and redox gradients create potentials that drive active transport of substrate against its concentration gradient in coupled processes and may regulate carrier-mediated substrate transport selectivity (e.g. K^+/Ca^{2+} ^[33e]).

Phase separation involves the creation of a gradient that may serve to drive transport in a three-phase system involving DCC processes.^[35] In particular, light-induced phase separation represents a photoswitchable liquid membrane system which may in principle be implemented in a three-phase

active transport system, whereby the phase separation establishes a photoinduced nonequilibrium state to drive a substrate through the membrane. Such a transport system would present the attractive feature of creating a potential by a clean stimulus (light) acting by a macroscopic effect (phase separation).

An out-of-equilibrium state may also result in the formation of a highly strained entity that can in principle activate chemical reactions. Activation by structural distortion is for instance well-documented for the amide functional group.^[36a] It has been shown that switching between two morphological states of a ligand component on metal cation coordination or removal causes interconversion between macrocycles and a polymers in a DCL of imines (see also Section 3.3).^[23] In this process, the removal of the metal cation

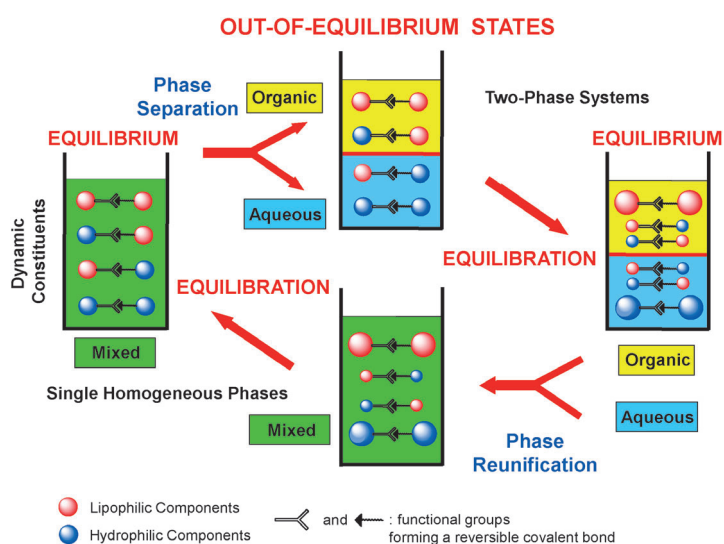


Figure 5. Generation of out-of-equilibrium states of a constitutional dynamic library by reversible phase separation. Kinetically controlled out-of-equilibrium conditions are created on phase separation and on reunification while the CDL progressively returns to equilibrium at a rate determined by the reversible reaction providing for the exchange of the components.

from the coordination stabilized macrocyclic complex, containing two reversible imine bonds, may be expected to yield a markedly strained uncomplexed macrocycle because of the strong driving force of the ligand component to switch shape from its U form in the complex to its stable extended W form in the uncomplexed state. This high-energy intermediate then undergoes fast imine disconnection activated by the resulting strain-induced distortion (Figure 2).^[36b]

5. Constitutional Dynamic Networks—Constitutional Information Storage and Transfer

As previously formulated,^[1–3] CDNs may be represented in terms of networks displaying the links and relationships between their constituents. Thus, the constituents of CDNs form *constitutional dynamic networks* (CDNs) of dynamically interconverting species connected either structurally (molecular and supramolecular arrays of components), or reactionally (sets of connected reversible reactions), or both. They present *agonistic* and *antagonistic* relationships depending on whether they do not share or share a component(s), and as a consequence the increased expression of a given constituent respectively increases or decreases the expression of one or more of the others. They may couple to thermodynamic or kinetic processes and respond to perturbations by physical stimuli or chemical effectors. As the concept and behavior of CDNs have been discussed and illustrated earlier in several instances,^[1–3] only some further considerations on specific features will be pointed out here.

