

# From supramolecular chemistry towards constitutional dynamic chemistry and adaptive chemistry

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Supramolecular chemistry has developed over the last forty years as chemistry beyond the molecule. Starting with the investigation of the basis of molecular recognition, it has explored the implementation of molecular information in the programming of chemical systems towards self-organisation processes, that may occur either on the basis of design or with selection of their components. Supramolecular entities are by nature constitutionally dynamic by virtue of the lability of non-covalent interactions. Importing such features into molecular chemistry, through the introduction of reversible bonds into molecules, leads to the emergence of a constitutional dynamic chemistry, covering both the molecular and supramolecular levels. It considers chemical objects and systems capable of responding to external solicitations by modification of their constitution through component exchange or reorganisation. It thus opens the way towards an adaptive and evolutive chemistry, a further step towards the chemistry of complex matter.

Tracing the birth of a scientific area has quite some arbitrary character. The moment when the seed was planted and

the identification of the roots are usually subject to scrutiny only once the tree has grown. This holds also for supramolecular chemistry and for the present “Anniversary”. In fact, the horizon has broadened progressively as the landscape has been revealed, from selectivity, to molecular recognition to supramolecular chemistry. The path followed by the present author has been briefly outlined earlier.<sup>1</sup> A reflection on these first

forty years is presented in a perceptive editorial.<sup>2</sup>

The concepts and the perspectives of supramolecular chemistry have been delineated.<sup>3</sup> The area has experienced an extraordinary development at the triple meeting point of chemistry with biology and physics. It has given rise to numerous review articles, special issues of journals and books.<sup>4–6</sup> Recognising that it is impossible and illusory to render justice to this intense activity, this special Anniversary Issue assembles expert presentations of some of the active areas of research in supramolecular chemistry.

The intention here is just to briefly provide what could be considered as a sort of blue print, emphasising however the more recent developments, as pursued especially in our laboratory, together with an outlook, along and beyond the lines of earlier horizons (Fig. 1).<sup>3,7–9</sup>

## From molecular recognition and information to self-organisation

Molecular chemistry has, over about two centuries, developed a wide range of very powerful procedures for creating

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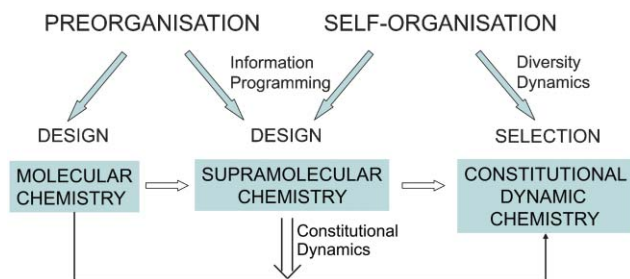
† Dedicated to the memory of Professor Guy Ourisson, mentor, researcher, teacher.



Jean-Marie Lehn

*Jean-Marie Lehn was born in Rosheim, France in 1939. In 1970 he became Professor of Chemistry at the Université Louis Pasteur in Strasbourg and since 1979 he has been Professor at the Collège de France in Paris. He shared the Nobel Prize in Chemistry in 1987 for his studies on the chemical basis of “molecular recognition” (i.e. the way in which a receptor molecule recognizes and selectively binds a substrate), which also plays a fundamental role in biological processes. Over the years his work led to the definition of a new field of chemistry, which he has proposed calling “supramolecular chemistry” as it deals with the complex entities formed by the association of two or more chemical species held together by non-covalent intermolecular forces, whereas molecular chemistry concerns the entities constructed from atoms linked*

*by covalent bonds. Subsequently, the area developed into the chemistry of “self-organization” processes and more recently into “constitutional dynamic chemistry”. Author of more than 700 scientific publications, Lehn is a member of many academies and institutions. He has received numerous international honours and awards.*



**Fig. 1** From Molecular, to Supramolecular and to Constitutional Dynamic Chemistry under Preorganisation and Self-organisation by design and with selection.

ever more sophisticated molecules and materials from atoms linked by covalent bonds.

Beyond molecular chemistry, *supramolecular chemistry* aims at constructing highly complex, functional chemical systems from components held together by intermolecular forces.

Numerous molecular receptors capable of selectively binding specific substrates *via* non-covalent interactions have been developed. They perform *molecular recognition* which rests on the *molecular information* stored in the interacting species. Suitably functionalised receptors may effect *supramolecular catalysis* and selective *transport processes*.

The control provided by recognition processes allows the development of *functional molecular* and *supramolecular devices*, defined as structurally organised and functionally integrated systems built from suitably designed molecular components performing a given action (*e.g.* photoactive, electroactive, ionoactive, *etc.*) and endowed with the structural features required for assembly into an organised supramolecular architecture. Thus emerged the areas of supramolecular photonics, electronics, ionics ...<sup>3,5,10–18</sup>

A most basic and far-reaching contribution of supramolecular chemistry to chemical sciences has been the implementation of the concept of molecular information and its corollaries, instructions and programmed chemical systems, with the aim of gaining progressive control over the organisation of matter, over its spatial (structural) and temporal (dynamical) features. It led to the ever clearer perception, deeper analysis and more deliberate application of information features in the elaboration and transformation of matter,

tracing the path from merely condensed matter to more and more highly organised matter, towards systems of increasing complexity.

Supramolecular chemistry has thus paved the way towards apprehending chemistry also as an *information science*. It started and developed as the chemistry of the entities generated *via* intermolecular non-covalent interactions. By the appropriate manipulation of these interactions, it became progressively the chemistry of molecular information, involving the storage of information at the molecular level, in the structural features, and its retrieval, transfer, processing at the supramolecular level, through molecular recognition processes operating *via* specific spatial relationships and interaction patterns (hydrogen bonding arrays, sequences of donor and acceptor groups, metal ion coordination units, *etc.*).

