

Multistate and Phase Change Selection in Constitutional Multivalent Systems

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Abstract Molecular architectures and materials can be *constitutionally self-sorted* in the presence of different biomolecular targets or external physical stimuli or chemical effectors, thus responding to an external selection pressure. The high selectivity and specificity of different bioreceptors or self-correlated internal interactions may be used to describe the complex constitutional behaviors through multistate component selection from a dynamic library. The self-selection may result in the dynamic amplification of self-optimized architectures during the phase change process. The *sol–gel resolution of dynamic molecular/supramolecular libraries* leads to higher self-organized *constitutional hybrid materials*, in which organic (supramolecular)/inorganic domains are reversibly connected.

Keywords Carbonic anhydrase · Dynamic constitutional chemistry · Dynamic interactive systems · Hybrid materials

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Abbreviations

CA	Carbonic anhydrases
CDC	Constitutional dynamic chemistry
DCC	Dynamic combinatorial chemistry
DCL	Dynamic combinatorial library(ies)

1 Introduction

Constitutional dynamic chemistry (CDC) [1–3] and its application dynamic combinatorial chemistry (DCC) [4–10] are new evolutionary approaches to produce *chemical diversity*. In contrast to the stepwise methodology of classic combinatorial techniques, DCC allows for the generation of large molecular libraries from small sets of building blocks based on reversible interconversion between the library species. With this DCC approach, the building elements are spontaneously assembled to virtually form all possible combinations using covalent or non-covalent interactions between the species. Compound libraries generated by DCC show special applications on biology and biomedicine. By virtue of the reversible interchanges, a DCL can adapt to the system constraints, for example allowing selection events driven by molecular recognition [4–6]. In this case, the target entity itself is used to select the active ligand, directly from a library pool, resulting in a screening process that is more efficient and greatly simplified [6–10]. As an added advantage, the screening signal is amplified, due to the adaptation process, facilitating detection and characterization.

The design and construction of supramolecular architectures has attracted intense interest during the last 40 years not only for their potential applications as new functional materials but also for their fascinating constitutional diversity. It is based on the structural organization and functional integration within a molecular/supramolecular architecture of components presenting features such as functional-activity. Self-organization of supramolecular entities may be directed by *design* or by *constitutional selection of dynamic combinatorial systems* [2].

CDC has also been identified as an especially promising means to explore spatial/temporal supramolecular evolution and this concept can also be used on a range of applications. A specific advantage with dynamically generated libraries gives the possibility for the compounds to self-adjust to a chosen target species at a given time in a certain environment. If libraries are produced in the presence of a bioreceptor, new ligands can be selected that resemble the naturally occurring ligands and new, potentially useful affinity molecules can be generated.

We therefore considered addressing in the first part of this review some of most representative examples in which specific molecular architectures and materials are *constitutionally self-sorted* in the presence of different biomolecular targets or

external physical stimuli/chemical effectors. They respond to an external selection pressure. The high selectivity and specificity of different bioreceptors may be used to describe a complex constitutional behavior through component selection from the DCLs, driven by the selective binding to the active sites. These multistate systems also point to the possibility of modulating the drug discovery methods by constitutional recombination induced by the specific bioreceptor targets.

On the other hand, the *self-organization by design* is based on the implementation of compounds containing specific molecular information stored in the arrangement of suitable binding sites and of external components reading out the structural information through the algorithm defined by their interactional preferences. Thus, this might allow the generation of dynamic molecular or supramolecular libraries presenting features such colloidal [10–12], gel [13, 14], or solid-state selection [15–25] of a constituent of an equilibrating collection of components reversibly switching between different arrays.

In this context the supramolecular crystalline [15–22] or hybrid materials [23–35] can be prepared and *constitutionally self-sorted* by using an irreversible kinetic process like crystallization or sol–gel polymerization. The self-selection is based on constitutional internal interactions of library components, resulting in the dynamic amplification of self-optimized architectures, during the phase change process. With all this in mind, the second part will be devoted to *sol–gel resolution of dynamic molecular/supramolecular libraries*, emphasizing recent developments, especially as pursued in our laboratory.

2 Multiple Expressions of Target-Encoded Dynamic Constitutional Libraries

2.1 *Enzyme-Encoded DCL: Towards the Discovery of Isozyme-Specific Inhibitors*

DCC [1–10] has been extensively implemented during the last decade as a powerful approach in drug discovery [5] that gives access to rapid and attractive identification of ligands and inhibitors for biological receptors and enzymes. The dynamic combinatorial approach is based on a shift of chemical equilibrium of a library of reversibly connected molecular components encompassing all possible combinations, driven by a biomolecular (molecular) target that favors the amplification of the fittest constituent forming the most stable non-covalent supramolecular entities with the target [36]. DCC has successfully implemented in a variety of biological systems non-exhaustively including lectins [37–40], acetylcholinesterase [41, 42], neuraminidase [43, 44], galactosyltransferase [45], glycosidase [46], DNA [47, 48] etc.

Carbonic anhydrases (CA) have been one of the early addressed biological targets for which the DCC [49–53] may offer a complementary route to high-throughput combinatorial methods [54].

The first example in this field has been pioneered by Lehn et al. who reported a library of 12 constituents containing different Zn^{2+} complexing groups and various aromatic moieties connected by the reversible imino-bond, generating thus a hydrophobic sulphonamide inhibitor possessing high affinity toward the bovine carbonic anhydrase (bCA II, EC 4.2.1.1) [49]. Then the feasibility of this concept has been extended by Nguyen et al. (Fig. 1) [50] and Poulsen et al. [51–53] including a kinetic and a thermodynamic approach based on cross-metathesis reversible reaction, all of which address the same challenge: the discovery of small molecule inhibitors of bCA II, an easily accessible and inexpensive enzyme, but not very useful for discovering human CA inhibitors [55].

