Dynamic Combinatorial Chemistry and Virtual Combinatorial Libraries

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Abstract: Whereas combinatorial chemistry is based on extensive libraries of prefabricated molecules, dynamic combinatorial chemistry (DCC) implements the reversible connection of sets of basic components to give access to virtual combinatorial libraries (VCLs), whose constituents comprise all possible combinations that may potentially be generated. The constituent(s) actually expressed among all those accessible is(are) expected 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. It comprizes both molecular and supramolecular events. The basic features of the DCC/VCL approach are presented together with its implementation in different fields and the perspectives it offers in a variety of areas of science and technology, such as the discovery of biologically active substances, of novel materials, of efficient catalysts, and so forth. Finally, it participates in the progressive development of an adaptive chemistry.

Keywords: combinatorial chemistry · dynamic processes · molecular recognition · supramolecular chemistry · virtual libraries

Introduction

The discovery of biologically active substances and, in particular, drug discovery require finding molecules that interact selectively with given biological targets. In recent years, a combinatorial chemistry (CC) approach has been very actively pursued, fueled especially by the hope to gain quick access to novel pharmaceuticals through the rapid generation and screening of vast collections of molecules.

The corresponding combinatorial libraries (CLs) consist in large, static populations of different, discrete molecules prepared by means of the methodologies of molecular chemistry and derived from a set of units connected in various sequences by the repetitive application of specific chemical reactions, with the aim of producing as high a structural diversity as possible.[1–6] This procedure can of course be extended to other areas, such as the combinatorial preparation of multicomponent materials and the rapid screening for their physical properties or the discovery of novel catalyst for specific reactions.

In the present essay, we wish to outline the conceptual framework of another approach to this new area of chemistry, to provide some illustration from our own work and related studies, and to point to possible extensions and perspectives.

Discussion

Basic concepts—from static to dynamic, from real to virtual, and from prefabricated to adaptive: This conceptually different approach resides in *dynamic combinatorial chemistry* (DCC). It is based on dynamically generated combinatorial libraries (DCLs), which are *virtual* in their generality, the actual constituents present at any moment being just the *real* subset of all those that are potentially accessible.[+] Its main

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[+] The use of the term *virtual* to designate the present combinatorial libraries made accessible by DCC, deserves some comments. The designation as dynamic combinatorial libraries is correct but incomplete, highlighting only one feature, that is, the ability of their constituents to reversibly interconvert. However, they contain all the *potentially* possible combinations of the components undergoing dynamic random connection, whether these combinations are or are not actually present in the conditions used. Thus, the virtuality expresses *both* the potential combinatorial space available to the system and the dynamic accessibility of these combinations. The actual reification, that is, the generation of a real entity from the virtual set, occurs in the presence of the target, whose preferential interaction with a given member of the set leads to its expression (or to its amplification within an equilibrating mixture of preformed constituents). As pointed out by a referee the Unabridged Webster Dictionary understands virtual as being a hypothetical particle, whose existence is inferred from indirect evidence, while the Oxford Dictionary of New Words, 1997, points out that the meaning of virtual is more and more shifted to not physically existing, but made to appear so from the point of view of the user. We prefer to return to the philosophical/literary meaning of virtual, that is, which is in the state of simple possibility in a real being or, more commonly, which contains in itself all the essential conditions to its own realization (Dictionnaire de la langue française, P. Robert). The latter corresponds to the meaning we wish to convey in designating the present combinatorial libraries as virtual.

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features are summarized in Figure 1 and are compared with those of CLs themselves.

DCC relies on reversible connection processes for the spontaneous and continuous generation of the *constituents* of the DCL, that is, of all possible combinations in nature, number, and arrangement of a set of basic *components*. Since such multicomponent self-assembly makes virtually available all structural and interactional features that these combinations may display, its amounts in effect to the presentation of a *virtual combinatorial library* (VCL), that is, dynamic, polymorphic, and multipotent. This DCC/VCL approach is *target-driven*: it rests on the conjecture that in the presence of the target, that member of the VCL possessing the features best suited for binding most strongly to the target site, that is, the constituent presenting highest *molecular recognition*, will be selectively expressed by the recruiting of the correct components from the set of those available. The VCL will narrow down to the thermodynamically-driven, preferential expression of a real constituent through receptor–substrate molecular recognition.

DCC is thus rooted in supramolecular chemistry,[7] being based on two of its main themes, *self-assembly* in the generation of the library constituents and *molecular recognition* in their interaction with the target entity. Self-assembly in a multicomponent system is a combinatorial process with a search procedure directed by the kinetic and thermodynamic parameters imposed by the nature of the components and their connections.

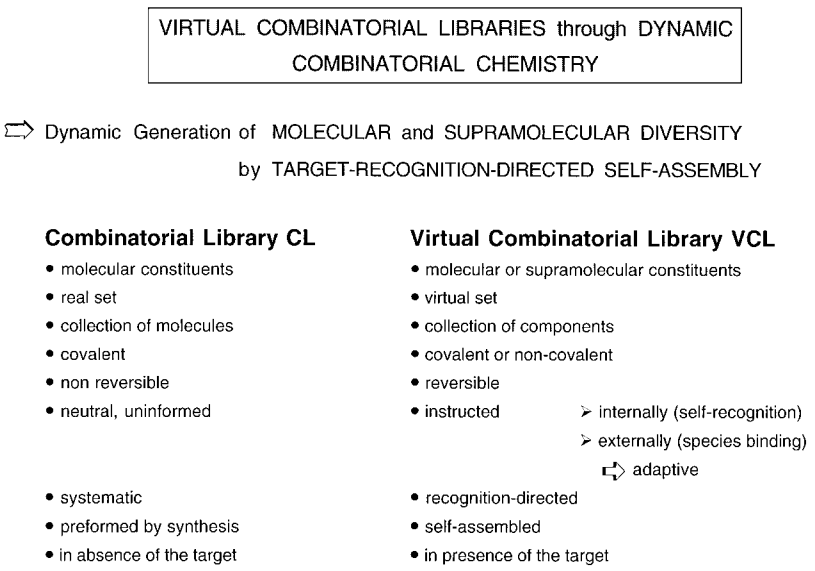

Figure 1. Static and dynamic combinatorial chemistry; comparative basic features of real and dynamic virtual combinatorial libraries.