Furthermore, in addition to this information sensing on direct intermolecular *contact*, the investigation of selective substrate (ions, molecules) transport through membranes has allowed the exploration of signalisation at a *distance*, through the generation of ionic or molecular fluxes.

Achieving optimal molecular recognition rests on the derivation of receptor–substrate pairs presenting complementarity in geometry and interactions, through correct construction of one (or both) of the interacting species. Beyond mastering such preorganisation and taking advantage of it, supramolecular chemistry has been actively exploring the design of systems undergoing *self-organisation*, *i.e.* systems capable of spontaneously generating well-defined, organised supramolecular architectures by self-assembly from their components.<sup>3,7,19–26</sup>

## From self-organisation by design to self-organisation with selection

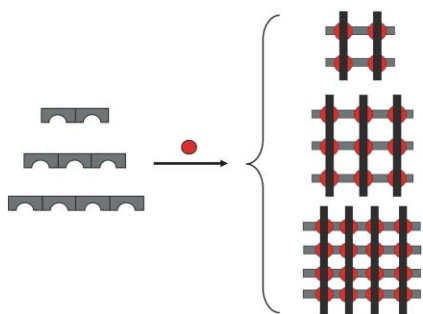
Self-organisation is the fundamental process that has led to the generation of complex matter, from particles to the thinking organism, in the course of the evolution of the universe. Unravelling the mechanisms of the self-organisation of matter offers a most challenging task to chemistry.<sup>7</sup> Along the way, as progress is being made, implementation in non-natural, abiotic chemical systems may be performed.

The spontaneous but controlled generation of complex supramolecular entities by means of suitable components and interactions amounts to performing self-organisation *by design*.

Self-organisation processes may be directed *via* the molecular information stored in the covalent framework of the components and read out at the supramolecular level through specific interaction/recognition patterns, that define processing algorithms. They thus represent the operation of *programmed chemical systems*,<sup>3,19,20</sup> and are of major interest for supramolecular science and engineering.

They give access to advanced *functional supramolecular materials*, such as supramolecular polymers,<sup>27–30</sup> liquid crystals and lipid vesicles<sup>31–33</sup> as well as solid-state assemblies.<sup>34,35</sup>

The design of molecular information controlled, “*programmed*” self-organising systems provides an original approach to *nanoscience* and *nanotechnology*. In particular, the generation of well-defined, functional supramolecular architectures of nanometric size through self-organisation represents a means of performing programmed *engineering* and *processing* of *nanomaterials*. Technologies resorting to self-organisation processes are in principle able to provide a powerful complement and/or alternative to nanofabrication and nanomanipulation procedures by making use of the spontaneous but controlled generation of the desired superstructures and devices from suitably instructed and functional building blocks. The long-range goal is to shift from entities that need to be made to entities that make themselves, *i.e.* from fabrication to self-fabrication.



**Fig. 2** Schematic representation of the self-assembly of metallosupramolecular  $[2 \times 2]$ ,  $[3 \times 3]$  and  $[4 \times 4]$  grid-type architectures from ligand strands possessing respectively 2, 3 and 4 complexation subunits. Subunits containing either 2 or 3 binding sites (e.g. N sites) correspond respectively to metal ions of tetrahedral and octahedral coordination.

A great variety of (functional) supramolecular architectures have been generated by complex self-assembly procedures, of purely “organic” as well as of “inorganic” nature.<sup>3,5,21–26,36–39</sup> The latter have led to a range of metallosupramolecular entities presenting original physical and chemical properties, as is the case for the grid-type arrays of ligands and metal ions extensively investigated in the author’s laboratory (Fig. 2).<sup>40</sup>

As the self-organisation of supramolecular entities takes place through progressive build up of the final entities, it has to explore the hypersurface of all available structure/energy combinations. Consequently, self-organisation processes are in principle able to select the correct molecular components for the generation of a given supramolecular entity from a collection of building blocks. Self-organisation may thus take place *with selection*, by virtue of a basic feature inherent in supramolecular chemistry, its *dynamic character*.

### From supramolecular chemistry to constitutional dynamic chemistry

Supramolecular chemistry has, from the start, been defined in its structural and bonding features as “chemistry beyond the molecule”, its entities being constituted of molecular components held together by non-covalent interactions.<sup>1,3,41</sup> The third feature defining its essence, resides in its dynamic nature,

that was always implicit and operating in all processes investigated, but has been explicitly taken advantage of and implemented only in more recent years. Indeed, supramolecular chemistry is intrinsically a *dynamic chemistry* in view of the lability of the non-covalent interactions connecting the molecular components of a supramolecular entity. The resulting ability of supramolecular species to reversibly dissociate and associate, deconstruct and reconstruct allows them to incorporate, decorporate and rearrange their molecular components. This dynamic character is essential as the supramolecular entities are synthesised or, better, synthesize themselves by self-assembly from their molecular components through more or less rapid exploration of the structure/energy hypersurface. It is thus at the basis of the generation of the highly complex architectures held together by hydrogen bonding, donor–acceptor interactions or metal ion coordination, reported by numerous laboratories. It also allows for self-organisation with selection and gives to supramolecular systems the ability to adapt their architecture as well as their constitution in response to factors such as the interaction with external entities, for instance, in the generation of circular helicates of different size depending on the anion present in the environment (Fig. 3).<sup>42</sup>

The next step consists in the recognition that molecular chemistry is also endowed with similar dynamic features, provided the molecular entity contains covalent bonds that may form and break reversibly, so as to allow a continuous change in constitution by reorganisation and exchange of building blocks. Thus, as an outgrowth of supramolecular chemistry, it leads to a *Constitutional Dynamic Chemistry*<sup>7,8,30</sup> (CDC) on both the molecular and supramolecular levels.