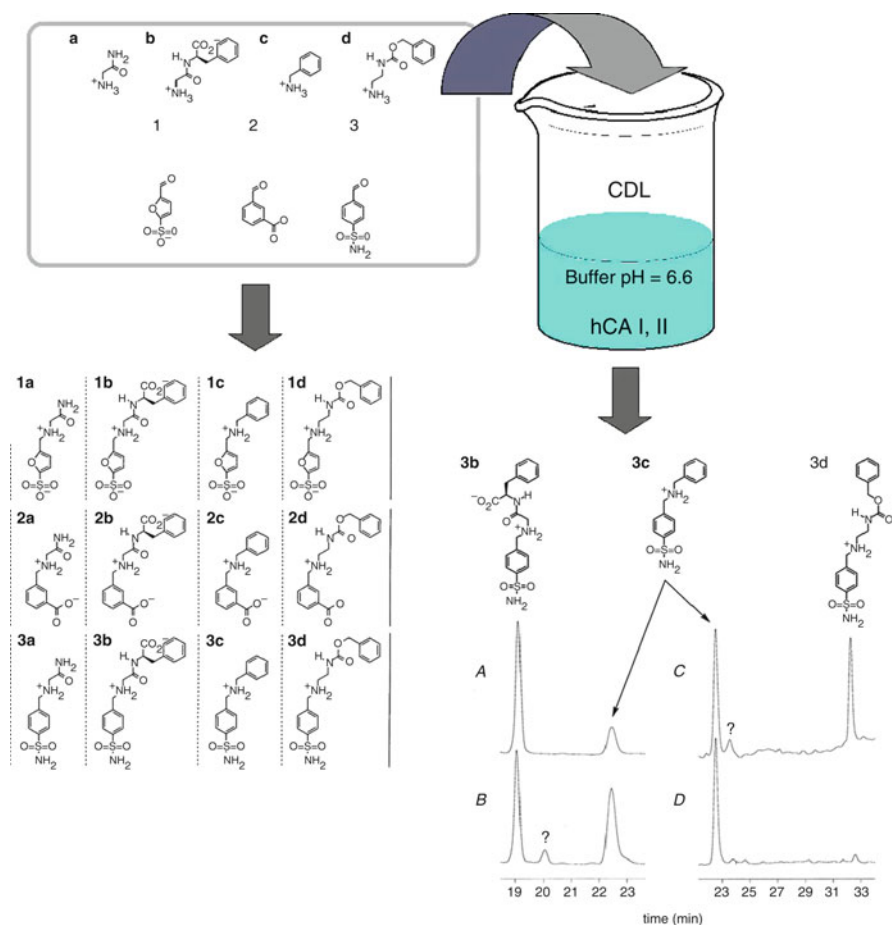


Fig. 1 Constitutional dynamic chemistry applied to bovine carbonic anhydrase bCA II isozyme and elaboration of constitutional dynamic library (CDL). Precursor amines **a–d** and aldehydes **1–3** and resulting components of the combinatorial library **1a–c–3a–c**. HPLC traces of the final reaction mixtures showing amplification of 3c and 3d (adapted from [49])

CA represent an important class of ubiquitously expressed zinc metalloenzymes catalyzing the reversible hydration of carbon dioxide to bicarbonate and a proton. Much progress has been achieved in the past decade in identifying selective CA inhibitors (CAIs) or activators by means of rational drug design [56–64]. The emergence of numerous families of selective CA inhibitors against several pharmacologically relevant isozymes are based on specific strategies including X-ray crystal structures for some enzyme-inhibitor complexes [58]. Among the 13 catalytically active α -CA isozymes currently known and studied as the drug targets, human carbonic anhydrases hCA I and hCA II are considered the most selective isoforms. Their inhibition has already offered important biomedical options in the development of antiglaucoma, antiepileptic, antiobesity, or anticancer drugs.

A recent study showed that a finer analysis can be performed to identify enzyme inhibitors and to evaluate their relative affinities toward the human hCA II, considered as one of the most active isoforms and studied as a drug target [65] (Fig. 2).

A DCL of 20 components has been generated under thermodynamic control by imine formation and exchange, combined with non-covalent bonding within the enzyme active site [65]. This method enabled the identification of a series of sulfonamide inhibitors **1D**, **1C**, and **2D** presenting a good inhibition and potent formation in the presence of hCA II isozyme (Fig. 2). Moreover, these data were beneficial to identify rapidly from a DCL of competitive components compound **4E**, which might represent a better compromise between entropic/enthalpic factors as a result of combined hydrophobic/H bonding binding effects of the component **4** present in a hydrophobic pocket. Finally, once the fittest structural features has been found, more precisely defined components can be developed in the next studies, allowing for the identification of enzyme inhibitors showing selectivity. Although the CA inhibitor field is a small one, these findings may be relevant to general drug design research, especially when enzyme families with a multitude of members and with similar active site features are targeted.

Indeed, the family of the CA, with a large number of representatives (13 catalytically active isoforms in mammals) playing fundamental physiological and pathological functions, can be used as a paradigm in non-conventional drug design studies aimed at obtaining compounds with selectivity for some isoforms, and thus drug candidates with reduced side effects. The observed high selectivity and specificity of hCA I and hCA II isozymes may be used to describe the complex behavior displayed by the constitutional recomposition of a dynamic library under the distinct and specific templating effect of the two enzymes.

A dynamic combinatorial library of six components can be generated under thermodynamic control by imine formation and exchange combined with non-covalent bonding within the enzyme binding site and DCL was evaluated for their relative affinities toward the physiologically relevant human carbonic anhydrase hCA I and hCA II isozymes [66].

In this context the constitutional dynamic library (CDL) is susceptible to change its composition (output expression) through component selection driven by the