1) *Reversibility* is an essential feature of DCC. It gives access to VCLs by the continuous recombination of the components to make available at any instant all possible constituents of the library. Whereas combinatorial chemistry is static, based on libraries of stable noninterconverting molecules, the present approach may be termed *dynamic*, since it exists in the reversible combination of components.

2) CLs are molecular and real, and their constituents are preformed by stepwise synthesis through covalent, nonreversible linkages. VCLs are molecular or supramolecular; they may be termed *virtual* because their constituents may not, and need not, exist in significant amounts in absence of the assembling target.[+] They are generated spontaneously through a reversible assembly process.[+]

The formation of the constituents of a VCL results from the combination of its components either by covalent assembly through a reversible chemical reaction *(molecular VCL)* or by self-assembly through reversible noncovalent binding interactions *(supramolecular VCL)*. VCLs thus rely on the spontaneous generation of *dynamic molecular or supramolecular diversity* for the efficient and economical exploration of the structure/energy hypersurface through reversible recombination of a set of components. They display a sort of molecular and supramolecular polymorphism.

The degree of completeness of the set of components depends on the extent to which their possible combinations cover the geometrical and interactional spaces of the target site. The number of constituents that may be generated amounts to $[n(n+1)(n+2)\ldots(n+p-1]/p!$ for the combination of n components p to p (without order) or to n^p arrangements when the combinations are ordered. The dynamic library of real constituents that actually exist at a

Abstract in French: *Alors que la chimie combinatoire est fondée sur de vastes bibliothèques de molécules préfabriquées, la chimie combinatoire dynamique (CCD) met en oeuvre la connexion réversible entre des ensembles d'unités de base pour donner accès à des bibliothèques combinatoires virtuelles (BCVs) dont les constituants forment l'ensemble de toutes les combinaisons possibles, potentiellement réalisables. Le(les) constituant(s) effectivement exprimé(s) parmi tous ceux qui sont accessibles, est(sont) celui(ceux) présentant la(les) plus forte(s) interaction(s) avec la cible, c'est-à-dire la meilleure reconnaissance moléculaire entre récepteur(s) et substrat(s). Le processus global est donc informé, combinatoire et dynamique. Il permet d'éviter la synthèse effective des constituants d'une bibliothèque combinatoire en laissant la cible réaliser elle-même l'assemblage du partenaire optimal. Il comprend à la fois des aspects moléculaires et supramoléculaires. Les caractéristiques de base de l'approche CCD/BCV sont décrites, de même que sa mise en oeuvre dans de nombreux domaines et les perspectives qu'elle offre dans différentes directions, telles que la découverte de substances biologiquement actives, de nouveaux matériaux, de catalyseurs efficaces, etc. Finalement elle participe au développement progressif d'une chimie adaptative.*

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given moment is a subset of the VCL of all possible constituents. In a CL there is a 1:1 correspondence between a member of the library and the target, whilst a VCL is a multiplexing system that establishes a *n*:1 *adaptive* correspondence between a set of components and the target site.

3) The expression of a given member of a VCL results from the fact that the dynamic process is conducted *in the presence of the target*, whereas the members of a CL are fabricated independently, in absence of the target. The entity expressed from the virtual set of constituents of a VCL is that forming the optimal supramolecular entity with the target site. In the same way that protein folding cannot occur through the successive exploration of all possible conformations at all positions of the chain, combinatorial chemistry cannot conduct a full exploration of all possible combinations and arrangements of molecular fragments into library molecules. DCC makes use of a search procedure that is thermodynamically-driven and bypasses the need to generate and screen all possible molecules by letting the target direct the evolution of the system towards the product that presents the strongest interaction.

4) To this end, it is desirable to achieve an unbiased, *isoenergetic DCL*, whose equilibrating constituents be of similar free energy, so as to generate a Boltzmann distribution displaying comparable population for its different states/constituents. With a biased library, where one or a few constituents would be highly favored, the preferred interaction of a minor constituent with the target may not be strong enough to overturn the equilibrium situation.

5) Dynamic combinatorial diversity may result in the generation of a given type of species either by virtue of internal properties of the product(s) (self-selection)[7b,8] or through interaction with external entities. The latter process amounts to the *generation of the fittest* and presents *adaptation* and *evolution* by spontaneous recombination under the selection pressure exerted by changes in the partner(s) or in the environmental conditions. It thus embodies a sort of *(supra)-molecular Darwinism!*

Components and processes: DCC presents three basic requirements: in addition to the selection of a satisfactory set of *components*, a major task in the development of VCLs is the search for suitable *reversible processes* to connect (or interconvert) them. Furthermore, it is desirable to devise procedures for quenching these processes so as to *lock-in* irreversibly the constituent(s) expressed. Finally, practical, but not minor, questions concern the characterization of the constituent of the VCL that is being expressed.

1) The *basic components* of DCL constituents may be either i) interactional, bearing the sites which provide interaction with the target, ii) organizational, serving as framework on which to assemble and arrange the first ones, or iii) combine both features. The choice of these components must take into consideration two main characteristics: the structural and interactional features for binding to the target, and the functional group(s) for reversible connection. Thus, the basic set comprises a variety of fragments of different shapes, sizes, and constitutions: aliphatic or aromatic, carbocyclic or heterocyclic, positively or negatively charged, polar or non-polar, electron donor or acceptor, hydrophilic or lipophilic, etc.

2) The *reversible connections* between the components concern two levels.

At the *molecular level*, various reactions producing covalent combinations between reagents may be considered (Figure 2). Functional groups involving a carbonyl unit (imines, esters, amides) are of special interest since they may undergo disconnection/reconnection cycles (trans-imination, -esterification, -amidation). In particular, the (amine + carbonyl) condensation into imine type compounds (such as imines, oximes, hydrazones) takes place in mild conditions and its products can be trapped irreversibly by reduction to amines. Reactions such as thiol exchange in disulfides or alcohol exchange in borate esters etc. are further candidates, as well as reversible Diels–Alder and Michael condensations or olefin metathesis with catalysts that may be water soluble. Photoinduced interconversions represent another possibility leading to *photodynamic* combinatorial processes.

At the *supramolecular level*, the connections between the components may involve organic (H-bonding, donor–acceptor, Van der Waals, …) or inorganic (metal-ion binding) interactions. The latter are particularly attractive in view of the variety of arrangement geometries, binding energies, and formation kinetics provided by metal-ion coordination.

