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Evolution of Dynamic Combinatorial Chemistry

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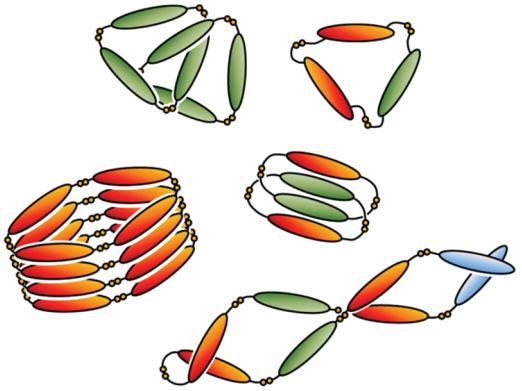
CONSPECTUS

Since its inception in the mid-1990s, dynamic combinatorial chemistry (DCC), the chemistry of complex systems under thermodynamic control, has proved valuable in identifying unexpected molecules with remarkable binding properties and in providing effective synthetic routes to complex species. Essentially, in this approach, one designs the experiment rather than the molecule. DCC has also provided us with insights into how some chemical systems respond to external stimuli. Using examples from the work of our laboratory and others, this Account shows how the concept of DCC, inspired by the evolution of living systems, has found an increasing range of applications in diverse areas and has evolved conceptually and experimentally.



A dynamic combinatorial library (DCL) is a thermodynamically controlled mixture of interconverting species that can respond to various stimuli. The Cambridge version of dynamic combinatorial chemistry was initially inspired by the mammalian immune system and was conceived as a way to create and identify new unpredictable receptors. For example, an added template can select and stabilize a strongly binding member of the library which is then amplified at the expense of the unsuccessful library members, minimizing the free energy of the system. But researchers have exploited DCC in a variety of other ways: over the past two decades, this technique has contributed to the evolution of chemistry and to applications in the diverse fields of catalysis, fragrance release, and responsive materials. Among these applications, researchers have built intricate and well-defined architectures such as catenanes or hydrogen-bonded nanotubes, using the ability of complex chemical systems to reach a high level of organization. In addition, DCC has proved a powerful tool for the study of complex molecular networks and systems.

The use of DCC is improving our understanding of chemical and biological systems. The study of folding or self-replicating macrocycles in DCLs has served as a model for appreciating how complex organisations such as life can emerge from a pool of simple chemicals. Today, DCC is no longer restricted to thermodynamic control, and new systems have recently appeared in which kinetic and thermodynamic control coexist. Expanding the realm of DCC to unexplored and promising new territories, these hybrid systems show that the concept of dynamic combinatorial chemistry continues to evolve.

A Successful but Naive Idea

Evolution has long been associated with the idea of a blind, random emergence of the best-adapted organism. However, in recent decades, many scientists have questioned whether evolution is truly random, and have shown it to be strongly constrained by the laws of physics and chemistry: in 1993, in his book *The Origins of Order*,[1] Kauffman used the perspective of mathematics to show that complex disordered systems (including, among others, living organisms) display an inherent property to self-organize and evolve in a way that was described as a "combinatorial optimisation process". Building on this notion, Williams and Fraústo Da Silva[2] proposed, from a purely biochemical point of view, that evolution can be predictably driven both by the nature of the chemicals accumulated within organisms and the way they interact with a changing environment.

Such concepts offer the opportunity of using complex networks of interactions to access highly organized structures and chemists, taking inspiration from nature, have since designed many artificial evolutionary systems.[3] Among them, dynamic combinatorial chemistry (DCC)[3−8] has proven to be a particularly fruitful approach: instead

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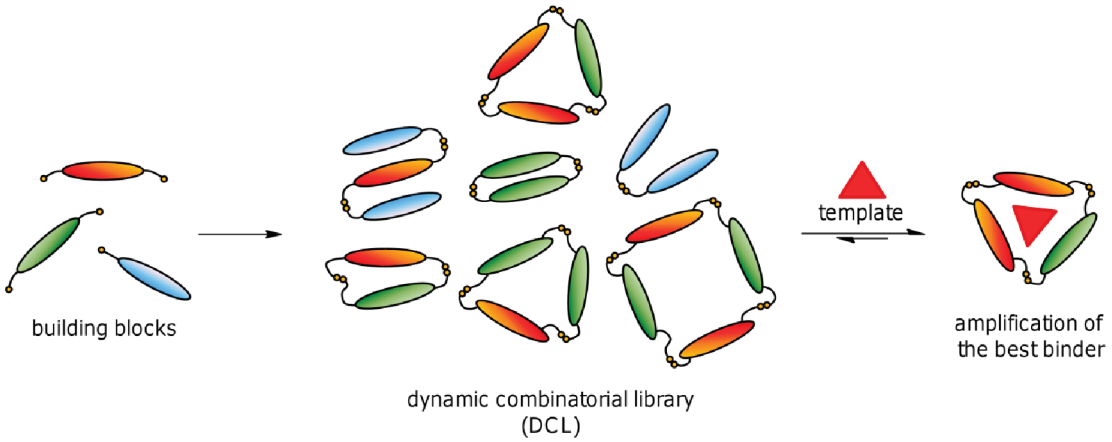

FIGURE 1. Schematic representation of a dynamic combinatorial library and amplification of the best binder in the presence of a template.

of designing a molecule to target a specific problem, the dynamic combinatorial chemist designs a system in which the most successful molecule is automatically selected and amplified from a pool of potential targets. In the beginning, DCC appeared to be a simple way to access many different and unpredictable receptors from a single pool of relatively simple components; we soon realized that it was a good way of discovering complex architectures and receptors that are normally inaccessible or unimaginable by rational design, and also a powerful tool for the study of systems chemistry.[9]

In dynamic combinatorial chemistry, simple molecular units (building blocks) are held together by noncovalent or reversible covalent bonds, generating a complex mixture of products which continuously interconvert: the composition of the mixture at equilibrium is thermodynamically controlled and is referred to as a dynamic combinatorial library (DCL, see Figure 1).