Dynamic chemistry may be generally understood as encompassing two broad areas:

- *reactional dynamics*, concerning the kinetics and mechanisms of chemical reactions;

- *motional dynamics*, concerning external reorientations (such as overall molecular motions in liquids), internal motions (such as rotations around bonds or site inversions), dynamics in

soft matter (polymer chains, colloids, *etc.*),<sup>43</sup> morphological dynamics involving changes in molecular shape; they also cover the intriguing systems presenting “molecular machine” and oriented motion properties.<sup>44–48</sup>

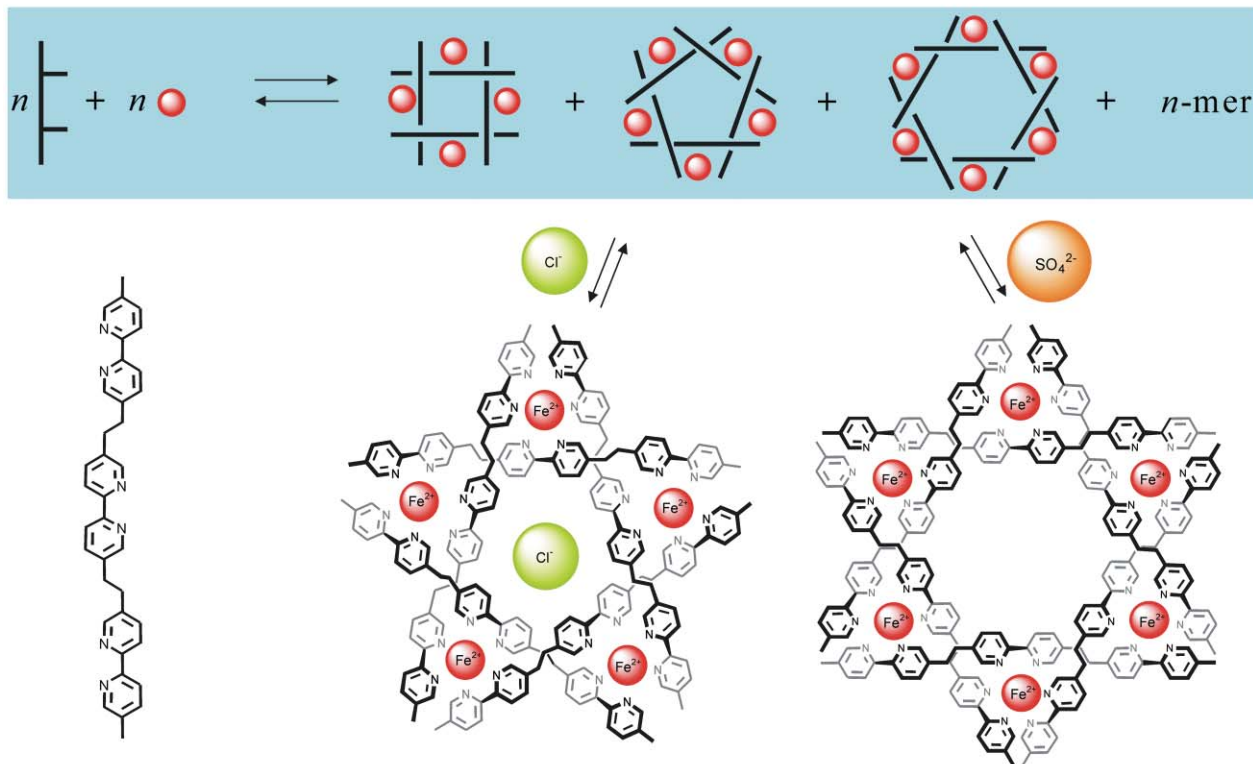
Both aspects apply to supramolecular entities as well as to molecules. A third novel type of dynamic processes is now to be considered, that opens wide perspectives. It consists in:

- *constitutional dynamics*, whereby a chemical entity, be it as well molecular as supramolecular, undergoes continuous change in its constitution through dissociation into various components and reconstitution into the same entity or into different ones.

The emergence of this third type of dynamic chemistry may be related to the explicit recognition of the dynamic features characteristic of supramolecular entities and their introduction into molecules. Importing such dynamic features into molecular chemistry requires shifting from static to “dynamic” covalent bonds, so as to endow molecular species with the ability to undergo similar dynamic exchange and reorganisation processes by virtue of the reversible formation and breaking of covalent connections. It implies looking at molecules as labile entities, in contrast to the usual longing for stability, and opens novel perspectives to covalent chemistry. It requires searching for reversible reactions and catalysts that allow the making and breaking of covalent bonds, preferably under mild conditions. Whereas the supramolecular entities are dynamic by nature, the molecular entities are dynamic by intent.

This radical change in outlook amounts to taking a standpoint opposite to the traditional one and to consider that the dynamic character, resulting from reversible connections, rather than being a drawback gives access both to the richness of constitutional diversity and to the benefits of adaptability. It stresses the virtues of instructed mixtures,<sup>3</sup> such as was revealed in the self-selection processes in the side-by-side self-assembly of helicates in mixtures of ligands and metal ions.<sup>49</sup> It is this work that led us in the early 1990s to envisage a dynamic chemistry bringing into play the constitution of chemical species.