The simplest case of a CDN is that of a CDL of four components **A**, **A'**, **B**, and **B'** generating a 2D square network of four constituents **AB**, **A'B**, **AB'**, **A'B'** by reversible connection of **A** and **A'** with **B** and **B'**. Such networks are adaptive, as the weights of their nodes and of their links respond to the application of a stimulus or an effector. As a consequence of their relationships, if an effector **E** acting on constituent **AB** drives the up-regulation of **AB** (the “fittest”, that is, the best-adapted to effector **E**) it also amplifies its agonist **A'B'** (the “unfittest” for this effector) and causes the down-regulation of the antagonists **AB'** and **A'B**. CDNs responding to orthogonal agents correspond to CDNs that undergo network switching between two or more distributions in response to these independent agents, as is the case for the action of metal ions or light on the same set of pyridylacetylhydrazones mentioned above (Figure 1).^[25a] One may note that self-recognition and self-sorting processes implement agonistic relationships between the members of the system (see Section 3.1.).

A perturbation by an agent acting at any node of a CDN induces changes in all the others in an agonistic or antagonistic fashion, leading to a redistribution of all the linked constituents in the CDN. Thus, a given perturbation will lead to a specific distribution, which may be considered as a sort of fingerprint, a “*constitutional engram*” of dynamic nature, characteristic of the perturbing agent. A case in point is that of the previously reported CDN of four polyimine-type dynamic polymers (dynamers; see Section 6) responding to the addition of alkali metal cations.^[37a–c] Each cation induces

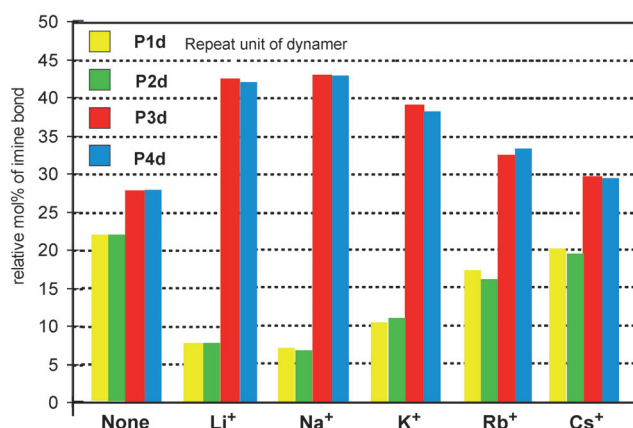


Figure 6. Distributions of the four constituents of a library of four dynamic polymers **P1**–**P4** in response to the addition of the alkali-metal cations Li^+ , Na^+ , K^+ , Rb^+ , and Cs^+ (see reference [37a–c]). **P1** and **P2**, **P3** and **P4** are pairs of agonists. **P1** and **P2** are antagonists to **P3** and **P4**. Each constitutional distribution represents a constitutional engram characteristic of the added cation and identifies that cation. In this rather simple case of just four constituents, the main feature is the ratio of **P1** and **P2** to **P3** and **P4**. **P1d**, **P2d**, **P3d**, and **P4d** indicate four dynamic imine links corresponding to the repeat unit of the respective dynamer.

a specific distribution of the four dynamer constituents that represents a constitutional engram characteristic of the cation acting on the CDL of dynamers (Figure 6). Conversely, a specific distribution allows in principle for the identification of the effector that gave rise to it.^[38] More complex CDNs can be envisaged involving larger CDNs with more constituents derived from a variety of components and responding in diverse fashion to several different chemical effectors.

CDNs may thus be considered as information devices, amounting to storage of information in a distribution and information transfer throughout the network without direct contact, without a vector. Such information remains dynamic and is erased by re-equilibration on removal of the effector or it may be fixed by performing a postadaptation modification, for example, a process that “freezes” the dynamic reaction, such as the reduction of imines to amines, $\text{C}=\text{N}$ to $\text{CH}-\text{NH}$. This ability stresses again the multiple attractive properties of imines as dynamic connections for CDC.