As a dynamic system, a library can respond to various stimuli that drive the constituents to reorganize in order to minimize the total free energy of the system. The stimuli that have been investigated include change of pH, temperature, or electric field, but the most exploited stimulus involves the introduction of a chemical template: libraries of macrocycles, for example, provide as many potential receptors as library members, and addition of a guest which binds strongly to one of the library components shifts the equilibrium toward its formation, resulting in the amplification of the successful receptor at the expense of the less successful. Allowing easy screening of potential receptors with different features, this approach has made DCC a powerful tool for the discovery of new receptors.

Most of the reversible reactions used in DCC have been summarized in previous reviews,[4−8] although the range of reversible bonds used continues to grow. Disulfide exchange has been much exploited in our laboratory because it offers several attractions: the disulfide bond is relatively robust but it exchanges under mild conditions. Disulfide DCLs can be generated simply by dissolution of thiol building blocks in water at pH 8.0 under air, allowing for the screening of biologically relevant target under near-physiological conditions. The exchange is generally accepted to proceed through the nucleophilic attack of a thiolate anion on the disulfide bond formed by the slow oxidation of the thiol building blocks. The process is reversible as long as thiolate anions are present in solution, but the oxidation process is irreversible, and the exchange stops after the building blocks are fully oxidized, allowing for easy purification of the macrocycles formed.

Complex libraries can easily be prepared with a limited number of building blocks. A library composed of only three building blocks (**1**, **2**, and **3**, Figure 2), for example, contains a large number of macrocycles, 45 of which could be differentiated by LC-MS.[10] The complexity of this particular library is further increased by the fact that **1** was synthesized as a racemic mixture, and most macrocycles were consequently present as a mixture of stereoisomers. The building blocks were inspired by a family of cyclophane receptors developed earlier by the Dougherty group.[11] Upon addition of the ammonium guest **4**, one of the best known binders to the negatively charged receptor developed by Dougherty, the cyclic trimer **7** was amplified. Although the receptor selected in the library shares many features with Dougherty's **8**, it is striking that **7** is not its exact analogue, thus demonstrating the power of DCC to uncover unexpected receptors. Moreover, addition of two other ammonium guests, **5** and **6**, resulted in the amplification of two different macrocyclic receptors, trimer **9** and tetramer **10**, showing that one single library with a sufficient diversity can be used to amplify more

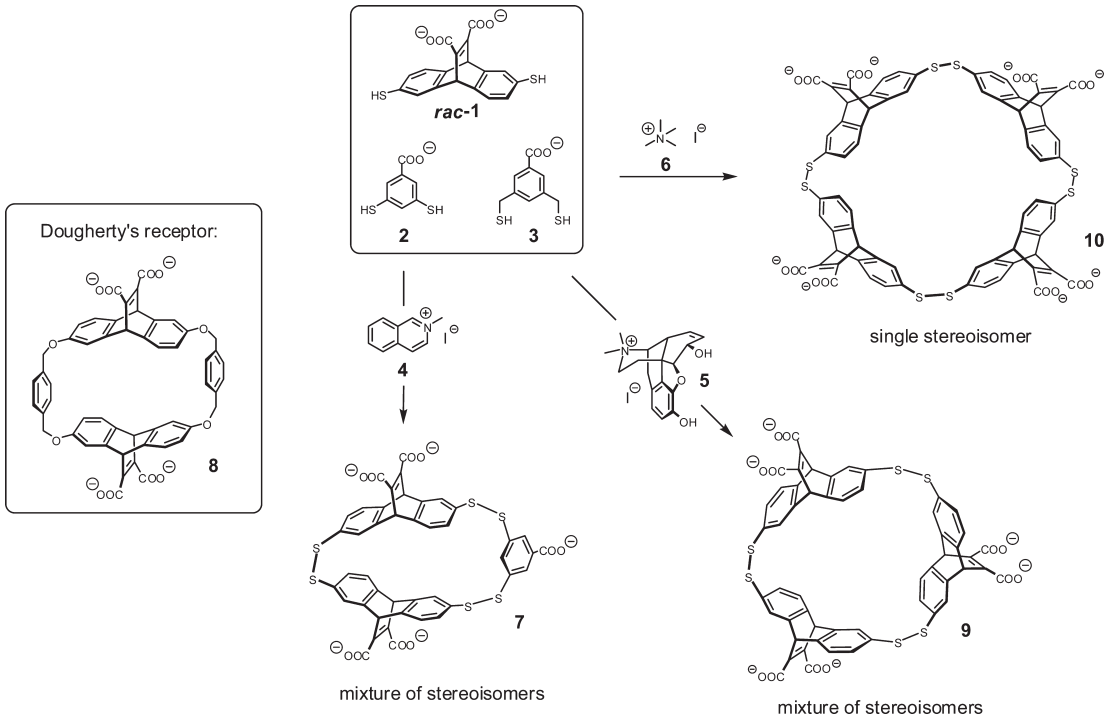

FIGURE 2. Amplification of three different receptors from one single library. Adapted from refs 10 and 12.

than one receptor, and that a small difference in binding affinity is sufficient to amplify selectively from a large number of similar structures.