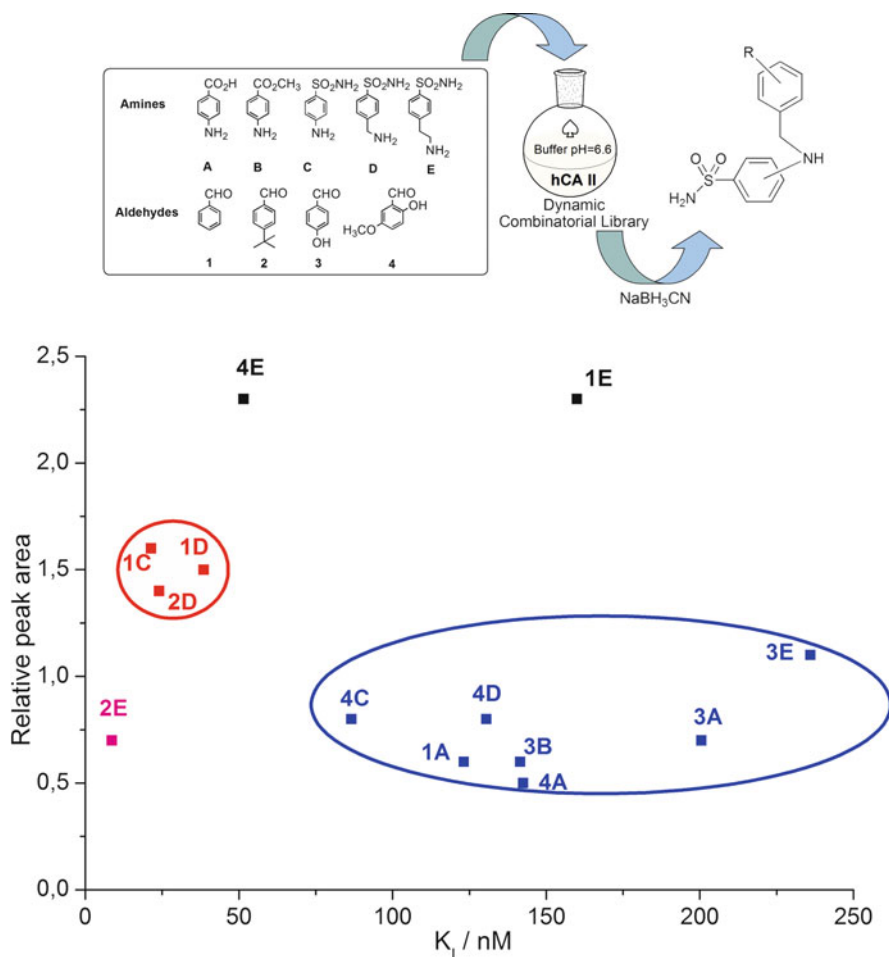


Fig. 2 Elaboration of the DCL of inhibitors and their relative peak area expressing the amplification relative to the free-enzyme DCL, function of inhibitory power against hCA II (adapted from [65])

selective binding to human hCAI and hCA II isozymes (Fig. 3). Among all possible imines formed, active compounds of appropriate geometry can be easily identified in competitive reactional conditions.

Similar studies by Beau et al. demonstrate the potential of a UDP-galactose library to search for selective binders to two galactosyltransferases enzymes using the same substrate. Despite the simplicity of the DCL composition, this adaptive DCL system is able to differentiate the two enzymes and identify very simple binders that may serve as starting points for the elaboration of selective inhibitors (Fig. 4) [45].

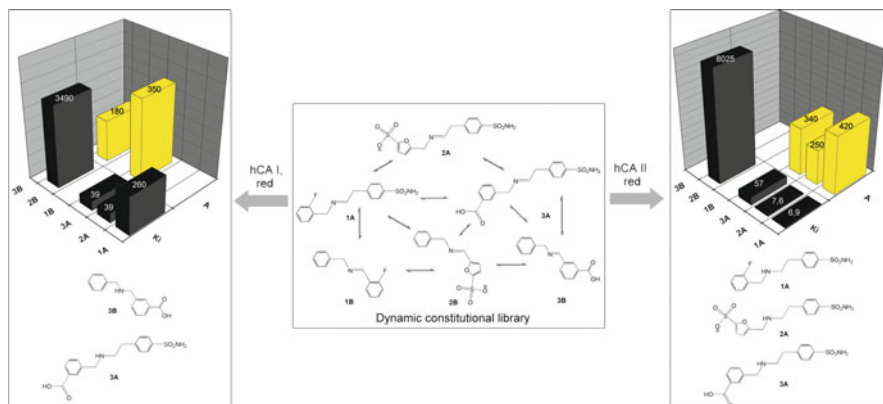


Fig. 3 Elaboration of the DCL of inhibitors' inhibition constants K_I and the amplification of the constitutional dynamic library (CDL) against catalytically active human hCA I and hCA II cytosolic isozymes (adapted from [66])

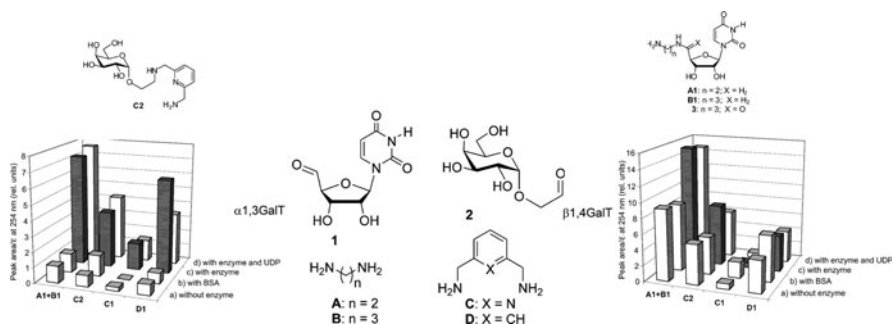


Fig. 4 Structure of the building blocks for a DCL designed to generate possible UDP-galactose mimics. Amplification of the constitutional dynamic library (CDL) against catalytically active α 1,3GalT and β 1,4GalT enzymes (adapted from [45])

2.2 External Stimuli Recomposition/Selection of DCL: Towards the “Dynamic Interactive Systems”

The reversibility of interactions between components of a system is a crucial factor and, accordingly, the dynamic interfaces might render the emergence system states self-adaptive, which mutually (synergistically) may adapt their spatial/temporal distribution based on their own structural constitution during the simultaneous formation of self-organized domains. The extension of the constitutional chemistry approach to nanoplateforms would be able to compete at multiple length scales within nanoscopic networks and to display variations in their sizes and functionality. Furthermore we can relate this behavior to purely synthetic compositions such as the “dynamic interactive systems” [19] characterized by their aptitude to

organize macroscopically (self-control) their distribution in response to external stimuli in coupled equilibria.

These concepts were first developed and described by Lehn [67] and Giuseppone [11]. The constitutional recomposition of a dynamic library of imines can display complex behavior under the effect of two external parameters: a physical (T) stimulus and a chemical effector ($[H^+]$) [67]. These results illustrate the possibility of modulating an optical by constitutional recomposition induced by a specific trigger. Such features have been used for the development of stimuli-responsive, functional dynamic materials.