In addition, molecular diversity can also be generated through modifications in shape and spatial disposition provided by *intramolecular dynamic processes*, conformational (internal rotation, ring or site inversion, rotation around metallic rotules as in sandwich complexes, e.g., ferrocene derivatives, etc.), and configurational (*cis*, *trans* interconversion) changes or internal reversible rearrangements (including fluxional changes in metallo-organic species) between multiple states of not too different energies so as to be populated to some extent. Tautomerism, in particular in heterocyclic compounds, gives rise to dynamic diversity, allowing a shift towards one of the tautomeric states in response to interaction with the target or to environmental factors. Protein folding makes in principle a very large variety of virtual tertiary structures accessible that may be expressed according to circumstances. An intriguing case of dynamic presentation of different arrangements of functional groups would be provided by multiply substituted derivatives of the fluxional bullvalene molecule.

Higher diversity may be generated through multiple combinations, by using *polyvalent frameworks* of various types and shapes (linear, branched, globular etc., including polymeric and dendrimeric structures) bearing several functional groups and/or interaction sites for reacting/binding with and collecting several different components.

In order to achieve an isoenergetic DCL (see above) it may be desirable to introduce a *spacer* between the reactive functional groups and the interaction/recognition subunits so that all connections between different components have similar strength.

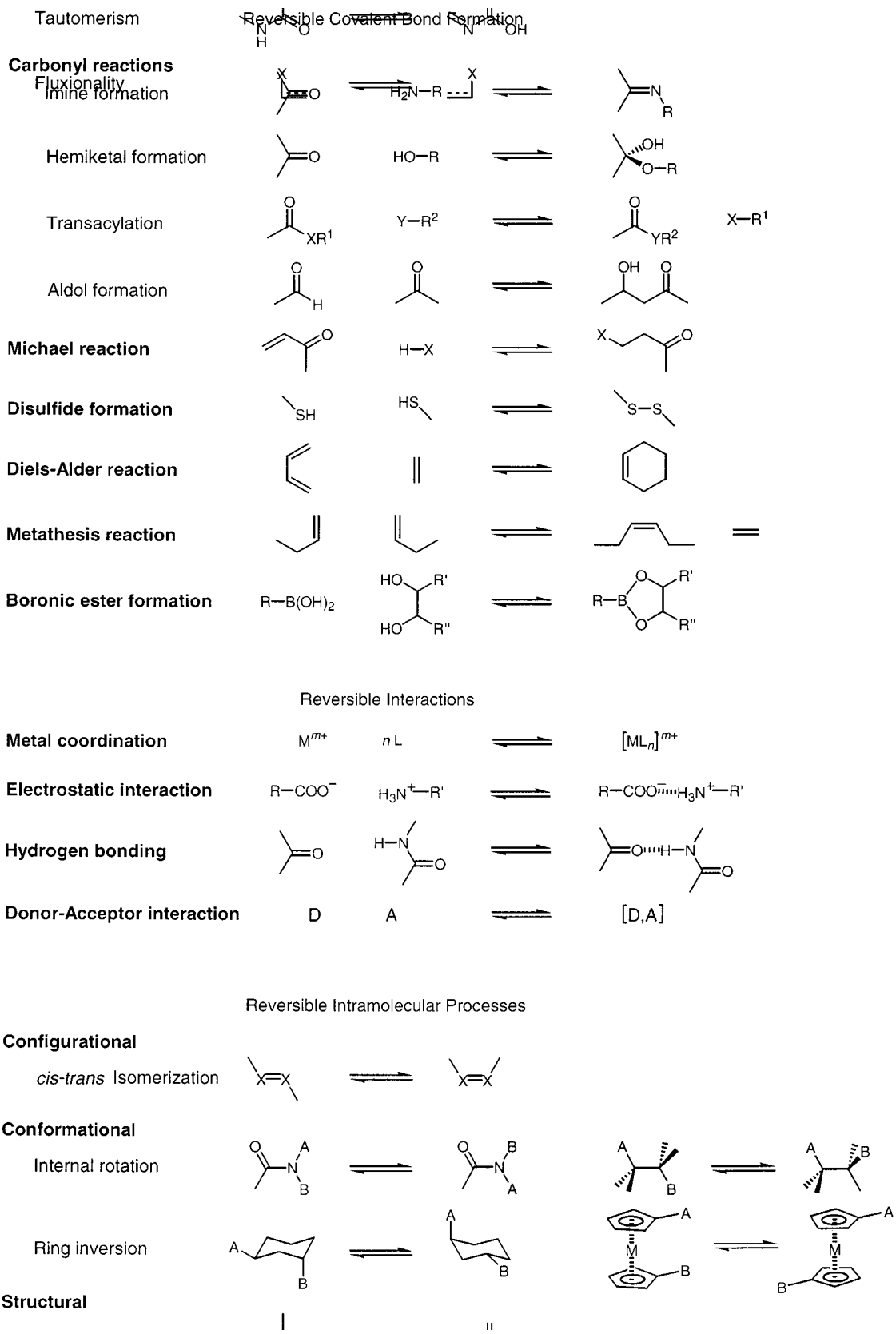

Figure 2. A selection of potentially reversible reactions, of interactions, and of intramolecular processes for the dynamic generation of virtual molecular and supramolecular combinatorial libraries/diversity.

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Thus, the diversity of the VCLs made accessible by DCC may originate in the structural plasticity resulting from a) recombination of two or more components in a molecular or b) in a supramolecular fashion, respectively through reversible reactions or through organic/inorganic interactions, and c) intramolecular interconversions in entities subject to conformational, configurational or fluxional changes, or to thermal or photoinduced rearrangements.

3) The *lock-in* of the self-assembled structures may be achieved by performing a chemical reaction that irreversibly links together the components of the entity represented by the optimal combination. This is the case for instance, in the reduction of imines to amines. On the other hand, a simple change in conditions, such as temperature or pH, may slow down the connective process so as to hinder the reversibility and stabilize the product(s) sufficiently for practical purposes of retrieval.

4) In addition to their difference in constitution, CLs and VCLs also differ in the requirements for *screening* of the library and *retrieval* of a given entity. Whereas the complex mixture represented by a CL requires encoding procedures (such as nucleotide sequences, chemical barcodes, radio frequency microchips, etc.)[9] and the development of high through-put screening (HTS) technologies, a VCL may in principle be reduced to a few constituents or even to a single one, thus bypassing the need to screen all constituents and greatly facilitating detection and identification of the active substance produced.