The 1000-fold amplification of the large tetramer **10** by the small tetramethylammonium iodide guest[12] is particularly surprising; even more remarkably, there are four diastereomers of the tetramer but only one is amplified in the presence of the ammonium guest as it is the only one that can efficiently fold around the template. In the absence of a template, macrocycle **10** adopts a variety of exchanging conformations and consequently displays extremely broad NMR resonances; these sharpen dramatically in the presence of the template, thereby highlighting the discriminating power of DCC through the induced-fit selection of not only one diastereomer but also just one specific conformation. The main attraction of this system was that it provided access to many new receptors without the need for long synthesis. Moreover, in optimized conditions, the yield of the amplified macrocycles was remarkably high, a noteworthy feat given the low yields commonly associated with macrocyclisation reactions.

The scope of DCC rapidly extended to more complex target structures. We demonstrated in collaboration with the Balasubramanian group that a DCL of small molecules could be templated by DNA G-quadruplexes.[13] The DCC approach enabled a high level of discrimination between different G-quadruplex targets with a disulfide library inspired by macrocycle **11**. The binding affinity of the ligands amplified in the libraries (such as **12**, Figure 3) was superior to the binding affinity of the similar macrocycle **11**. However, these libraries are of relatively modest size: a similar level of discrimination could be obtained using regular parallel synthesis, and for this reason, increasing the size of the libraries soon became a topic of major interest.[14]

As one might expect, increasing the size of the library increases the probability of generating potential binders, but as the concentration of the library members decreases in large libraries, the limit of analytical instrumentation is rapidly reached and the fear of entropy increases. Otto and Ludlow recently showed that the size of the library could be extended to up to 9000 members by using equimolar amounts of eight building blocks.[15] In this large library, addition of ephedrine resulted in the unexpected amplification of macrocycles which were previously undetectable in the absence of template. The experiment clearly showed that a receptor does not need to be significantly present in the untemplated library to be amplified. As in the previous case, the amplification correlated well with a good binding affinity between the isolated receptor and the guest, and the amplified receptors turned out to have among the highest affinities reported for ephedrine in water. The analytical challenge posed by such large libraries has been met

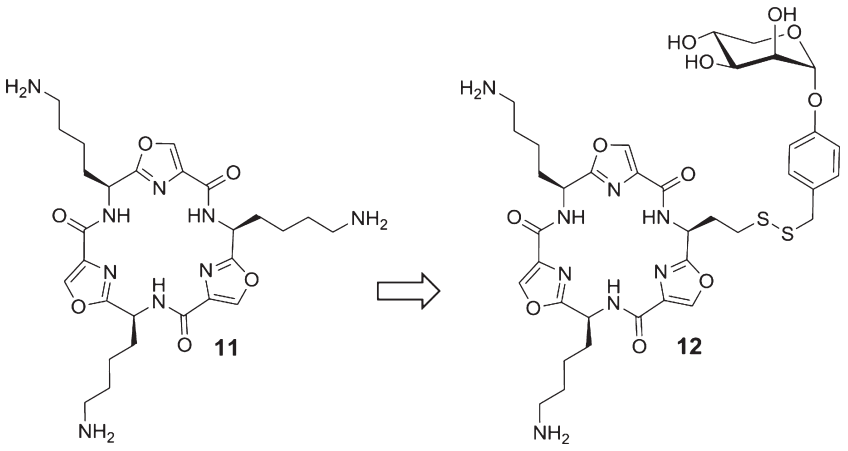

FIGURE 3. G-quadruplex ligands: a known binder (**11**) and an improved version (**12**) amplified from a DCL in the presence of c-Kit21. Adapted from ref 13.

by Miller et al.,[16] who developed a RBDCC (resin-bound dynamic combinatorial library) technology that allows identification of effective binders for fluorescently labeled target RNA in a library of small peptides with a theoretical size of 11 325 members.

While the above examples imply that library size is limited only by technological constraints, other factors need to be considered in order to understand the response of a DCL to the addition of template. For example, we[17] and Severin[18] showed that when the concentration of template is too high, the amplification of weaker binders may compete with the amplification of stronger binders. More specifically, the amplification of weaker-binding mixed-macrocycles may be favored over stronger-binding homomacrocycles, and the amplification of small macrocycles that are weak binders may be favored over the amplification of better but larger receptors in order that the whole system gains maximum free energy. Although these problems can be avoided at low template concentration, using DCC to study host–guest interactions appears to be more complicated than initially expected.[19,20] Furthermore, the composition of the library and its behavior may also be complicated by other issues described below.

In spite of these limitations, DCC exhibits an amazing propensity to form complex architectures, and some most surprising examples are depicted in the following section: DCC offers a unique approach for exploring and exploiting the properties of templating, self-folding or self-replicating molecules, and has rapidly grown as an ideal testing ground to improve our understanding of complex reversible systems.