Basically, the CDC implements a dynamic reversible interface between interacting components. It might mediate the structural self-correlation of different domains of the system by virtue of their basic constitutional behaviors. In contrast, the self-assembly of the components controlled by mastering molecular/supramolecular interactions, may embody the flow of structural information from the molecular level to nanoscale dimensions. Understanding and controlling such up-scale propagation of structural information might offer the potential to impose further precise order at the mesoscale and create new routes to obtain highly ordered ultradense arrays over macroscopic distances.

Within this context, Giuseppone et al. showed that, by coupling DCC with the autocatalytic formation of specifically designed supramolecular assemblies, a self-replicating selection can occur at two length scales with a sigmoid (cooperative) concentration–time profile. Indeed, they have found that by dynamic amphiphilic block copolymers (dynablocks), in which a hydrophobic block is reversibly linked to a hydrophilic one, the formation of micelles can have autopoietic growth in water (Fig. 5). Such systems, combining cooperative processes at different length scales in networks of equilibria and displaying autocatalysis within DCLs, are of interest for the understanding of the emergence of self-organizing collective properties but also for the design of responsive systems [11, 12, 68, 69].

The selection of one or more components occurs as function of either internal (the nature and the geometry of the binding subunits, the stoichiometry, etc.) or external factors (nature of the solvent, the presence of specific molecules or ions, etc.). In view of the lability of the reversible molecular and supramolecular interactions (H-bonding, van der Waals, coordinative bonds, etc.) the self-assembly processes may present a number of novel features such as cooperativity, diversity, selection, or adaptation.

Within this context, the dynamic constitutional (i.e., covalent or supramolecular) systems can undergo constitutional recomposition under the effect of different parameters, marking changes in global properties and in the functional behaviors of the new evolving systems. Lehn and Giuseppone illustrate the selective response of this specific dynamic system to chemical effectors (Zn^{2+}) resulting in the constitutional recomposition of the system in response to a specific effector. In addition to inducing selection, Zn^{2+} ions also lead to a fluorescence shift/enhancement (Fig. 6).

On a conceptual level, both features brought together express a synergistic adaptive behavior: the addition of an external effector drives a constitutional

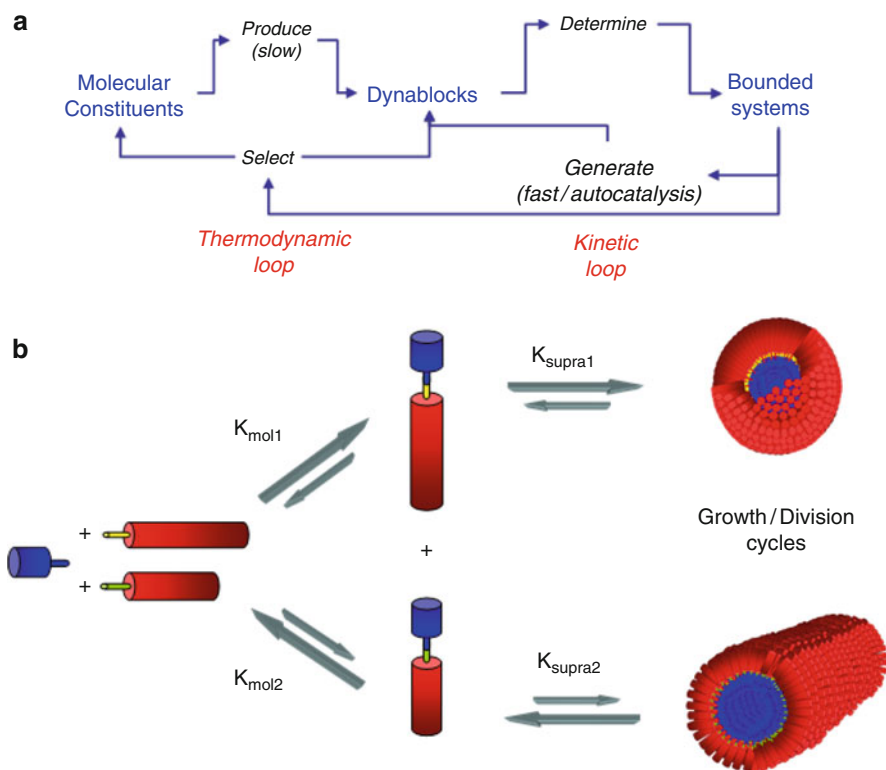


Fig. 5 (a) Synergistic constitutional relationships observed at two length scales within (b) a model minimal self-replicating DCL. For clarity, the growth/division cycles of micellar structures are not represented (adapted from [11])

evolution of the dynamic mixture towards the selection and amplification of the species that in return allows the generation of a signal indicating the presence of the very effector that promoted its generation in the first place [68, 69].

Such constitutional reorganization can be emphasized at supramolecular/nanometric level by designing columnar ion-channel architectures confined within scaffolding hydrophobic silica mesopores [70]. Evidence has been presented that such a membrane adapts and evolves its internal structure so as to improve its ion-transport properties: the dynamic non-covalent bonded macrocyclic ion-channel-type architectures can be morphologically tuned by alkali salts templating during the transport experiments or the conditioning steps. The dynamic character allied to reversible interactions between the continually interchanging components makes them respond to external ionic stimuli and adjust to form the most efficient transporting superstructure in the presence of the fittest cation, selected from a set of diverse less-selective possible architectures which can form by their self-assembly. From the conceptual point of view these membranes express a synergistic adaptive behavior: the addition of the fittest alkali ion drives a constitutional evolution of the