5) The *characterization* of the expressed constituent of a VCL is greatly facilitated by the availability of efficient analytical methods such as mass and NMR spectrometries, capillary electrophoresis, micro HPLC, etc. These can be applied either to the isolated constituent or even directly to its complex with the target.[10] It is clear that the development of micro methods and laboratory-on-a-chip[11] procedures will have a strong impact on the implementation of combinatorial chemistry approaches.

Complementary morphogenesis—casting and molding: The generation of CLs or of VCLs may be applied either to the discovery of a substrate for a given receptor or to the construction of a receptor for a given substrate.

In the spirit of Emil Fischer's Lock and Key metaphor, the constitution of a CL of substrates amounts to the fabrication of a large collection of keys, with the goal (hope?) that one of them will fit the target lock/receptor and be retrievable from the mixture. On the other hand, a substrate VCL derives from a set of parts that may spontaneously and reversibly assemble so as to generate potentially a large set of different keys, one of which could fit the lock/receptor, the degree of complementarity depending on the way in which the features of the available parts are able to cover the space of all possible shapes. The same image can be applied to CLs and VCLs of receptors for a given substrate.

Thus, in the framework of VCLs two processes may be considered, depending on whether a receptor or a substrate acts as target-template for the assembly of the other partner: *casting* involves the receptor-induced assembly of a substrate that fits the receptor; conversely, *molding* involves the substrate-induced assembly of a receptor that optimally binds/fits the substrate (Figure 3). Both processes involve 1) a set of components, 2) their reversible combination for spontaneous diversity generation, and 3) the recognition-directed selection of one partner by the other one (in fact, both partners could in principle be self-assembled species). In these processes the role of the target is related to the classical template effect of coordination chemistry.

Implementation of the dynamic combinatorial approach: Although its basic concepts have been formulated only recently, the DCC/VCL approach has already been implemented in inorganic, organic, and bioorganic processes. It may operate in solution and also in organized phases, on a surface (onto which one of the components could self-assemble or be attached), or in molecular layers or membranes (containing freely diffusing components).

Coordination chemistry offers by essence the possibility to generate chemical diversity. Mixtures of ligands and metal ions in exchange define a *dynamic combinatorial coordination chemistry*. It is in the context of the reversible connection of ligand components by means of metal ion coordination that we were first led to consider such a dynamic combinatorial process. The concept of the dynamic generation of molecular and supramolecular diversity from the reversible recombination of building blocks emerged initially from our studies on

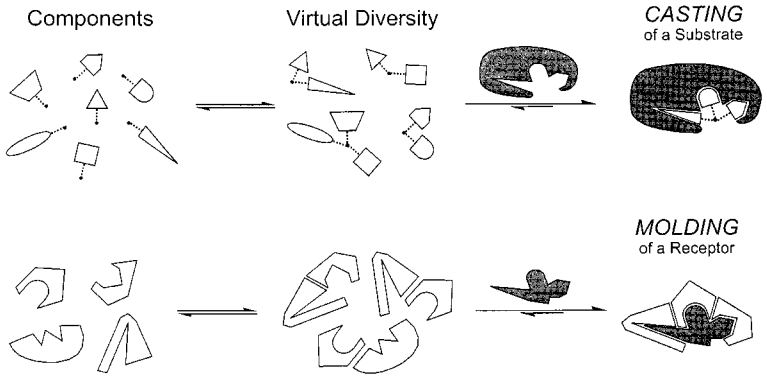


Figure 3. Dynamic generation of virtual combinatorial libraries. Top: casting process—receptor-induced self-assembly of the complementary substrate from a collection of components serving as building blocks; it amounts to the selection of the optimal substrate from a virtual substrate library. Bottom: molding process—substrate-induced self-assembly of the complementary receptor from a collection of structural components; it amounts to the selection of the optimal receptor from a virtual receptor library. The diverse potential constituents of the libraries (center, top, and bottom) are either covalently linked or noncovalently bound, reversibly generated species that may or may not exist in significant amount(s) in the free state, in absence of the partner. The components may either be directly connected or assemble reversibly on polyfunctional-supporting frameworks of various structural types.

the self-selection of ligands occuring in the formation of double helical metal complexes (helicates), in which only the correctly paired double helicates were produced from a mixture of ligands and metal ions in dynamic coordination equilibrium.[8] Indeed, such self-recognition already displays basic features of DCC and VCLs: i) the *self-assembly* of a supramolecular structure ii) by a *reversible* process with iii) *selection* of the correct partner.

The VCL concept was then introduced and exemplified in the dynamic, multicomponent self-assembly of circular double helicates.[12] The coordination of several trisbipyridine strands with hexacoordinated metal ions may in principle generate circular helicates of any size, giving thus reversibly access to a VCL of oligomeric circular helicates; this is schematically represented in Figure 4. The actual complex obtained depends on the conditions. Thus, the pentameric entity **1** is expressed quantitatively in the presence of chloride anions, owing to the strong binding of a single chloride ion in the central cavity, a process that amounts to a molding event. The corresponding hexameric species **2** is formed when the larger tetrafluoroborate or sulfate anions are used. One may point out that in analogy to biological processes, the chloride anion plays here the role of a *chaperone* species, directing the assembly towards a given architecture, which would not be formed in its absence and which is conserved when the anion is removed in non-equilibrating conditions after the structure has been formed.