Unexpected and Delicate Architectures

Although we showed above that large macrocycles can fold in a suitable conformation in order to optimize their interaction with a guest,[12] macrocyclic receptors often lack flexibility. We recently reported the amplification of highly flexible linear oligomers at the expense of macrocycles by dihydrogen phosphate anion acting as template.[21] A hydrazone-based library was formed in a mixed chloroform/methanol solvent using commercial mono- and dialdehydes, and a dihydrazide building block, composed of a ferrocene unit coupled to an amino acid (valine). The library contains both linear and cyclic oligomers. However, in the presence of the anion, only the linear species were amplified. The presence of the chiral *L*-valine induces a *P* helicity around the ferrocene unit, which dictates the structure of the linear oligomers: being simultaneously organized and flexible, they can easily adopt a suitable conformation to wrap efficiently around the anion.

The amplified linear oligomers are unusually large and incorporate five, seven, or nine building blocks. Intuitively, the fear of entropic costs would have inhibited the design of such large and flexible anion receptors, and the formation of these large oligomers should be entropically unfavorable in the library. Their formation can only be explained by the cooperative binding of multiple dihydrogen phosphate anions: indeed, the pentamer **13** (Figure 4) binds two anions, and the more complex and larger oligomers are thought to bind more than two anions.

Surprisingly, complex structures such as catenanes, can also turn out to be good receptors. The amplification of an acetylcholine-binding [2]catenane (**14**, Figure 4) in a hydrazone-based DCL is perhaps one of the most striking examples.[22] As we saw in the previous example, peptide moieties in synthetic building blocks can serve as scaffolds with useful recognition properties. In the presence of the neurotransmitter acetylcholine, a library composed of only

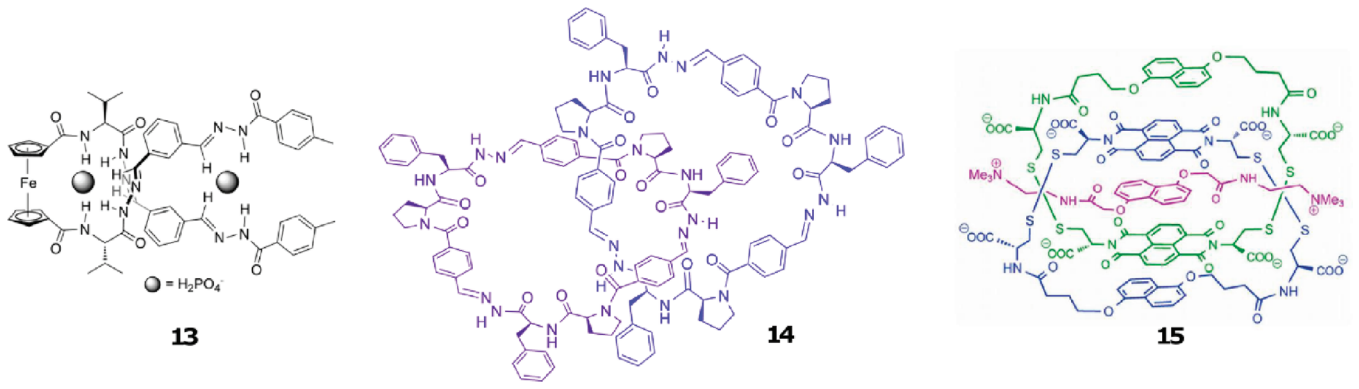

FIGURE 4. Unexpected receptors discovered by DCC: a helical linear receptor for dihydrogen phosphate ions (**13**), a peptide-based catenane binding to acetylcholine (**14**), and a donor–acceptor catenane binding to a donor-template (**15**). Adapted from refs 21, 22 and 24.

one peptide-based building block (derived from phenylalanine and proline) resulted in the formation of a hexameric [2]catenane originally not detectable in the untemplated library. Because of the presence of chiral centers in the initial building block, two diastereomeric [2]catenanes are possible. However, acetylcholine promotes the formation of only one of these diastereomers. Moreover, although this diastereomer can adopt many conformations, only one of these conformations binds acetylcholine.

Recently, Gagné et al. have reported the dynamic combinatorial syntheses of several [2]catenanes derived from similar building blocks, in which the phenylalanine unit was replaced by non-natural amino acids such as dimethylglycine or amino(1-naphthyl)acetic acid.[23] In this case, octameric [2]catenanes spontaneously formed under the dynamic combinatorial conditions. The [2]catenane self-templation is very dependent on both the amino acid incorporated in the building block and its chirality; also, the complementarities of the H-bonding motifs and of other noncovalent interactions, such as CH–π interactions, are important features of this self-assembly process.

Our dynamic combinatorial donor–acceptor [2]catenane **15** (Figure 4) also exhibits interesting binding properties.[24] This [2]catenane has an unusual stacking arrangement of the donor (D) and acceptor (A) units, and its formation in aqueous medium hints that its assembly is governed mainly by hydrophobic effects. However, donor–acceptor interactions can be favorably used to form a host–guest complex in the presence of a donor template, allowing the formation of a stable DADAD stack. Further stabilization of the complex apparently comes from the interaction between the ammonium cations of the guest and the carboxylic anions of the host catenane.