## Dynamic Library of Circular Helicates



**Fig. 3** Dynamic (virtual) library of circular helicates generated from a tritopic ligand strand and octahedrally-coordinating metal ions, expressing different constituents depending on the counter ion (chloride or sulfate) present.<sup>42</sup>

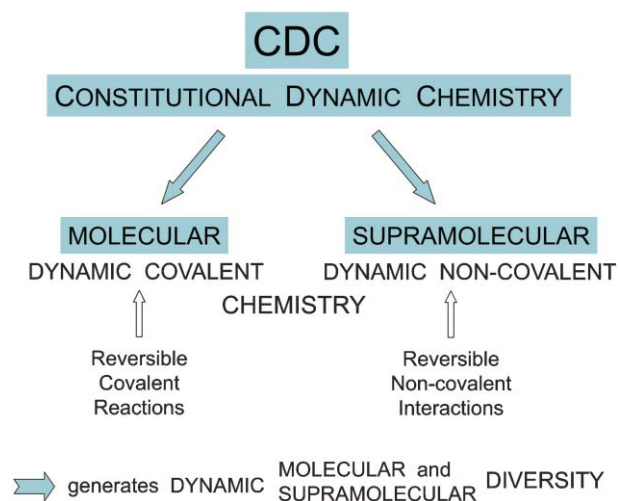
In the context of the evolution of chemistry from molecular to supramolecular, it represents a sort of “back to the future” step, going back to molecular chemistry to endow (provide) it with novel perspectives by introducing into it and fertilising it with supramolecular-type dynamic features.

An intriguing line of development of chemistry is thus being fuelled by a basic paradigm shift from a constitutionally static chemistry to a *constitutionally dynamic chemistry* (CDC),<sup>7,8,30</sup> encompassing *both* covalent molecular and non-covalent supramolecular entities,<sup>9,50–55</sup> defining respectively a *dynamic covalent chemistry* (DCC) and a *dynamic non-covalent chemistry* (Fig. 4). The formation and dynamic character of these entities result respectively from reversible condensation of components through *complementary functional groups* (molecular, covalent, chemical, *functional recognition*) and from recognition-directed reversible association of components through *complementary*

*interactional groups* (supramolecular, non-covalent, physical, *interactional recognition*). They may thus be considered either as *chemically dynamic*, involving chemical reactions or as

*physically dynamic*, based on physical non-covalent interactions.

As at both levels the processes may involve component recombination, they define a *dynamic combinatorial chemistry*



**Fig. 4** Constitutional dynamic chemistry (CDC) covers both dynamic molecular chemistry and supramolecular chemistry that involve respectively dynamic covalent (dynamic covalent chemistry, DCC) and non-covalent connections.

of supramolecular as well as of molecular nature.<sup>50,53</sup> This denomination stresses their combinatorial character, whereas CDC highlights the fact that they concern the basic feature of chemical entities, their constitution.

*Constitutional dynamics* imply changes in constitution concerning the nature, number and arrangement of the components of molecular or supramolecular entities, thus generating *molecular and supramolecular diversity* through continuous recombination, recombination, reorganisation, construction and deconstruction by either external (incorporation, decorporation, exchange of components) or internal (rearrangement, reshuffling of components) processes, under the pressure of internal factors or external environmental stimuli. The system may respond to such effects by expressing the constituent(s) presenting best adaptation to a given situation, through selection of the most suitable components among those available.

A set of interconverting supramolecular or molecular entities represents a real or virtual<sup>30,56</sup> *constitutional dynamic library* (CDL). It may modify its composition, *i.e.* the relative amounts of its constituents, and be characterised by three main features:<sup>57</sup>

1) *conversion*, the total amount of constituents generated with respect to the free components;

2) *composition*, the distribution or relative amounts of the different constituents, that also represents the selectivity of the system;

3) *expression* of a given constituent, that may be defined as the product of conversion and selectivity.

The simultaneous modulation of these three parameters of a CDL results in the expression of different constituents, through component selection driven by chemical and/or physical stimuli. Such is, for instance, the case for sets of imine constituents, under changes in protonation and/or temperature.<sup>57</sup>

Changes in expression of the different constituents as a factor of external parameters represent an adaptation of the system to environmental conditions, such as medium (solvent), presence of interacting species (protons, metal ions, substrate molecules, *etc.*) or physical factors (temperature, pressure, electric or magnetic fields, *etc.*).

## Implementation of CDC

The basic feature of CDC is its dynamic character that allows for the generation of constitutional molecular and supramolecular diversity on which to operate selection in response to the pressure of chemical or physical internal or external factors, thus enabling adaptive chemistry.

Implementation of CDC may be considered from three points of view:

– the exploration of *synthetic systems* directed at revealing the basic features of CDC;

– the application to the search for *bioactive substances*;

– the development of *dynamic materials*.

1) Numerous studies have been performed on either the substrate-assisted moulding of molecular receptors for substrates or the receptor-assisted casting of substrates for receptors from dynamic combinatorial libraries (DCLs).<sup>50–53</sup> Work in our group has been directed in particular towards the influence of physical and chemical effectors on the behaviour of DCLs, as for instance in the case of the constitutional dynamic reorganisation exerted by temperature and protonation on imine libraries<sup>57</sup> or the induction of liquid crystal properties by an electric field acting on a dynamic library.<sup>58</sup>

On the other hand, in the formation of guanine quartet-based hydrogels, it was shown that the system selected the components that generated the most stable gel (Fig. 5).<sup>59</sup> Such a self-optimisation behaviour may be of broader significance, namely for prebiotic chemical evolution, whereby selection is driven by phase cohesion, the entity selected being that giving the most stable organised supramolecular assembly in a sort of *prebiotic Darwinism* driven by self-organisation. The supramolecular organisation drives the selection of the components giving the “fittest” constituent.<sup>60</sup>

Chemical evolution occurs through selection operating on structural diversity, directed by intra and intermolecular electromagnetic forces implementing molecular information and leading to the progressive complexification of matter.