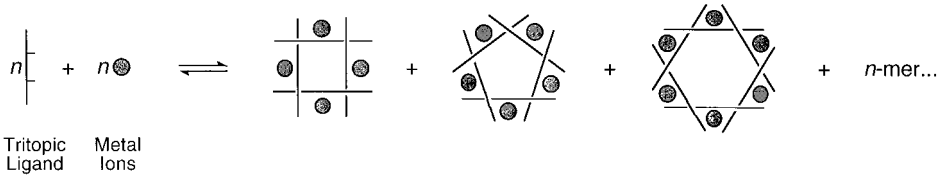


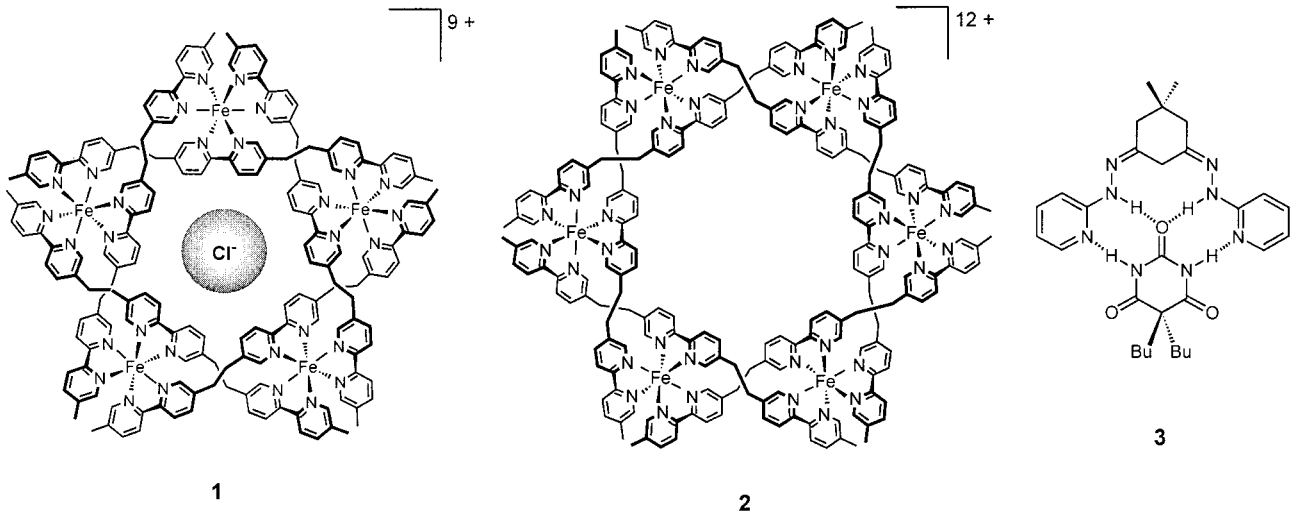
Figure 4. A virtual dynamic combinatorial library of oligomeric circular helicates generated from a tritopic trisbipyridine ligand and metal ions of octahedral coordination. All constituents of the dynamic library are potentially accessible at any time by reversible interconversion.

The DCC/VCL concept was presented in detail and implemented through a casting process involving the recognition-induced assembly of inhibitors of the enzyme carbonic anhydrase.[13] In this study it was found that the reversible recombination of structural fragments bearing aldehyde and amine groups into a library of imines (Figure 5) led to a shift of the equilibrium population towards that imine product that was closest in structure to a known strong inhibitor of the enzyme. A relevant study described the template-directed imine formation between two trinucleotides in the presence of the complementary hexamer.[14]

One may note that DCC should be well suited for the exploration of protein surfaces and the inhibition of protein–protein interactions, in particular, towards the discovery of allosteric effectors binding to locations not put to use in the natural processes.

A molding process operates in the induced fit selection of a receptor for dibutyl barbiturate **3** from a dynamic structural and configurational/conformational library.[15] Other illustrations from work in our laboratory concern the formation of an equilibrating collection of copper(I) coordination architectures, which narrows down to the expression of a single constituent in the solid state,[16] the directed assembly of receptors based on bipyridine metal complexes by substrate H-bonding,[17] the selective substrate binding by lectins from a VCL of saccharides,[18] and the generation of conformational diversity in *N*-alkylated oligopeptides.[19] Numerous other applications may be imagined and a great variety of extensions may be envisaged, also into nonbiological areas.

The DCC/VCL approach bears relation to a number of dynamic processes scattered through the chemical and biochemical literature (see refs. [6–19] in ref. [13]). Its timeliness is indicated by recent reports describing, for instance, the interconversion of macrocyclic structures,[20] the dynamic screening of a peptide library by binding to a molecular trap,[21] the generation of peptide recognition sites in mixed peptide monolayers[22] and of DNA-binding compounds from an equilibrating mixture of zinc complexes,[23] the assembly of



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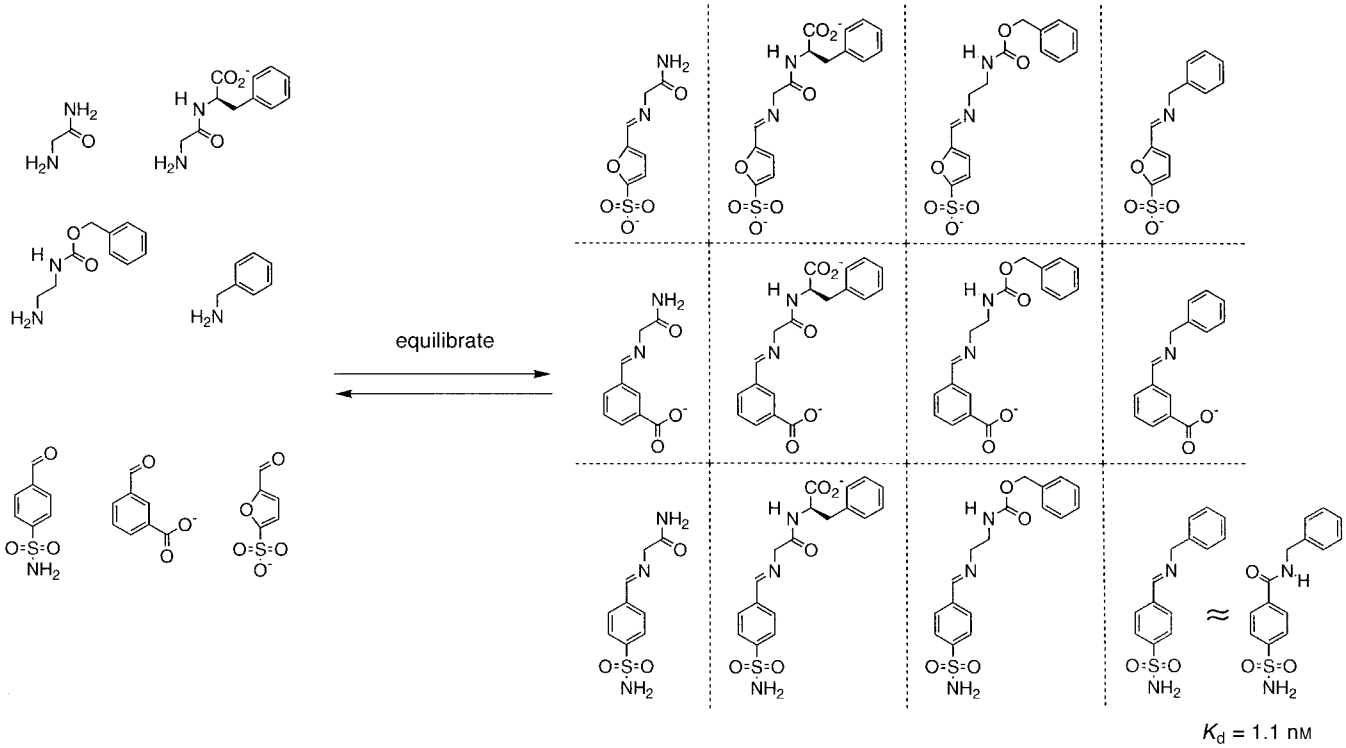