In all these cases, access to these remarkably complex architectures is the result of both the recognition of the catenanes' components with themselves (self-templation) and host–guest recognition (templation). These two phenomena are not necessary complementary and can be antagonistic: dynamic combinatorial systems have been reported in which the spontaneously assembly of [2]catenanes is reversed by the presence of a template that binds preferentially to simpler macrocycles.[25]

The intricate network of interactions in dynamic combinatorial systems has been exploited to self-assemble many other receptors and complex structures.[4–8] Subtle differences in the building block structure or in the library conditions can be reflected in the library diversity, leading to the formation of either simple or complex libraries. The flexibility (or lack thereof) of the building blocks may affect their properties of molecular recognition, self-aggregation, or self-replication within the library, but it seems that the most successful building blocks tend to possess both a rigid and a flexible component.

The aptitude of peptide-based building blocks to organize into complex dynamic combinatorial systems has brought a valuable insight into the rules governing biomolecular processes.[26] Otto et al. recently showed that a hexamer formed from a fully synthetic peptide-based building block (**16**) can self-replicate through the formation of three-dimensional fibres (Figure 5).[27] These fibers, held together by β sheets, are fragile, breaking when subjected to moderate shear forces, but they can be covalently captured upon UV irradiation.[28] The ability to replicate is an essential characteristic of life, and such self-assembly processes could, plausibly, lie at the origin of living systems. As such, the scope of dynamic systems can be expanded far beyond the initial realms of dynamic combinatorial chemistry.

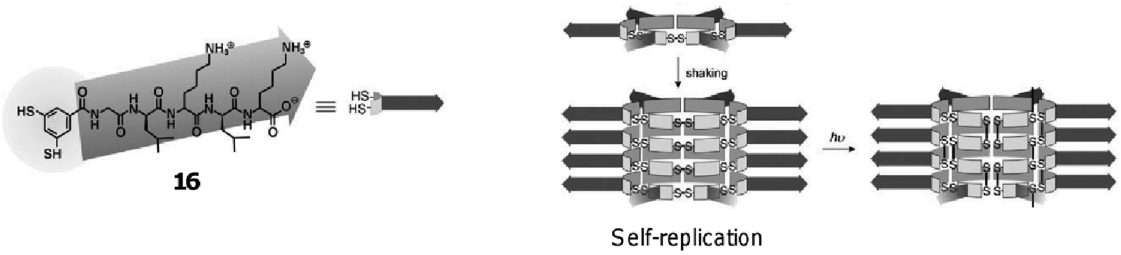

FIGURE 5. Self-replication of a hexamer and covalent capture of the fibers upon UV irradiation. Adapted from refs 27 and 28.

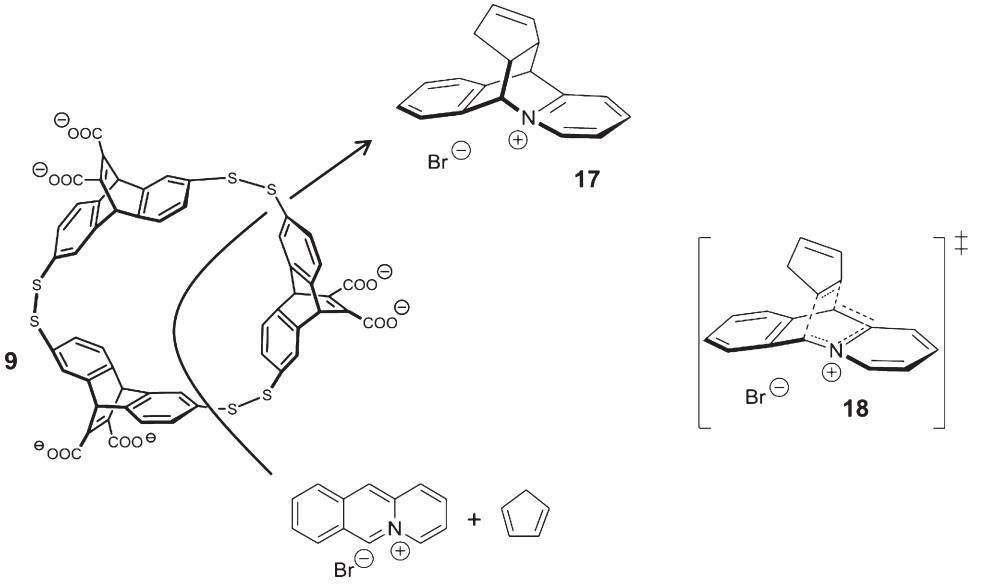

FIGURE 6. Toward an application of DCC for the discovery of catalysts. Adapted from ref 36.

Expanding the Scope of Dynamic Combinatorial Chemistry

Dynamic combinatorial chemistry has been extended to several other fields, some illustrated in Figure 6, such as drug delivery,[29,30] two-phase transport,[31] fragrance delivery,[5,32] biosensing,[33,34] or systems chemistry.[35] We described how DCC can be used as an approach to finding new catalysts, inspired by the example of catalytic antibodies. Used as a template, **17** (Figure 6) amplified significantly two macrocycles in the disulfide DCL shown earlier in Figure 2.[36] Template **17** is the product of the Diels–Alder reaction shown in Figure 6, and may be considered as a stable analogue of the transition state **18**. The envisaged stabilizing interaction between the amplified macrocycles and the transition state of this reaction led us to reason that these macrocycles may act as catalysts: the two macrocycles were isolated and their potential to catalyze the Diels–Alder reaction was evaluated. While the first macrocycle was found to bind better to the starting material than to the product and thus be catalytically inactive, the second macrocycle (**9**, Figure 6) induced a modest acceleration of the reaction rate. Although this macrocycle exhibits a limited catalytic activity, it showed that a correlation exists between the observed amplification and the catalytic activity. A similar strategy was also applied to the catalysis of acetal hydrolysis.[37] Prins et al. have further developed this approach to screen and understand catalytic processes, using phosphonate as a model for the transition state of carboxylic ester hydrolysis.[38]