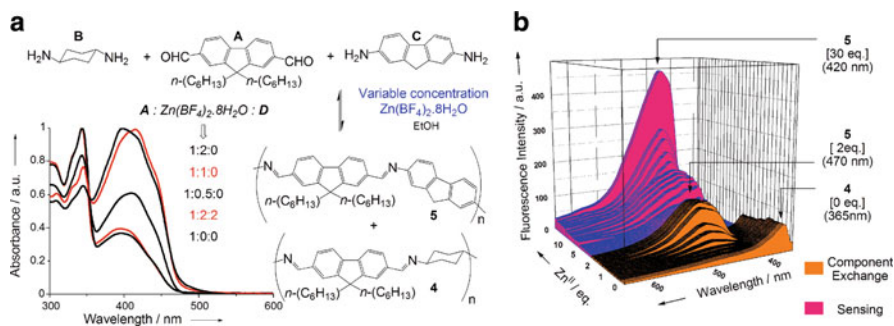


Fig. 6 Fluorescence spectra at in CHCl_3 of the CDL II of fluorene polyimines, on addition of increasing amounts of $\text{Zn}(\text{BF}_4)_2 \cdot 8\text{H}_2\text{O}$ (equivalent with respect to initial A in CDL II); excitation at 320 nm (adapted from [68, 69])

membrane pores toward the selection and amplification of the specific transporting superstructures within the membrane in the presence of the cation that promoted its generation in the first place. This is a nice example of dynamic self-instructed (“trained”) membranes where a solute induces the upregulation (prepare itself) of its own selective membrane.

3 Sol–Gel-Driven DCL Constitutional Amplification-Toward Constitutional Hybrid Materials

Hybrid organic–inorganic materials produced by sol–gel processes are the subject of various investigations, offering the opportunity to achieve nanostructured materials first from robust organogel systems or second from self-organized supramolecular silsesquioxane systems [71]. Of special interest is the structure-directed function of biomimetic and bioinspired hybrid materials and control of their build-up from suitable units by self-organization. The main interest focuses on functional biomimetic materials in which the recognition-driven properties could be ensured by a well-defined incorporation of receptors of specific *molecular recognition and self-organization* functions, incorporated in hybrid solid dense or mesoporous materials [72–77]. Moreover, the different interconverting outputs resulting from such supramolecular systems may form by self-organization a dynamic polyfunctional diversity from which we may “extract selectively” a constitutional preferred hybrid architecture by sol–gel polymerization in the solid state, under the intrinsic stability of the system.

Considerable challenges lie ahead and the more significant one is the “dynamic marriage” between *supramolecular self-assembly* and the *sol–gel process*, which kinetically and stereochemically might communicate in order to converge toward self-organized functional hybrid materials. The weak interactions (H-bonds, coordination or van der Waals interactions, etc.) positioning of the molecular components

to give the supramolecular architectures are typically less robust than the cross-linked covalent bonds formed in a specific polymerization process. Accordingly, the sole solution to overcome these difficulties is to improve the binding (association) efficiency of molecular components generating supramolecular assemblies. At least in theory, an increased number of interactions between molecular components and the right selection of the solvent might improve the stability of the templating supramolecular systems, communicating with the inorganic siloxane network.

Nucleobases oligomerization can be an advantageous choice to reinforce the controlled communication between interconnected “supramolecular” and “siloxane” systems. Moreover, the different interconverting outputs that nucleobases may form by oligomerization define a dynamic polyfunctional diversity which may be “extracted selectively” by sol–gel polymerization in solid state, under the intrinsic stability of the system. In this context, alkoxy silane nucleobases form in solution different types of hydrogen bonded aggregates which can be expressed in the solid state as discrete higher oligomers. Three heteroditopic nucleobase ureido-silsesquioxanes **A_{Si}**, **U_{Si}**, **G_{Si}** receptors have been recently reported by the Barboiu group [25–27] (Fig. 7). They generate self-organized continual superstructures in solution and in the solid state based on three encoded features: (1) the molecular recognition, (2) the supramolecular H-bond directing interactions, and (3) the covalently bonded triethoxysilyl groups.

The inorganic precursor moiety allows us, by sol–gel processes, to transcribe the solution self-organized dynamic superstructures in the solid heteropolysiloxane materials. The **A_{Si}** and **U_{Si}** compounds were designed as rigid H-bonding modules. For instance, by introducing bulky blocking alkoxy silanepropylcarboxamide groups in N9 (A) and N1 (U) positions we limit only the Watson–Crick and the Hoogsteen interactions as preferential H-bonding motifs. The **A_{Si}** and **U_{Si}** precursors generate self-organized superstructures based on two encoded features: (1) they contain a nucleobase moiety which can form ribbon-like oligomers via the combination of H-bond pairings and (2) the nucleobase moiety is covalently bonded to siloxane-terminated hydrophobic groups packing in alternative layers, allowing them, by sol–gel process, to transcribe their self-organization in the hybrids.

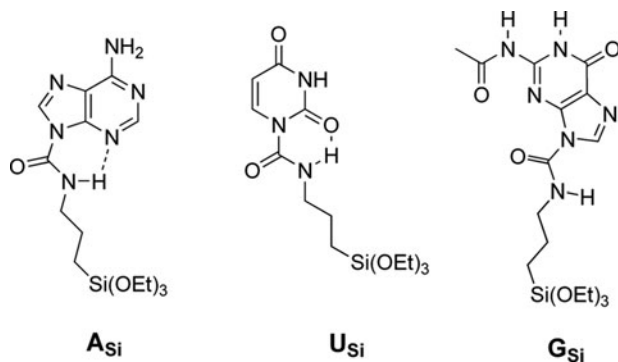


Fig. 7 Molecular structures of nucleobase ureido-silsesquioxanes **A_{Si}**, **U_{Si}**, **G_{Si}**

The dynamic self-assembly processes of such supramolecular systems undergoing continuous reversible exchange between different self-organized entities in solution may in principle be connected to kinetically controlled sol-gel process in order to extract and select an amplified supramolecular device under a specific set of experimental conditions. Such “dynamic marriage” between supramolecular self-assembly and in sol-gel polymerization processes which synergistically might communicate leads to “constitutional hybrid materials.”