Figure 5. A dynamic combinatorial library of imines generated by reversible combination of a set of aldehydes and of amines. One member of the library (bottom right corner) has features close to those of a strong inhibitor of carbonic anhydrase.

cyclic inorganic architectures depending on substrate binding,[24] the selection of a bismacrocyclic receptor for a tripeptide,[25] and the generation of a library of calixarene-derived hydrogen-bonded assemblies under thermodynamically controlled conditions.[26] A case of fluxional-configurational diversity is represented by the dynamic molecular recognition of a metal complex bearing carbohydrate residues by lectins.[27] An olefin library for potential use in receptor-assisted combinatorial synthesis (RACS) has been produced by the metathesis reaction.[28] Molecular imprinting and template processes display analogies through the adaptation of the matrix to the substrate.[29–31] Of particular interest is the generation of oligopeptide libraries through reversible pairing of oligonucleotides bearing peptide units.[32]

Cases in which diversity generation is neither due to multicomponent assembly nor thermally spontaneous, but is based on photoinduced changes within a single molecule are found in the selection of an arginine receptor molecule[33] and of substituted diazobenzene substrates for a macrocyclic receptor molecule;[34] in these instances the structural changes are produced by *cis*–*trans* isomerization around double bonds that requires light irradiation. They represent examples of photodynamic combinatorial processes.

Recent reports have already reviewed and commented upon the early stages of development of this highly promising DCC approach.[35–38]

Dynamic combinatorial materials: The combinatorial approach has also been applied to the fabrication of new materials and the discovery of novel properties.[39] This is the case for instance in the exploration of the electrical or optical properties of solids. A significant further step is brought about by the introduction of reversibility, which confers the dimension of dynamic diversity to the generation of novel materials.

We define *dynamic materials* as materials whose constituents are linked through *reversible* connections and undergo spontaneous and continuous assembly/deassembly processes in a given set of conditions. They are in fact either of molecular or of supramolecular nature depending on whether the links between the components are reversible covalent connections or noncovalent ones.

Because of their intrinsic ability to exchange their constituents, dynamic materials also offer combinatorial capability thus giving access to *dynamic combinatorial materials* (DCMs), whose composition, and therefore also properties, may change by the reversible incorporation of different components in response to internal or external factors (Figure 6), such as structural compatibility, an electric or magnetic field, temperature, pressure, medium, etc. The selection of a given constitution occurs here on the basis of a given property rather than of a binding/recognition process. This applies of course as well to biomaterials based on derivatives of biomolecules such as amino acids, nucleosides, or saccharides. There is no doubt that the merging of dynamic with combinatorial features offered by the extension of the DCC/VCL concept to materials science, provides a range of novel perspectives and may be expected to rapidly become an area of active investigation and of great potential for application.

Supramolecular materials are by nature dynamic; they rely on the explicit manipulation of the noncovalent forces that hold the components together and of the recognition processes that they underlie, for their controlled and reversible

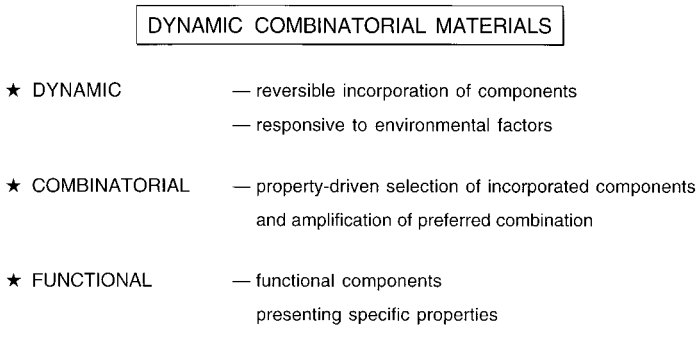

Figure 6. Basic features of dynamic combinatorial materials.

build-up from suitable units by self-assembly. Hence, supramolecular materials are *instructed*, *dynamic*, and *combinatorial*; they may in principle select their components in response to external stimuli or environmental factors and thus behave as *adaptive materials* (Figure 6).

Supramolecular polymer chemistry and dynamic combinatorial polymers: The combination of polymer chemistry with supramolecular chemistry defines a supramolecular polymer chemistry.[7a, 40, 41] It involves the designed manipulation of molecular interactions (hydrogen bonding, donor–acceptor effects, etc.) and recognition processes to generate main-chain (or side-chain) supramolecular polymers by the self-assembly of complementary monomeric components (or by binding to lateral groups). In view of the lability of these associations, such entities present features of living polymers capable of growing or shortening, of rearranging their interaction patterns, of exchanging components, and of undergoing annealing, healing, and adaptation processes (Figure 7).

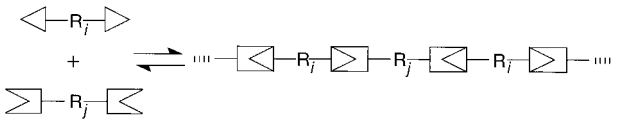

Figure 7. Formation of main-chain supramolecular polymers by polyassociation of complementary components. R_i, R_j represent different subunits fitted with recognition groups; a variety of such groups may be used. Cross-linking components may also be introduced. The process is instructed, dynamic, and combinatorial.

Supramolecular polymer chemistry is thus both dynamic and combinatorial, and supramolecular polymers may be considered as DCMs. Similar considerations apply to the generation and behavior of *supramolecular liquid crystals*,[40] and extensions to other properties, such as optical ones,[42] may be envisaged.