The knowledge produced by dynamic combinatorial systems may be used to access quantitative assembly of well-defined molecular structures. Sleiman et al. developed DNA-branched building blocks that generate a library of macrocycles under thermodynamic control, including the dimer, tetramer, and hexamer (Figure 7a).[39] Addition of the ruthenium template $Ru(bpy)_3^{2+}$ produced the quantitative reorganization of the library into the square tetramer **19**. Based on this result, the Sleiman group designed a new generation of building blocks which formed, in the presence of the ruthenium template, the DNA-based ladder **20**,

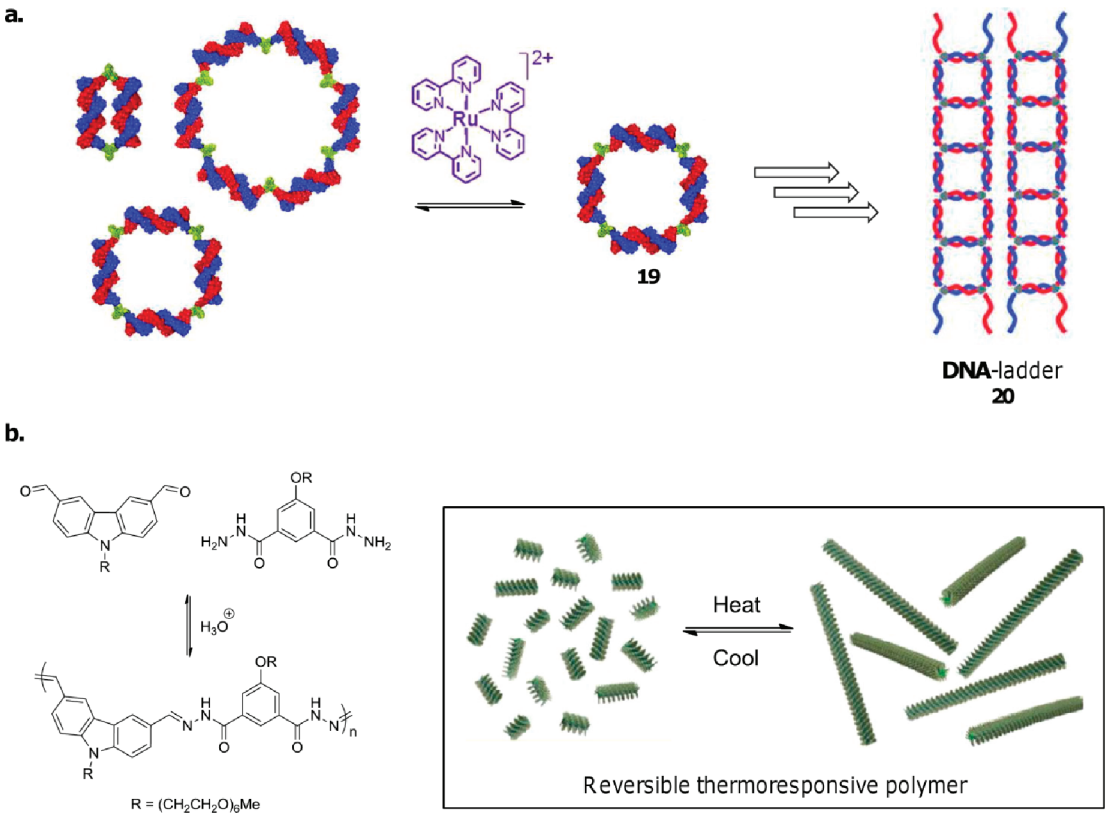

FIGURE 7. From molecular level to macroscopic scale. These two examples show that the control of reversible systems on the molecular level can be used to create much larger assembly: (a) a DNA-based ladder or (b) thermoresponsive polymers. Adapted from refs 39 and 40.

a single nanostructure based on the previously amplified square.

This latest example shows how the understanding and control of self-assembly at a molecular level can result in the formation of precisely controlled micrometer DNA fibers. Lehn and co-workers recently demonstrated that dynamic systems could be used to form reversible thermoresponsive polymers (Figure 7b),[40] or to switch between macrocycles and polymers in the presence or absence of Zn^{2+}.[41,42] More generally, the adaptative response of reversible systems to external stimuli offers a method of altering the properties of a system on the macroscopic scale, leading to the recent emergence of dynamic materials whose formation and properties can be triggered by diverse stimuli.[43,44]

Dynamic combinatorial chemistry has promoted the evolution of knowledge and new technologies, but its scope may be limited by its intrinsic requirements. Above all, thermodynamic control is a key requirement to generate a truly dynamic combinatorial system. We proved that thermodynamic equilibrium could be reached in a variety of conditions, in organic or aqueous media, and recently even in the solid state.[45] To generate a sufficiently diverse library under thermodynamic control, different conditions must be fulfilled: the linkage between the building blocks must be fully reversible and the energy landscape of the library must be relatively shallow to allow rapid interconversion. Hydrogen bonding may be used for this purpose, but unlike the covalent and slow metal exchange processes that we described above, the exchange process cannot be turned off, making the isolation of the individual library members impossible.