The generation of hybrid materials \mathbf{M}_A , \mathbf{M}_U , and \mathbf{M}_{A-U} can be achieved using mild sol-gel conditions. X-ray powder diffraction experiments show that well-defined long-range order is present in the precursors \mathbf{A}_{Si} and \mathbf{U}_{Si} , but also in the hybrid materials \mathbf{M}_A , \mathbf{M}_U , and \mathbf{M}_{A-U} after the sol-gel polymerization step. As a general rule, as proved by the differences between the values of interplanar Bragg diffraction distances, d_{Si-Si} the condensation process between the ethoxysilane groups during the sol-gel process results in the formation (extraction) of the *most compact hybrid materials* \mathbf{M}_A , \mathbf{M}_U and \mathbf{M}_{A-U} compared with the unpolymerized \mathbf{A} , \mathbf{U} , and \mathbf{AU}_{mix} powders (Fig. 8). After the sol-gel process, the constitutional preference for compact geometries in hybrid materials is most likely dictated by hydrophobic interactions and Hoogsteen H-bonding self-assembly. These examples unlock the door to the *self-organized constitutional hybrid materials*. This shows that the primary supramolecular dynamic systems generated under thermodynamic control can successfully be coupled with a secondary synthetic sol-gel resolution under kinetic resolution. The sol-gel dynamic resolution can also be related to synthetic innovative strategies for which a reduced need for purification of final materials is advantageous.

Another interesting nucleoside motif is the *G-quartet*, formed by the hydrogen-bonding self-assembly of four guanosine molecules and stabilized by alkali cations, which play an important role in biology in particular in nucleic acid telomers of potential interest to cancer therapy. [78, 79] The role of cation templating is to stabilize by coordination to the eight carbonyl oxygens of two sandwiched *G-quartets*, the *G-quadruplex*, the columnar device formed by the vertical stacking of four *G-quartets*. The *G-quadruplex* with a chiral twisted supramolecular architecture represents a nice example of a dynamic supramolecular system when guanine and guanosine molecules are used.

The extension of CDC to phase-organization and phase-transition events has been elegantly demonstrated by Lehn et al. by using a gelation-driven self-organization process with component selection and amplification in constitutional dynamic hydrogels based on G-quartet formation and reversible covalent connections [13, 14]. Within this context, when a mixture of aldehydes is employed to decorate a G-quartet system the dynamic system selects the aldehyde that leads to the most stable gel. Thus, gelation redirects the acylhydrazone distribution in the dynamic library, as guanosine hydrazide scavenges preferentially a specific aldehyde under the pressure of gelation because of the collective interactions in the assemblies of G-quartets, despite the strong preference of the competing components in the system.

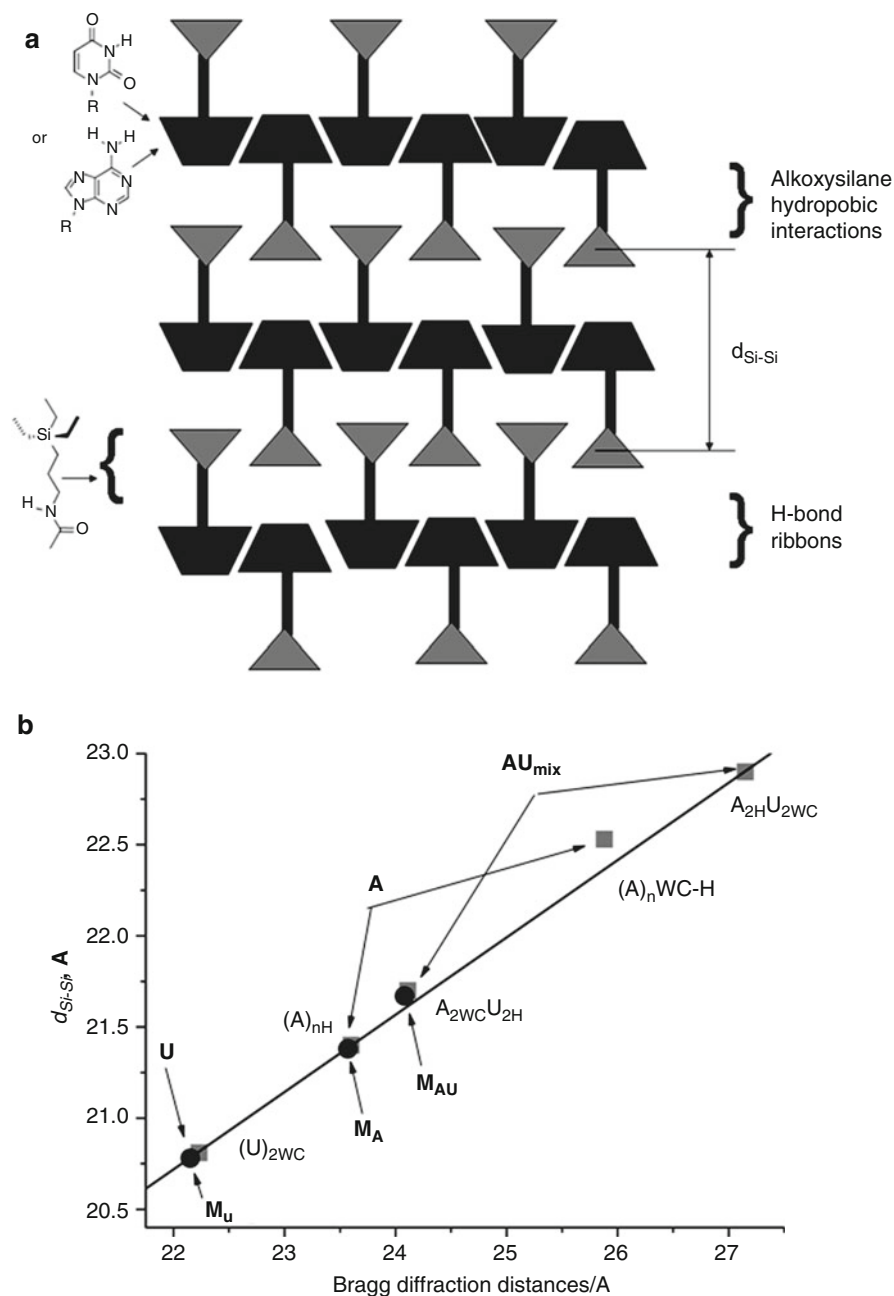


Fig. 8 Toward a constitutional transcription of base-pairing codes in hybrid materials. **(a)** Postulated model of self-organization of parallel H-bonded nucleobase aggregates and hydrophobic propyltriethoxysilane layers. **(b)** Guide to the eye interplanar $d_{\text{Si-Si}}$ distances calculated from the geometry of minimized structures vs experimental interplanar Bragg diffraction distances. The squares correspond to the unpolymerized powders of precursors **A**, **U**, and their 1:1 mixture AU_{mix} , while circles correspond to hybrid materials M_A , M_U , and $M_{\text{A-U}}$.