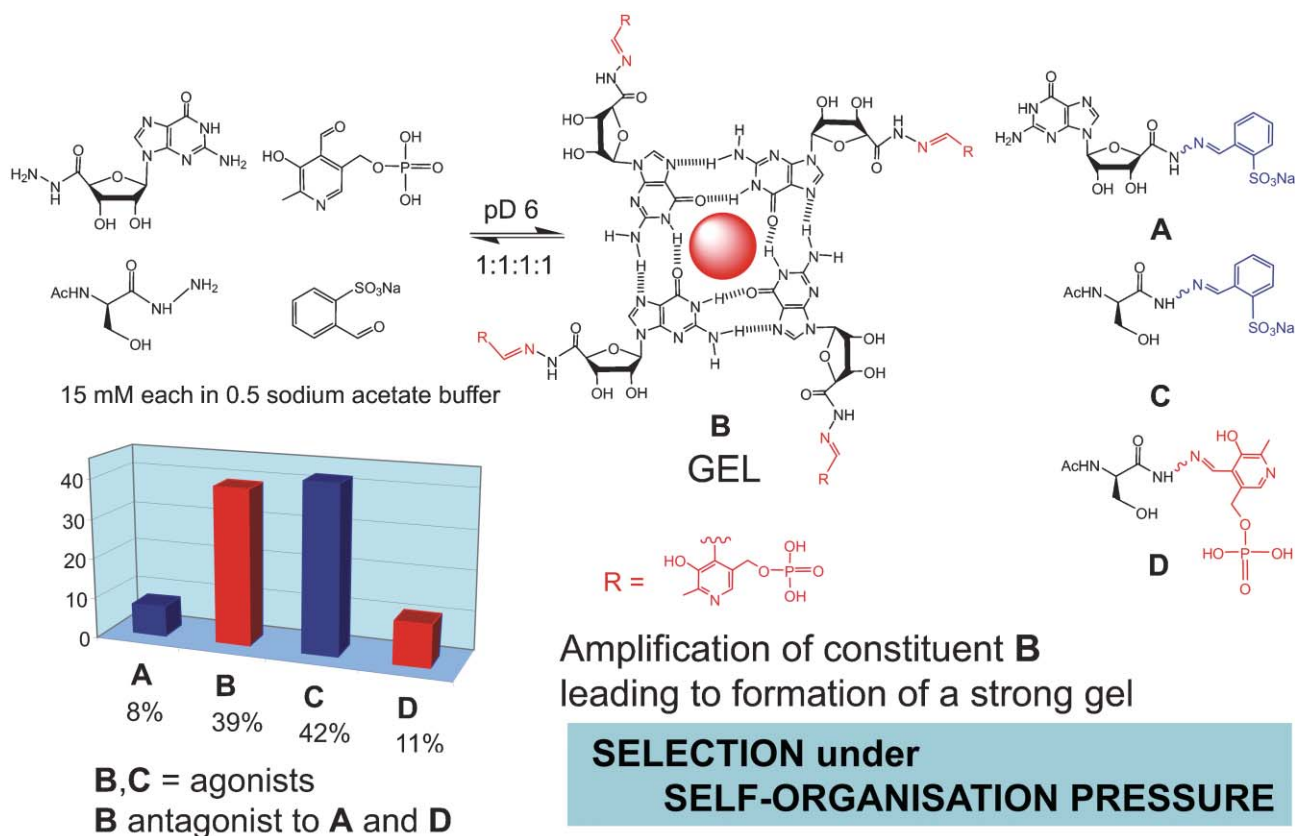
CDC also encompasses *dynamic coordination chemistry*,<sup>50,53,54</sup> whereby the coordination of metal ions induces the

preferential formation of specific ligand molecules and/or induces reversible changes in them. Such processes may be traced back to early work on coordination reactions of imine-based ligands, that may now be revisited in the light of constitutional dynamics, but were not perceived as such at that time.<sup>61</sup>

Self-organisation with selection occurs in the metal cation driven build-up of the ligand that allows the generation of a [2 × 2] grid-type metallosupramolecular architecture by selection of the proper components from a virtual DCL (Fig. 6).<sup>62</sup> The addition of Zn<sup>II</sup> cations to a CDL of helical ligands drives the system towards the expression of a [2 × 2] grid-type complex (Fig. 7).<sup>63</sup> An intriguing case of self-sensing is found in the Zn<sup>II</sup> cation-induced rearrangement of a polyimine towards the polymer that, once formed, generates a strong fluorescence signalling the presence of the very species, the Zn<sup>II</sup> cations, that have led to its formation (Fig. 8).<sup>64</sup> In these three cases the evolution of the system is driven by cation coordination pressure.

CDC allows for “double dynamic” processes, that combine and take advantage of both non-covalent and covalent dynamics, as in the assembling of metallo-architectures bearing functional groups,<sup>62,65</sup> or for performing *constitutional dynamic synthesis* (CDS). In the latter case, supramolecular dynamics enable the assembly of functional components with suitable selection and structural control, whereas molecular covalent dynamics operate in post-assembly connection between the assembled components, resulting in molecular architectures of high complexity, as described in the formation of interlocked structures from metal-coordination<sup>66</sup> or donor–acceptor interaction<sup>67</sup> directed assembly combined with imine formation.

2) The search for bioactive substances amounts to searching for a molecular key for a biological lock.<sup>50–53</sup> Apart from the random screening of natural or synthetic compounds, two “classical” approaches may be distinguished: 1) rational design, which resides in looking for a single key, the correct one; 2) combinatorial chemistry, which relies on the generation of vast collections of keys that may all be assayed by high throughput screening with fast robotics. A third approach results from the implementation of