One of the most representative examples might be the fully reversible and highly dynamic formation of supramolecular nanotubes (Figure 8). In halogenated solvents, 1,4,5,8-naphthalenetetracarboxylic diimide functionalized with amino acids (**21**) form a library of hollow organic nanotubes of different sizes through carboxylic acid dimerization.[46] Studies of the thermodynamic parameters of the nanotubes[47] brought valuable insight into the possibility of forming nonclassical hydrogen bonds (C−H−O) in solution. Due to the delicate balance between the enthalpic gain and the entropic loss necessary to the formation of the nanotubes, we demonstrated that the free energy of shorter helical oligomers was equivalent to the free energy of the longer ones, leading to a statistical distribution of chain length.

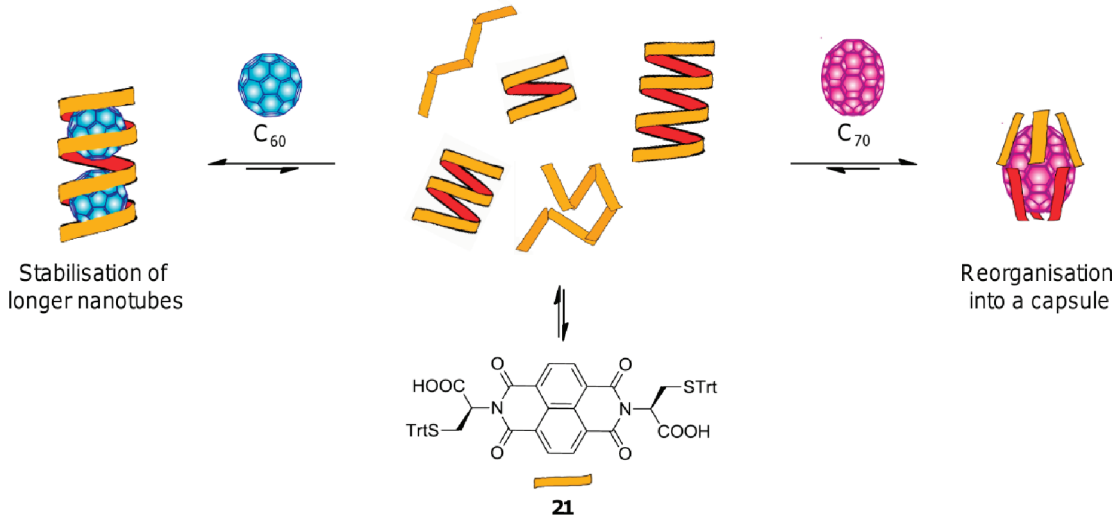

FIGURE 8. Library of hydrogen-bonded helical nanotubes. Templation in the presence of C_{60} or C_{70} allows amplification of longer nanotubes or of a hexameric capsule, respectively. Adapted from ref 52.

In such a perfectly iso-energetic library, templation was easily observed:[47−52] upon addition of C_{60}, which fills the nanotubes' cavity and dramatically stabilizes them, we observed the amplification of longer nanotubes, shifting the degree of polymerization from 5.3 to 15.7 (1 mM solution in 1,1,2,2,-tetrachloroethane at 273 K).[47,48] Addition of C_{70} led to a complete restructuring of the whole library, from nanotubes to a hexameric capsule wrapped around the solvophobic surface of the fullerene.[49] Moreover, the reversible nature of the system allows a pH-dependent and selective binding of C_{60} or C_{70} in a mixture of both guests.[52]

However, in most libraries, the library members do not interconvert so easily. Indeed, if one of the library members is particularly stabilized, for example by intramolecular interactions, it can act as a kinetic trap, accumulating at the expense of the other library members. Furthermore, high effective molarity within the macrocycles promotes intramolecular reaction, and the macrocycles may consequently be located in a relatively deep energetic well, inhibiting the exchange necessary for thermodynamic control. We recently described such a system,[53,54] in which hydrazone-based macrocycles are kinetically trapped and do not freely exchange. In this case, a small excess of monoaldehyde was shown to favor the formation of linear oligomers and facilitate the exchange between the macrocycles.

Kinetic control is not always a constraint and it has been used as a complementary alternative to thermodynamic control to expand the limits of dynamic combinatorial chemistry. Ashkenasy et al. have described in detail the kinetic behavior of replicating peptide-based DCLs under partial thermodynamic control,[55] and the possibility of manipulating the replication processes either with light or by addition of a template. The contrast between kinetically and thermodynamically controlled libraries has been elegantly illustrated by Krishnan-Ghosh and Balasubramanian.[56] As mentioned above, disulfide exchange can be easily promoted by slow oxidation of thiol building blocks under air. However, the exchange stops after the thiol building blocks are completely oxidized into disulfides, and these libraries do not always reach thermodynamic equilibrium. Under air oxidation, a library composed of two peptide-based thiol building blocks reached the kinetically controlled statistical distribution. When the same library was prepared under thermodynamic control (redox buffer under argon), a significant amplification of one of the library members was observed. This amplification, which would have not been obvious if the experiment had only been run under thermodynamic control, is due to the self-recognition between two building blocks with a complementary peptide sequence allowing for the formation of a stable β-hairpin.