Barboiu et al. recently reported a new way to transcribe the supramolecular chirality and functionality of *G-quadruplex* at the nanometric and micrometric scale [26, 27]. *Molecular chirality* may be used as a tool to assemble molecules and macromolecules into supramolecular structures with dissymmetric shapes. The *supramolecular chirality*, which results from both the properties and the way in which the molecular components associate, is by constitution dynamic and therefore examples of large scale transcription of such *virtual chirality* remain rare. The generation of *G-quadruplex hybrid materials* can be achieved by mixing **G_{Si}** derivative with potassium triflate, where G-quartet superstructures have been amplified. Then the *sol-gel selection process* (Fig. 9) has been followed by a second *inorganic transcription* into inorganic silica replica materials by calcination (Fig. 10). Long-range amplification of the *G-quadruplex* supramolecular chirality into hybrid organic-inorganic twisted nanorods followed by the transcription into inorganic silica microsprints can be obtained.

Amazingly, these materials are, at the nanometric or micrometric scale, topologically analogous to its *G-quadruplex* supramolecular counterpart. After the sol-gel process, the preformed helical silica network has embedded probably enough chiral information to be irreversibly amplified (reinforced) during the calcination process when almost total condensation of Si-OH bonds occurs. By calcinations of the hybrid material, the templating twisted G-quadruplex architectures are eliminated and inorganic silica anisotropic microsprints are obtained. They present the same helical topology, without inversion inside the helix. These objects have a different helical pitch, which strongly depends on the self-correlation between hexagonal twisted mesophase domains at the nanometric level. Moreover, we obtain *chiral materials* by using a starting *achiral* guaninesiloxane **G_{Si}** as precursor of *achiral G-quartet* and of *chiral supramolecular G-quadruplex*. Figure 10 represents the first

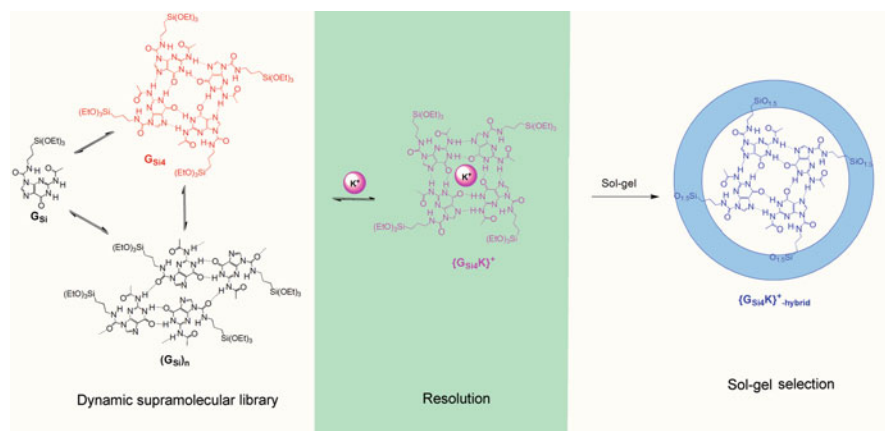


Fig. 9 Cation-template resolution of a dynamic supramolecular guanine system in which G-quartet is reversibly exchanging with linear ribbons followed by a secondary irreversible sol-gel selection of G-quadruplex hybrid materials