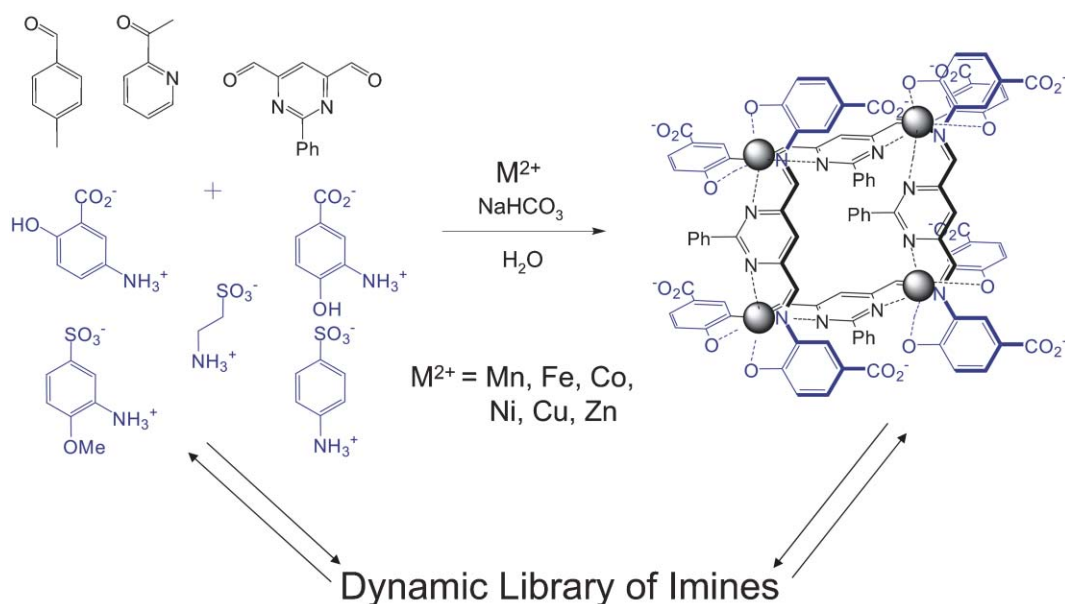


**Fig. 5** Constitutional dynamic selection driven by self-organisation in the formation of a G-quartet based gel: selection of the components that generate the constituent **B** forming a strong gel.<sup>59</sup> **A**, **C** and **D** do not form a gel.

CDC: 3) *dynamic combinatorial/covalent chemistry* (DCC), that relies on the dynamic generation of interconverting keys resulting from all the possible combinations of fragments of keys, with

the goal that this virtual set of potential keys may contain one (or more) that fits the lock, under either *thermodynamic selection*, expressing the constituent/key that presents the strongest interaction

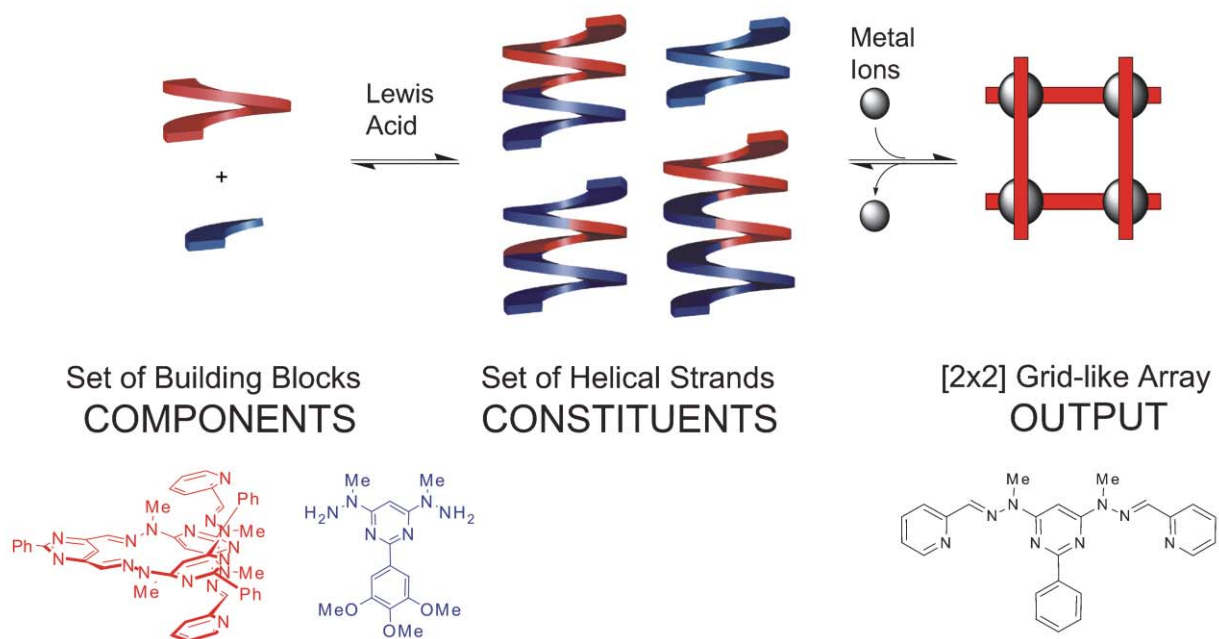
with the target/lock, or *kinetic selection*, giving the key that forms fastest within the lock.<sup>52b</sup> In both cases, the supra-molecular lock/key recognition interactions direct the process (Fig. 9).