We were recently faced with a similar conundrum involving π-acceptor and π-donor thiol building blocks. The libraries were formed in water under air oxidation, leading to a variety of donor−acceptor catenanes. These [2]catenanes exhibit previously unobserved stacking arrangements: the conventional alternating DADA catenane was found to be just one of a wider family containing the AADA, DAAD, and DADD catenanes (Figure 9).[24,57−60] The discovery of this family of catenanes opens the possibility of synthesizing these new structures by more traditional

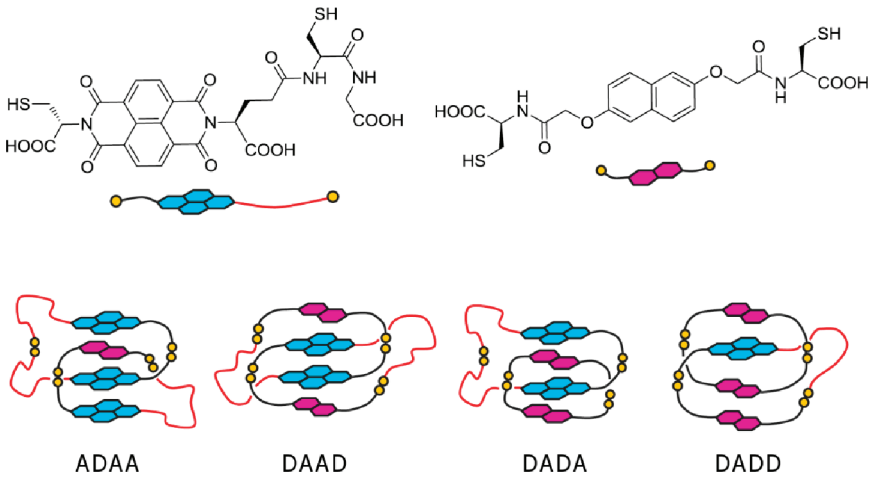

FIGURE 9. Unusual donor–acceptor catenanes identified from DCC. Adapted from ref 57.

ways, and of exploiting their electrochemical, optical, and recognition properties. Here, again, the exchange stops before reaching thermodynamic equilibrium, placing the libraries in a previously unexplored region between kinetic and thermodynamic control. These libraries present some advantages compared to traditional thermodynamically controlled libraries, allowing the elucidation of the mechanism of catenane formation, and an evaluation of the role played by donor–acceptor interactions and hydrophobic effect at each step of their formation. This approach has now been extended to a one-step synthesis of a [3]-catenane in water from linear precursors.[61]

These latest examples clearly show that apparent limitations of dynamic combinatorial chemistry, instead of acting as a hindrance, can promote its evolution toward new promising horizons.

Conclusion

Inspired by the evolutionary systems found in nature, dynamic combinatorial chemistry has broadened our knowledge of complex chemical interactions. Two apparently general conclusions emerging from our adventures in DCC are that large, highly flexible linears and macrocycles are better receptors than small rigid macrocycles, and that (certain) catenanes are actually rather easy to prepare. The first of these conclusions should not surprise any chemist familiar with molecular recognition by biopolymers, but it contradicts received wisdom in much of the supramolecular community. From a purely "chemical" point of view, DCC has offered a new route for the synthesis of complex architectures and understanding and control of reversible systems, giving rise to new technologies in diverse fields, from molecular recognition to material sciences.

The original idea of DCC is still used for a variety of purposes, but we can also increasingly appreciate, with more subtlety, its complexity and explore its limitations. We are confident, therefore, that dynamic combinatorial chemistry will engender a new generation of ingenious concepts and lead to new, as yet unpredictable, discoveries.

J.K.M.S. is grateful to the EPSRC for many years of support for this project, to Dr. Sijbren Otto for his major contributions to our understanding of DCC, to Dr. Ana Belenguer for her HPLC expertise without which almost none of our results could have been achieved, and to the many other group members who have contributed so much over so many years.

BIOGRAPHICAL INFORMATION

Fabien B. L. Cougnon graduated from the University of Strasbourg (Louis Pasteur) in France. He has recently finished his Ph.D. studies in the Sanders group working on the dynamic combinatorial synthesis of catenanes. He will begin his postdoctoral career with David Leigh in Edinburgh.

Jeremy K. M. Sanders obtained his B.Sc. from Imperial College, London, in 1969, and then his Ph.D. at the University of Cambridge working with Dudley Williams on lanthanide shift reagents. After a postdoctoral year (1972–1973) in the United States, working on protein NMR, he returned to Cambridge, where he has remained ever since. He was appointed to his present Chair in 1996, and he is also currently a Pro-Vice-Chancellor. His past NMR interests have included two-dimensional NMR and NOE difference spectroscopy, metabolism in live cells, and the biophysics of biodegradable plastics. His current research is focused on molecular recognition and supramolecular chemistry. He is particularly well-known for templated syntheses of receptors based on metalloporphyrins, for studies of molecular recognition by metalloporphyrins, for the synthesis of catenanes, and for the development of the concept of dynamic combinatorial chemistry.

FOOTNOTES

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