The behavior of a CDL in a two-phase system presents some specific features with respect to the single-phase system. In the case of a CDL with four constituents, it may be represented by a 3D square-prism CDN where the constituents are linked through the interface (Figure 7).^[1,27] A perturbation by an agent in one of the phases/compartments will be reflected in the other one by a redistribution of the constituents between the two phases. The four constituents in each phase form a 2D square CDN and the corners of the two squares are connected through the interface, thus defining a 3D square prism CDN (Figure 7). The trans-phase edges of the square prism connect identical constituents distributed between the two phases. The trans-phase diagonals connect the agonists between the two phases which represent the *fittest constituent in each phase*. Thus, the up-regulation of a constituent **AB** in one phase by a given effector **E** will lead

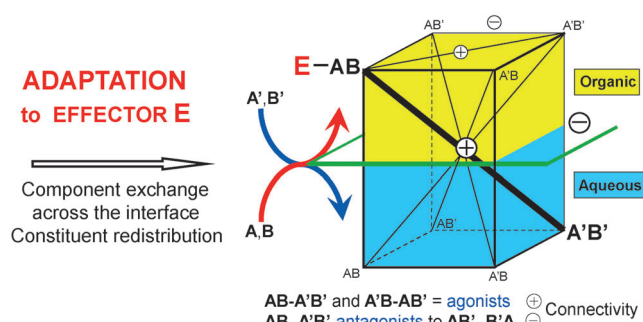


Figure 7. Constitutional dynamic networks as informed adaptive networks: 3D square-prism CDN describing a liquid/liquid two-phase system (see Figure 5). A perturbation by an agent acting on a constituent in one of the phases/compartments will be reflected in the other one by a redistribution of the constituents between the two phases through component exchange in an agonistic or antagonistic fashion, depending on whether they share or do not share a component with the perturbed constituent. The diagonals and the vertical edges of the prism link respectively agonistic and antagonistic constituents across the interface. The up-regulation of constituent **AB** in the organic phase by an effector **E** causes up-regulation of its agonist **A'B'** in the aqueous phase at the expense of the amphiphilic constituents **AB'** and **A'B** in both phases. One may note that the interface plane makes a given constituent antagonistic to itself from one phase to the other. A given perturbation will lead to a specific distribution, amounting to storage of information in a distribution and message transfer between two separate regions/domains of the system without a specific messenger, signalization without signal carrier, providing information about the effector and the perturbation effected in one domain to the other domain.

to up-regulation of its agonist **A'B'** in the *other phase* but to down-regulation of that same agonist in its own phase. Simultaneously, the antagonists **AB'** and **A'B** are down-regulated in both phases. These events take place for a CDL contained initially in a single phase on splitting into two phases by various agents^[27a] or by light irradiation.^[27b] Such a CDN presents three main features: 1) agonist amplification with up-regulation of the fittest constituent for each phase, each of them occupying their preferred compartment/environment; 2) information presentation in a distribution, information storage in a constitutional state; 3) signal generation and message transfer without messenger between two separate regions/domains of the system, signalization without signal carrier, through dynamic redistribution providing information about the effector and the perturbation exerted in one domain to the other domain without the intervention of a specific transmitter (electron, ion, molecule), in contrast for instance to the operation of neurotransmitters (e.g. acetylcholine). These informational features of CDNs make them *informed adaptive networks* (Figure 7).

In addition to being constitutionally defined, the constituents of a CDN may also carry out a function, such as molecular recognition or chemical reaction, giving rise to recognition and reaction networks, whereby the dynamic interconversion and adaptation features of the CDN confers higher selectivities and reactivities by function-driven processes.^[39] Such features suggest intriguing possibilities from both the basic and applied points of view.

As pointed out earlier,^[1] constitutional adaptive systems and networks lead to higher levels of complex matter with the emergence of novel features under coupling to the environment and responding to it. They offer developments towards functions, such as training, learning, and decision making.

6. Constitutional Dynamic Materials—Adaptive Materials and Technologies

The basic principles of CDC may be extended to materials science, thus leading to the definition of an area of constitutional dynamic materials, CDMs or dynamats,^[2,3,37] which implement the basic tenets of CDC and may present special opportunities for technological development and innovation. They comprise both supramolecular and molecular CDMs based on components linked by reversible connections, respectively noncovalent interactions and reversible covalent reactions. They may undergo dynamic changes in constitution by constitutional variation by assembly/disassembly processes under a given set of conditions, with component selection in response to physical or chemical agents and to environmental factors. They thus represent *adaptive materials* of either molecular or supramolecular nature.