**Fig. 6** Self-organisation with selection: dynamic selection of the components that generate the ligand forming a  $[2 \times 2]$  grid-type complex driven by metal ion coordination.<sup>62</sup>

## DYNAMIC LIBRARY : DIVERSITY GENERATION

## AMPLIFICATION



**Fig. 7** Driven evolution of a constitutional dynamic library of helical strands under the pressure of metal ion coordination towards the generation of the ligand strand (bottom right) that forms a  $[2 \times 2]$  grid-type complex.<sup>63</sup>

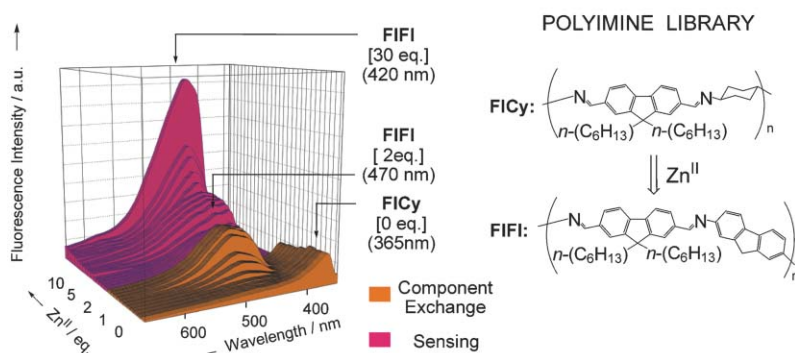
Whereas the usual “static” combinatorial chemistry is based on extensive libraries of prefabricated molecules, DCC implements the reversible connection of sets of basic components to give access to virtual combinatorial

libraries,<sup>30</sup> whose constituents comprise all possible combinations that may potentially be generated (but do not need to be present initially). It represents a powerful means for generating dynamic, effector-responsive diversity.

The constituent(s) actually expressed/selected among all those accessible is(are) expected, under thermodynamic control, to be that(those) presenting the strongest interaction with the target, that is, the highest receptor/substrate molecular recognition. The overall process is thus instructed (target-driven), combinatorial, and dynamic. It bypasses the need to actually synthesize the constituents of a combinatorial library by letting the target perform the assembly of the optimal partner from a virtual set<sup>30,56</sup> of components.<sup>68</sup>

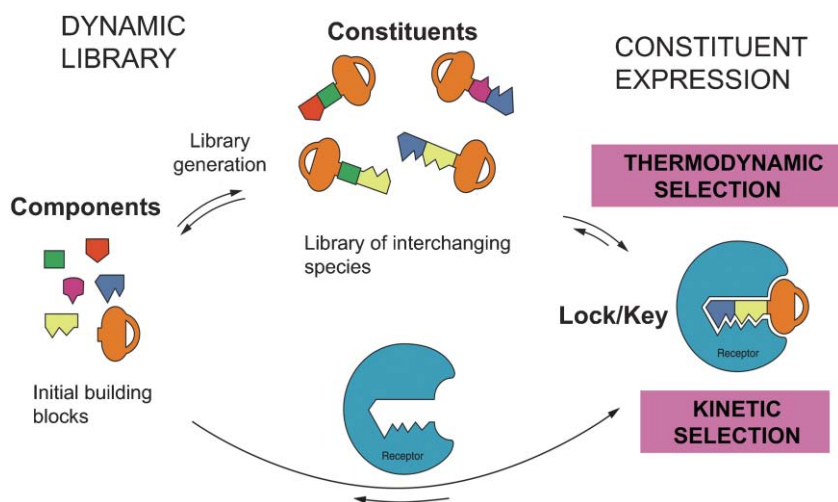
## FLUORESCENCE SPECTRA of the DYNAMER LIBRARY as a function of the amount of added $Zn^{II}$ cations

$Zn^{II}$  DRIVEN COMPONENT SELECTION  $\rightleftharpoons$  SENSOR GENERATION  
 $Zn^{II}$  INDUCED OPTICAL SIGNAL  $\rightleftharpoons$  SENSING



**Fig. 8** Constitutional dynamic self-sensing: constitutional transformation of an aromatic-aliphatic dynamic polyimine (FICy) into an aromatic-aromatic (FIFI) copolymer induced by zinc(II) cations, with generation of a strong fluorescence signal in the presence of excess zinc ions. The metal ions drive the formation of the entity that reveals their very presence in a self-sensing process.<sup>64</sup>

3) One may define molecular and supramolecular *dynamic materials*, as materials whose components are linked through reversible covalent or non-covalent connections and undergo spontaneous and continuous change in constitution by assembly/deassembly processes in a given set of conditions. *Via* recognition-directed association and self-organisation processes, supramolecular chemistry has opened new perspectives in materials science towards the design and engineering of *supramolecular materials*. These, again, are dynamic by nature, whereas molecular materials must be rendered dynamic by introduction of reversible covalent connections



**Fig. 9** Schematic representation of the principle of dynamic combinatorial/chemical (DCC) as applied in particular to the discovery of leads for bioactive compounds. A dynamic library of constituent keys is generated from reversibly connecting fragments of the keys. The receptor/lock amplifies/favours the expression of the constituent/key that binds best to it (thermodynamic selection) or that forms fastest within it (kinetic selection). Bottom: the library constituents/keys do not need to be formed before the addition of the receptor/lock, illustrating the notion of virtual dynamic library.<sup>50,51</sup>

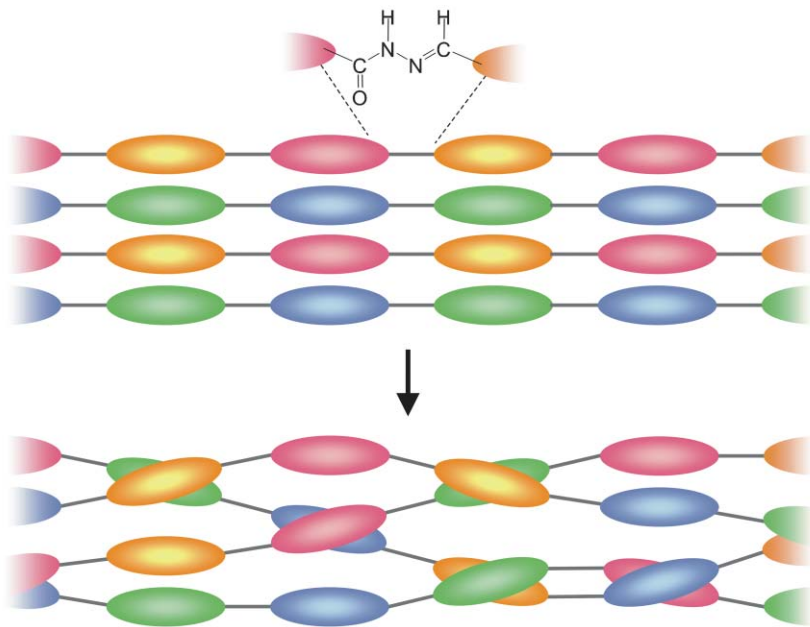
between building blocks. Because of their intrinsic ability to exchange their components, they may in principle select them in response to external stimuli or environmental factors and therefore behave as *adaptive materials* of either molecular or supramolecular nature.<sup>7,9,30</sup>