Nanochemistry—nanomaterials: Nanoscience and nanotechnology have become very active areas of investigation, in view of both their basic interest and their potential applications. The spontaneous but controlled generation of well-defined, functional molecular or supramolecular architectures of nanometric size through the programmed self-assembly from mixtures of instructed components offers a very powerful alternative to nanofabrication and to nanomanipulation.[7] It provides a chemical approach to nanoscience and technology that does not have to resort to stepwise bottom-up construction or to top-down prefabrication of specific nanostructures. Self-assembling nanostructures possess dynamic and combinatorial features that confer to them the potential to undergo healing and adaptation, as required for the development of *smart nanomaterials.*

Dynamic combinatorial, what else?: In addition, to the extension to materials science, one may envisage the implementation of dynamic combinatorial approaches in other areas. Of major interest, is the development of combinatorial methodologies for the discovery of novel *catalysts*.[43] The DCC/VCL scheme may be applied towards the same goal by grafting reactive groups to the basic components so as to generate DCLs of potentially catalytic constituents. The self-assembly of an inorganic catalyst represents a case in point.[44]

Transport processes and *signal transduction* may also take advantage of DCC. For instance the dynamic assembly of several different peptide chains in a membrane offers the possibility to generate combinatorial multisubunit ion channels.[45–47] Dynamical combinatorial processes may be envisaged in and between molecular assemblies such as monolayers, membranes and vesicles containing suitably designed and functionalized lipids. Information and signal transduction through a membrane may make use of the dynamic combinatorial positioning of several components in and out of the plane of a membrane to provide a very large number of transmembrane patterns (see Figure 28, p. 126 in ref. [7a]).

Thus, the selection leading to the expression of a specific constituent of a VCL is, in its generality, *function-driven*; it concerns not only target binding/recognition processes or physical properties, but also chemical transformation and catalysis as well as translocation and transduction events. The DCC/VCL approach bears conceptual or formal analogies to processes belonging to other areas of science, in particular to biology. Such is for instance the case for the operation of the immune system, which leads to the amplification of the active component of the full antibody library. Combinatorial aggregates of regulatory proteins allow the build-up of a large number of regulatory circuits in cell function and in developmental biology. Also, in the scheme of assembly forming connections of brain functions,[48] individual brain cells rapidly change the partners with which they synchronize their responses, so that the same cells are used in different constellations, in a sort of VCL of neurons.

Conclusion

The DCC/VCL concept provides a unifying framework within which the various entities and processes considered above can be brought together in a coherent fashion. It emphasizes that *informed diversity* is the goal, not diversity by sheer number. It opens the way to the development of instructed, target- or function-directed combinatorial chemistry, that is, of smart combinatorial chemistry, where the sought-after property

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does the driving! It is clear that we are just at the start of the exploration of the potential of dynamic combinatorial systems and of virtual diversity presentation. Rapid and vigorous development of this field may be expected.

In a quite different vein, combinatorial procedures with dynamic features have also been implemented in the written word and the arts, as illustrated for instance in contemporary literature[49] and music.[50]

Finally, the DCC/VCL approach contributes to the perception of chemistry as an information science, spanning the domains from biology to materials, and to its progression towards complexity.[7] By its adjustability and evolutionary character, it participates in the emergence of an *adaptive chemistry*.[51]