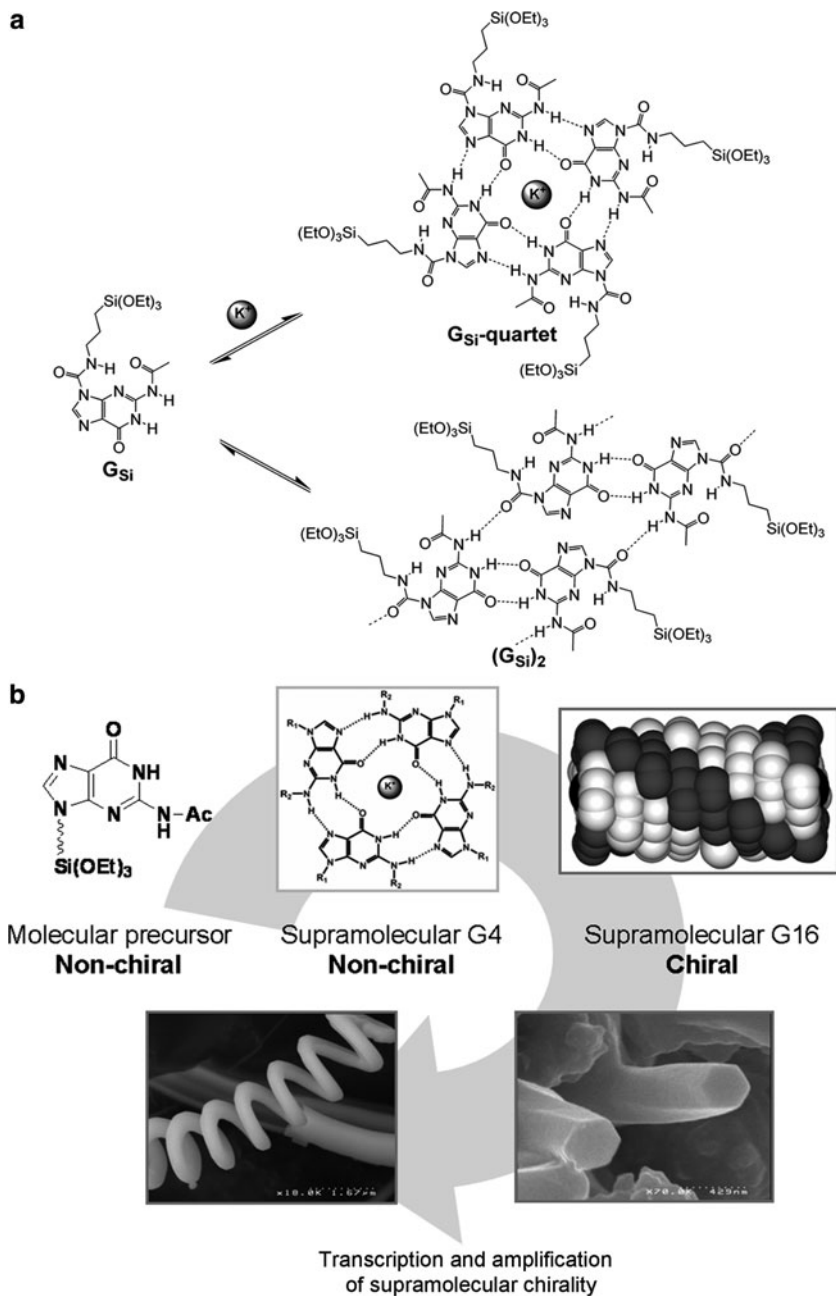


Fig. 10 (a) The cation-templated hierarchic self-assembly of guanine alkoxyasilane gives the *G-quartet* in equilibrium with *G-ribbons*, (b) the chiral *G-quadruplex* transcribed in solid hybrid materials by sol-gel in the presence of templating K^+ cation

picture of the *dynamic G-quadruplex* constitutionally transcribed at the nanometric level; it unlocks the door to the new materials world paralleling that of biology.

Biomimetic-type hybrids can be generated by using another strategy to transcribe and to fix the self-assembly of the G-quadruplex architectures in self-organized nanohybrids which is based on a *double reversible covalent* iminoboronate connection between the guanosine moiety and the hybrid [32] or dynameric [27] matrix. This contributes to the high level of adaptability and correlativity of the self-organization of the supramolecular G-quadruplex and the inorganic siloxane systems (Fig. 11).

The same strategy to transcribe the supramolecular dynamic self-organization of the G-quadruplex and ureidocrown-ether ion-channel-type columnar architectures in constitutional hybrids has been applied by using a “dynamic reversible hydrophobic interface” which can render the emerging hybrid mesophases self-adaptive. The reversible hydrophobic interactions allow both supramolecular and inorganic silica components to adapt mutually (synergistically) their spatial constitution during simultaneous (collective) formation of micrometric self-organized hybrid domains (Fig. 12) [30]. Such “dynamic marriage” between supramolecular self-assembly and

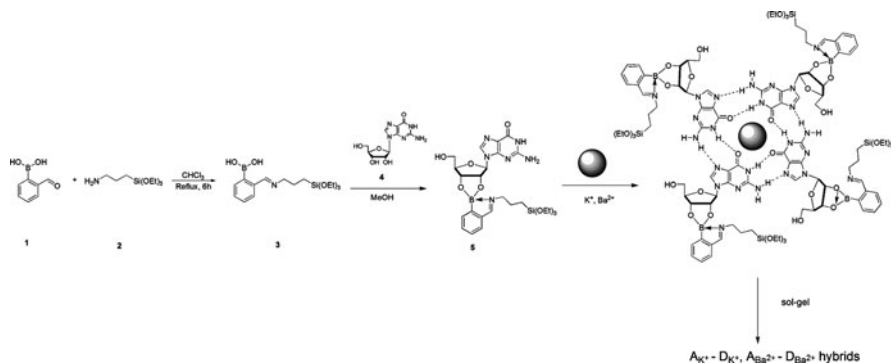


Fig. 11 Synthesis of iminoboronateguanosine precursor **5** followed by ion-template resolution of G-quartet architectures and sol-gel selection of hybrid materials $A_K^+-D_K^+$, $A_{Ba}^{2+}-D_{Ba}^{2+}$

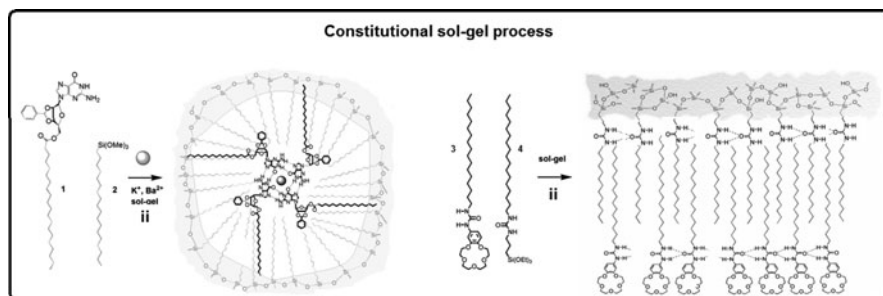


Fig. 12 Constitutional hybrid materials based on G-quadruplex and ureidocrown-ether architectures applied by using a “dynamic reversible hydrophobic interface” between the organic and inorganic phases

inorganic sol–gel polymerization process, which synergistically communicate, leads to higher self-organized hybrid materials with increased micrometric scales.

4 Conclusions

Complex dynamic and positive feedback between molecular/supramolecular partners in dynamic combinatorial libraries (DCLs) gives rise to emergent functional systems with a collective behavior. From the conceptual point of view, these systems express a synergistic constitutional self-reorganization (self-adaptation) of their configuration, producing an adaptive response in the presence of internal or external structural factors.

All the examples presented in this review shed light on the most major advantage with reversible DCLs over their irreversible systems [54], which is their potential adaptability to express the sorting constituent in response to an external selection pressure, based on constitutional dynamics within a confined enzymatic pocket, under the pressure of internal constitutional organization or by phase-change amplification.

Dynamic self-assembly of supramolecular systems prepared under thermodynamic control may in principle be connected to a kinetically controlled sol–gel process in order to extract and select the interpenetrated hybrid networks. Such “dynamic convergence” between supramolecular self-assembly and inorganic sol–gel processes, which synergistically communicate, leads to higher self-organized hybrid materials with increased micrometric scales.

Sol–gel constitutional resolution of constitutional hybrid architectures from DCLs toward *Dynamic Interactive Materials – systems materials* should expand the fundamental understanding of nanoscale structures and properties as it relates to creating products and manufacturing processes. More generally, applying such consideration to materials leads to the definition of *constitutional hybrid materials*, in which organic (supramolecular)/inorganic domains are reversibly connected. Considering the simplicity of this strategy, possible applications on the synthesis of more complex architectures might to be very effective, reaching close to novel expressions of complex matter.

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