One may make the conjecture that CDMs and the resulting adaptive materials open a new era in materials science. They are of broad basic interest considering the challenges raised by understanding and controlling their complex behavior in terms of structure, thermodynamics, and kinetics. They also have wide practical interest extending over all types of materials, in view of the novel features brought about by their constitutional dynamic character. The dynamic and combinatorial features of CDMs provide new ways and means for the design of functional materials and devices,^[40] and give access to a range of novel properties not present in constitutionally “static” materials, such as self-healing, tuning of mechanical and optical properties, bio- and environmental degradability, response to agents such as heat, light, and chemical additives. These prospects apply also to biopolymers and derivatives thereof, as well as to hybrid^[40b] and stimuli-responsive^[40c] materials. Self-healing materials are an active field of investigation^[41] and were listed as being among the ten emerging technologies in 2013 by the World Economic Forum.

Furthermore, in the present context, it must be mentioned that CDC may also have a deep impact on industrial processes, as it provides new avenues for accessing bulk as well as advanced materials. The potential in this respect has still to be realized.

Applying such considerations to an emblematic type of materials, polymers, leads to the definition of a field of *constitutionally dynamic polymers, dynamers*, of both molecular and supramolecular types. They possess the possibility of adaptation by component exchange, incorporation and decorporation through association/growth/dissociation sequences.

In view of the availability of recent reports on dynamers,^[37a,d] in particular one^[37a] written as a contribution to the celebration of the 60th anniversary of Herrmann Staudinger

winning the 1953 Nobel Prize in Chemistry,^[42] only a few specific points will be considered here. The reader is referred to these publications and extensive literature citations for further discussions.

Supramolecular polymer chemistry has actively developed over the years, concerning polymeric entities resulting from the polyassociation of molecular monomers interconnected through complementary interaction/recognition groups.^[37a,d,43] Main-chain supramolecular polymers are generated by supramolecular polyassociation/polymerization of molecular monomers bearing terminal noncovalent interaction groups, in particular complementary hydrogen-bonding patterns. Recently, the converse process, covalent polymerization of supramolecular monomers has also been reported.^[44] One may envisage numerous applications, for instance in areas such as self-healing materials,^[41] supramolecular gels,^[45a] stimuli-responsive supramolecular materials,^[45b] and supramolecular biomaterials.

Indeed, the features of supramolecular polymers make them high-potential candidates for the development of biocompatible materials. In a recent most notable application, a supramolecular polymeric material has been developed and used for the surgical treatment of children born with severe congenital cardiac malformation, requiring cardiac reconstruction. Cardiac implants based on supramolecular polymers have been fabricated and several successful implantations in children have been achieved, representing a breakthrough in surgical practice^[46a] (see also Figure S3). This case illustrates again how difficult it is to foresee the outcome, how unpredictable is the path, and how long it may take from basic research to its applications, here, from the initial introduction of the supramolecular polymer concept in 1990^[43a,b] and its development^[43] to its therapeutic implementation 23 years later! Supramolecularly engineered polymers are amenable to numerous biomedical applications^[46b] and materials for regenerative medicine may take advantage of various types of supramolecular approaches.^[46c,d]

Several aspects of molecular dynamers have been explored, but much remains to be done in view of the great variety of basic investigations as well as of potential applications. Covalent dynamers have been shown by us to allow for blending between polymer films and show environmental degradability (“green dynamers”), progressive variation in mechanical properties from soft to tough, and modification of optical properties by cross-recombination of dynamer films (for the original literature, see references in [2,3,37]).

Biodynamers of the covalent type, such as glycodynamers,^[47a] dynamic proteoids,^[47b] and dynamic nucleic acid analogues^[47c] have been investigated. As in the supramolecular case (see above),^[46] they have potential applications as biocompatible materials.