Applying such considerations to polymer chemistry leads to the definition of *constitutionally dynamic polymers, dynamers*, of both molecular and supramolecular types,<sup>27–30</sup> that have a constitutional/combinatorial diversity determined by the number of different monomers. The components effectively incorporated into the polymers depend on the nature of the connections (recognition or functional groups) and core groups, as well as on the interactions with the environment, so that dynamers possess the possibility of adaptation by association/growth/dissociation sequences. The dynamic and combinatorial features of dynamic polymers give access to higher levels of behaviour such as self-healing, adaptability, response to external stimulants (heat, light, chemical additives, etc.).

In particular, a *supramolecular polymer chemistry* has developed, concerning polymers of supramolecular nature generated by the self-assembly of monomers interconnected through complementary interaction/recognition groups.<sup>27–30</sup>

Covalent dynamers may also present a range of unusual properties such as cross-over component recombination between neat films in dynamic polymer blends (Fig. 10)<sup>69</sup> and soft-to-hard transformation of polymer mechanical properties through component incorporation.<sup>70</sup>

Dynamic biomaterials may be of interest for biodegradability<sup>71</sup> as well as



**Fig. 10** Dynamic polymer blends: schematic representation of crossover component recombination between neat films of dynamic covalent polyaclyhydrazone copolymers. The coloured units represent different monomers.<sup>69</sup>

for time-delayed, dynamic formulation and controlled release strategies for instance of antimicrobial agents<sup>72</sup> or of fragrances.<sup>73</sup> Fully inorganic materials of spherical shape have been generated from dynamic libraries.<sup>74</sup>

CDC introduces into the chemistry of materials a basic shift with respect to constitutionally static materials and opens new perspectives in materials science. A rich variety of novel architectures, processes and properties may be expected to result from the blending of supramolecular and molecular dynamic chemistry with materials chemistry.

## Conclusion. Outlook: Chemistry in five dimensions

Supramolecular chemistry has thus progressed over the years along three overlapping phases. The first is that of molecular recognition and its corollaries, supramolecular reactivity, catalysis, and transport; it relies on design and pre-organisation and implements information storage and processing.

The second concerns self-assembly and self-organisation, *i.e.*, self-processes in general; it relies on design and implements programming and programmed systems, which involve messages in molecules controlling the generation of specific entities in complex mixtures.<sup>75</sup>



The third concerns constitutional dynamics of both molecular and supramolecular entities, defining constitutional dynamic chemistry as a unifying concept; it allows for adaptation and evolution; it relies on self-organisation with selection in addition to design, and implements chemical diversity and “informed” dynamics.<sup>75</sup>

CDC represents a paradigm shift with respect to constitutionally static chemistry. The latter relies on design for the generation of a target entity, whereas CDC takes advantage of dynamic diversity to allow variation and selection. The implementation of selection in chemistry introduces a fundamental change in outlook. Whereas self-organisation by design strives to achieve full control over the output molecular or supramolecular entity by explicit programming, self-organisation with selection operates on dynamic constitutional diversity<sup>76</sup> in response to either internal or external factors to achieve adaptation in a Darwinistic fashion.

In the process of reaching higher levels of self-organisation, CDC gives access to the generation of networks of dynamically interconverting constituents connected either structurally (molecular and supramolecular arrays) or reactionally (set of connected reactions or interactions) or both. They define a class of *constitutional dynamic networks* (CDNs) that may in particular couple to either reversible or irreversible thermodynamic processes and present a specific stability/robustness with respect to external perturbations. Connectivities between the constituents of a dynamic library may define *antagonistic* and *agonistic* relationships depending on whether the increased expression of a given constituent respectively decreases or increases one or more of the others.<sup>77</sup>

Such CDNs also may in principle perform connected evolution, whereby feedback between two (or more) species (e.g. a substrate and its receptor) leads to simultaneous optimisation of both (some), a sort of “*co-evolution*” process, where the generation of a potential receptor favours the expression of the corresponding substrate and conversely. Such a process is somewhat reminiscent of the law due to the economist Jean-Baptiste Say, that may be paraphrased as: “L’offre crée sa propre demande”.<sup>78</sup>

Highly interconnected networks (reactionally, but also constitutionally) relate to a systems chemistry.<sup>79</sup> Further developments also involve sequential, hierarchical self-organisation on increasing scale,<sup>80</sup> with emergence<sup>81</sup> of novel features/properties at each level, self-organisation in space as well as in time,<sup>82</sup> and passage beyond reversibility, towards self-organisation and constitutional dynamics in non-equilibrium systems.

One may consider that CDC confers to chemistry a *fifth dimension*, that of constitution, in addition to the three dimensions of space (structure) and of time (kinetics). Thus, self-organisation plays on a *five-dimensional chemistry* to achieve complexification of matter.<sup>83</sup>

In the context of the “big” problems challenging science, where physics addresses the origin and laws of the universe, and biology those of life, chemistry may claim to provide the means for unravelling the progressive evolution towards complex matter by uncovering the processes that underlie self-organisation,<sup>7</sup> and for implementing the knowledge thus acquired to create novel expressions of complex matter.

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