[1] G. Lowe, *Chem. Soc. Rev.* **1995**, *24*, 309.
[2] N. K. Terrett, M. Gardner, D. W. Gordon, R. J. Kobylecki, J. Steele, *Tetrahedron* **1995**, *51*, 8135.
[3] *Acc. Chem. Res.*, special issue (Eds.: A. W. Czarnik, J. A. Ellman), **1996**, *29*, 112; *Combinatorial Chemistry—Synthesis and Applications* (Eds.: S. R. Wilson, A. W. Czarnik, Wiley, New York, **1997**.
[4] F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288.
[5] *Curr. Opin. Chem. Biol.*, special issue (Eds.: K. T. Chapman, G. F. Joyce, W. C. Still) **1997**, *1*, 1.
[6] *Chem. Rev.*, special thematic issue (Ed.: J. W. Szostak), **1997**, *97*, 347–510.
[7] a) J.-M. Lehn, *Supramolecular Chemistry—Concepts and perspectives*, VCH, Weinheim, **1995**; b) J.-M. Lehn, *Supramolecular Chemistry—Concepts and perspectives*, VCH, Weinheim, **1995** p. 180; c) J.-M. Lehn, *Supramolecular Chemistry—Concepts and perspectives*, VCH, Weinheim, **1995**, chapter 10.
[8] R. Krämer, J.-M. Lehn, A. Marquis-Rigault, *Proc. Natl. Acad. Sci. USA*, **1993**, *90*, 5394; for the possibilities that may be offered by mixed ligands/metal ions combinations, see: V. S. Smith, J.-M. Lehn, *Chem. Commun.* **1996**, 2733.
[9] A. W. Czarnik, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 12738.
[10] For the use of mass spectrometry see: B. Ganem, J. D. Henion, *Chemtracts* **1993**, *6*, 1; M. Przybylski, M. O. Glocker, *Angew. Chem.* **1996**, *108*, 878; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 807.
[11] D. Craston, S. Cowen, *Science Progress* **1998**, *81*, 225.
[12] B. Hasenknopf, J.-M. Lehn, B. O. Kneisel, G. Baum, D. Fenske, *Angew. Chem.* **1996**, *108*, 1987; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1838; B. Hasenknopf, J.-M. Lehn, N. Boumediene, A. Dupont-Gervais, A. Van Dorsselaer, B. Kneisel, D. Fenske, *J. Am. Chem. Soc.* **1997**, *119*, 10956.
[13] I. Huc, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 2106; I. Huc, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 8272.
[14] J. T. Goodwin, D. G. Lynn, *J. Am. Chem. Soc.* **1992**, *114*, 9197.
[15] V. Berl, I. Huc, J.-M. Lehn, A. DeCian, J. Fischer, *Eur. J. Org. Chem.* **1999**, in press.
[16] P. N. W. Baxter, J.-M. Lehn, K. Rissanen, *Chem. Commun*. **1997**, 1323.
[17] I. Huc, M. J. Krische, D. P. Funeriu, J.-M. Lehn, *Eur. J. Inorg. Chem*. **1999**, in press.
[18] O. Ramström, J.-M. Lehn, unpublished work.
[19] T. Bunyapaiboonsri, J.-M. Lehn, unpublished work.
[20] P. A. Brady, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans 1* **1997**, 3237.
[21] P. G. Swann, R. A. Casanova, A. Desai, M. M. Frauenhoff, M. Urbancic, U. Slomczynska, A. J. Hopfinger, G. C. Le Breton, D. L. Venton, *Biopolymers* **1996**, *40*, 617.
[22] X. Cha, K. Ariga, T. Kunitake, *J. Am. Chem. Soc.* **1996**, *118*, 9545.
[23] B. Klekota, M. H. Hammond, B. L. Miller, *Tetrahedron Lett.* **1997**, *38*, 8639.
[24] M. Fujita, S. Nagao, K. Ogura, *J. Am. Chem. Soc.* **1995**, *117*, 1649; S. B. Lee, S. Hwang, D. S. Chung, H. Yun, J.-I. Hong, *Tetrahedron Lett.* **1998**, *39*, 873; M. Albrecht, O. Blau, R. Frölich, *Chem. Eur. J.* **1999**, *5*, 48.
[25] H. Hioki, W. C. Still, *J. Org. Chem.* **1998**, *63*, 904.
[26] M. C. Calama, R. Hulst, R. Fokkens, N. M. M. Nibbering, P. Timmerman, D. N. Reinhoudt, *Chem. Commun.* **1998**, 1021.
[27] S. Sakai, Y. Shigemasa, T. Sasaki, *Tetrahedron Lett.* **1997**, *38*, 8145.
[28] T. Giger, M. Wigger, S. Audétat, S. A. Benner, *Synlett* **1998**, 688.
[29] K. Mosbach, *Trends Biochem. Sci.* **1994**, *2*, 166; G. Wulff, *Angew. Chem.* **1995**, *107*, 1958; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1812.
[30] For the adjustment of inorganic cluster cages to included anions, see for instance: A. Müller, *J. Mol. Struct.* **1994**, *325*, 13.
[31] For an approach based on diversity generated in random copolymers, see: M. Jozefowicz, J. Jozefowicz, *Biomaterials*, **1997**, *18*, 1633.
[32] C. Miculka, N. Windhab, G. Quinkert, A. Eschenmoser, German Patent, DE 19619373 A1, **1997**; *Chem. Abstr.* **1998**, *128*, 34984.
[33] A. V. Eliseev, M. I. Nelen, *J. Am. Chem. Soc.* **1997**, *119*, 1147.
[34] P. Cudic, J.-M. Lehn, unpublished work.
[35] P. A. Brady, J. K. M. Sanders, *Chem. Soc. Rev.* **1997**, *26*, 327.
[36] A. Ganesan, *Angew. Chem.* **1998**, *110*, 2989; *Angew. Chem. Int. Ed.* **1998**, *37*, 2828.
[37] A. V. Eliseev, *Curr. Opin. Drug Discov. Develop.* **1998**, *1*, 106.
[38] A. V. Eliseev, J.-M. Lehn, *Curr. Top. Microbiol. Immunol.* **1999**, *243*, 159.
[39] a) D. R. Liu, P. G. Schultz, *Angew. Chem.* **1999**, *111*, 36; *Angew. Chem. Int. Ed.* **1999**, *38*, 36; b) T. Bein, *Angew. Chem.* **1999**, *111*, 335; *Angew. Chem. Int. Ed.* **1999**, *38*, 323; c) W. F. Maier, *Angew. Chem.* **1999**, *111*, 1294; *Angew. Chem. Int. Ed.* **1999**, *38*, 1216.
[40] J.-M. Lehn, *Makromol. Chem. Macromol. Symp.* **1993**, *69*, 1.
[41] M. Antonietti, S. Heinz, *Nachr. Chem. Techn. Lab.* **1992**, *40*, 308; C. M. Paleos, D. Tsiourvas, *Angew. Chem.* **1995**, *107*, 1839; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 1696.
[42] For a case of combinatorial color generation, in which a dynamic aspect is introduced by time dependence of coloration, see: A. Fernandez-Acebes, J.-M. Lehn, *Adv. Mat.* **1999**, in press.
[43] A. Hoveyda, *Chem. Biol.* **1998**, *5*, R187; S. M. Senkan, S. Ozturk, *Angew. Chem.* **1999**, *111*, 867; *Angew. Chem. Int. Ed.* **1999**, *38,* 791.
[44] C. L. Hill, X. Zhang, *Nature*, **1995**, *373*, 324.
[45] For an analogy, see the oligomeric alamethicin ion pore: R. Nagaraj, P. Balaram, *Acc. Chem. Res.* **1981**, *14*, 356; R. O. Fox, Jr., F. M. Richards, *Nature* **1982**, *300*, 325.
[46] For the cation dependent self-assembly of ionophores, see for instance: J. T. Davis, S. Tirumala, J. R. Jensen, E. Radler, D. Fabris, *J. Org. Chem.*, **1995**, *60*, 4167.
[47] For a combinatorial approach towards gene delivery agents, see: J. E. Murphy, T. Uno, J. D. Hamer, F. E. Cohen, V. Dwarki, R. N. Zuckermann, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 1517.
[48] W. Singer, *Science* **1995**, *27*, 758.
[49] See the OULIPO (Ouvroir de littérature potentielle, Workshop of potential literature); one may cite *Cent Mille Milliards de Poèmes* by R. Queneau (the verses of four sonnets are printed on superposed separate paper strips so that novel poems can be generated at will by turning the strips), and *Composition No. 1* by M. Saporta (a novel printed on free pages which may be redistributed like a stack of game cards, producing a new arrangement/novel each time); in both cases, a specific arrangement produces one specific expression from the very large set of all virtual combinations possible.
[50] Consider for instance: P. Boulez, *…explosante-fixe…* based on dynamic combinations of basic musical cells and some aspects of I. Xenakis, in *Musiques Formelles*, la revue musicale, (Ed. R. Masse), Paris, **1963**.
[51] J.-M. Lehn, in *Supramolecular Science: Where It Is and Where It Is Going*, (Eds.: R. Ungaro, E. Dalcanale), Kluwer, Dordrecht, **1999**, pp. 287–304.

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