CDLs may be driven by soft-matter properties, as in the case of selection and amplification occurring upon sol–gel transitions^[48a–c] or phase change,^[49] in particular in response to physical stimuli such as light,^[21,22] an electric field,^[30] or sound.^[50] Dynamic membranes,^[48b–d] coatings, and constitutional hybrid materials,^[48b,c] thermosetting materials based on supramolecular^[51a,b] or on dynamic covalent arrays,^[51c,d]

dynamic nanoparticle assemblies,^[52a] hybrid nanoobjects^[52b] and solid-state molecular networks,^[52c] as well as self-constructing materials,^[53] have been investigated and represent other areas where numerous potential applications of adaptive materials for soft-matter technologies may be imagined and sought, extending further into a systems materials science.^[37a,48]

Both molecular and supramolecular constitutional dynamic features may be implemented for the controlled delivery and release of bioactive or environmentally active substances, such as drugs, agrochemicals, and compounds for home and personal care. Applications for dynamic fragrances have been explored.^[54] One notes that the possibility to control the rate of release by using different (orthogonal) dynamic reactions, which will also depend on environmental conditions (such as temperature or pH), allows for sequential release of different substances from a cocktail owing to the type of reversible process in action. Thus, different types of C=N groups are hydrolyzed at different rates, so that, for instance, a dynamic perfume would change in fragrance as a function of time (and temperature, pH, etc.)! Extension of such considerations to other bioactive compounds for developing “dynamic” drugs, insecticides, or herbicides offers also intriguing perspectives.

7. Conclusions

As stated at the start, the present text builds upon lines of research presently pursued in our laboratory and in many others around the world. I have not touched upon some issues that are facing chemical industry these days, such as being “sustainable”, which may take up the form of an incantatory exhortation. I would think that any bona fide chemist would strive to follow, without having it forced upon her/him, the triple minimization of matter consumption, of energy utilization, and of waste production. In this respect, considering the topics discussed above, multiple developments towards a chemistry presenting adaptive features await to be implemented from the practical point of view too. In particular, there is little doubt that constitutional dynamic materials, dynamic polymers, and CDC in general are likely to find their applications in the development of adaptive technologies, involving both the materials and the processes to access them. One would think (and hope) that companies, especially such a powerful one as that celebrated in the present instances, will explore and achieve the potentials ahead.

Chemistry is a most powerful expression of *Homo Faber*, acting, fabricating, *industriously* ... There are numerous instances where fabricating came before understanding, the chemical opus before the explanation, the novel composition of matter before the use of it, the answer before the question, often the two deeply entangled, searching for the right feature, but not knowing in which corner. Such is the case for instance, for high-temperature superconductivity^[55a] and solar-cell implementation^[55b] of perovskites at the interface of chemistry with physics and materials, on one hand, and on the other hand, for numerous bioactive substances and drugs at the interface with biology and medicine (such as the

anticancer agent ITPP, to cite just one of much personal interest^[56], where the materials and the molecules preceded the discovery of their remarkable properties, which still lack a full explanation, opening the door to novel routes of empirical investigation and to future novel understandings. “Dream” and “try” are two major legs, among all those on which chemistry stands, towards goals sometimes predictable/predicted, sometimes unexpected, empirically discovered or theoretically delineated ... Chemistry continuously reinvents and recreates itself by recomposition of the basic building blocks of matter, the elements displayed in the Periodic Table,^[57] one of the greatest achievements of mankind... and the playground of chemistry!

We chemists have to be deeply thankful to chemical companies, which bring to society and mankind the fruits of chemical research and progress in the science of chemistry. In doing so, we have to acknowledge the work of the researchers of course, but as well of the engineers and technicians who enable the transition from the discovery to the product, from the laboratory to the market, and of the management who ensures that this process to happen.

More specifically, we are particularly grateful to BASF for its collaboration with our institute ISIS for over twelve years now, through the establishment of a sizable research group on our premises, a testimony to the implication of the company in the international university environment, recently extended into the JONAS program which now includes groups in ISIS at the University of Strasbourg, at the University of Freiburg, and at the ETH in Zurich.

By its creative power over the expressions of matter, chemistry is the Promethean science, at the triple merging point of science, art, and industry, as aptly expressed in the recent change in the BASF motto from “The chemical company” to “We create chemistry”. Quite an ambitious program for the future! Bon vent!

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