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Perspective

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Dynamic Combinatorial Libraries: From Exploring Molecular Recognition to Systems Chemistry

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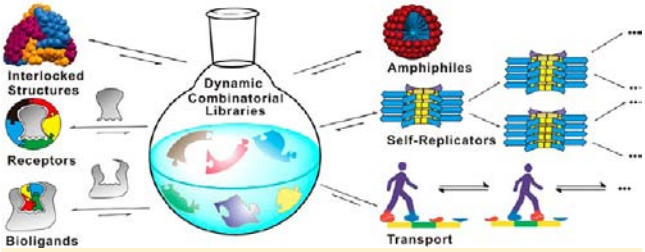

ABSTRACT: Dynamic combinatorial chemistry (DCC) is a subset of combinatorial chemistry where the library members interconvert continuously by exchanging building blocks with each other. Dynamic combinatorial libraries (DCLs) are powerful tools for discovering the unexpected and have given rise to many fascinating molecules, ranging from interlocked structures to self-replicators. Furthermore, dynamic combinatorial molecular networks can produce emergent properties at systems level, which provide exciting new opportunities in systems chemistry. In this perspective we will highlight some new methodologies in this field and analyze selected examples of DCLs that are under thermodynamic control, leading to synthetic receptors, catalytic systems, and complex self-assembled supramolecular architectures. Also reviewed are extensions of the principles of DCC to systems that are not at equilibrium and may therefore harbor richer functional behavior. Examples include self-replication and molecular machines.

1. INTRODUCTION

Chemistry has focused for a long time on the synthesis and properties of pure molecules. Yet, with the analytical tools now at the disposal of the modern chemist, complex mixtures are becoming tractable. Such mixtures may exhibit unique new properties. Life is one of the most compelling and inspiring examples of what complex chemistry may give rise to. Yet life is only one manifestation of complexity in chemistry; many other functional systems may be synthesized that are only limited by the creativity of the chemist. The rapidly developing discipline of systems chemistry[1−7] studies complexity and emergence in chemical systems. It tries to uncover the theory behind the system-level properties which are not simply the sum of the attributes of the individual components.

Dynamic combinatorial chemistry (DCC)[1,4,7−14] is a promising tool to create and study chemical complexity as it allows easy access to molecular networks. It can be defined as combinatorial chemistry, where the library members interconvert continuously by exchanging building blocks with each other. The members of a dynamic combinatorial library (DCL) are formed in a combinatorial way by linking building blocks together through reversible chemical bonds. The distribution of all molecules in such a network is typically, but not necessarily, governed by thermodynamics. Changing the experimental conditions may alter the stability of the library members and thereby alter the composition of the library.

The first and most explored approach to changing the product distribution of DCLs is through external templating, i.e. the addition of chemical templates that cannot take part in the reversible chemistry that connects the building blocks. Molecular recognition between the template and library species often leads to useful changes in the product distribution of DCLs.[15] The library members which bind to the template will be amplified. This effect may be utilized for the discovery of synthetic receptors and ligands for biomacromolecules, in many cases leading to unexpected supramolecular structures.[16]

Recently it has been demonstrated that DCLs may also show fascinating results as a consequence of internal templating, where molecular recognition takes place between or within library members. Such interactions may give rise to interlocked structures. If library species can bind intermolecularly to copies of themselves, this will lead to self-assembly, which provides the driving force to shift the equilibrium in favor of the very molecules that self-assemble.[17−20] We have coined the term self-synthesizing materials to describe the resulting structures.[17] Note that self-recognition of species in a DCL also constitutes a new mechanism for self-replication with implications for origin-of-life scenarios and potential for creating life *de novo*. This is particularly true where the production of replicators is no longer governed by equilibrium thermodynamics but is under kinetic control.

This perspective gives a somewhat selective overview over DCC and its impact on some adjacent areas. We cannot be comprehensive, but give examples that illustrate the latest developments in the field. First, we will briefly highlight new methodologies and give some selected examples of the more traditional dynamic combinatorial approaches to synthetic receptors, ligands for biomolecules, capsules and molecular cages. This is followed by a discussion of catalysis in dynamic combinatorial systems, multiphase systems and DCC on surfaces, dynamic combinatorial materials and interlocked structures. In nearly all of these examples the DCLs are under thermodynamic control. However, DCC is now also expanding into the rich realm of out-of-equilibrium systems, including self-replicators and molecular machines, which is the subject of the final part of this perspective article.

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2. METHODOLOGICAL ASPECTS OF DCC

DCC was originally envisaged as a tool for developing ligand−receptor systems. Ideally, the product distribution of the library will shift to the species which binds the template most strongly. However, such correlation between amplification and binding efficiency is not always perfect since a DCL will maximize the binding energy of the entire system, and this may not always mean the best binder is the one that is most amplified.[21−24] For example, the library made from two dithiol building blocks **1** and **2** contains macrocycles **4** and **5** that both bind ammonium template **3**, with host **5** binding the strongest.[23] If amplification would be selective for the fittest, then the library species **5** should be amplified more than **4**, but we found that their relative amplification factors depend on the concentration of template **3** (Figure 1). At a low concentration of **3**, the stronger

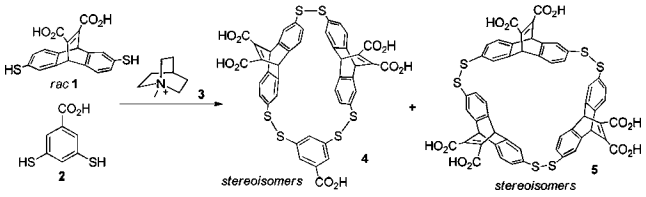

Figure 1. A small DCL made from thiol building blocks **1** (3.33 mM) and **2** (1.67 mM) produces a mixture of receptors **4** and **5** for guest **3**.

binder **5** is amplified more than **4**. However, when the template concentration is increased, the reverse is observed. This may be explained by the fact that at high template concentrations the system is able to harvest more of the **3**−**4** binding energy than of the **3**−**5** binding energy, since at a fixed amount of **1** it can make more copies of the **3**−**4** complex than of the **3**−**5** complex. The trend shown in this system that template binding affinity and amplification correlate better at low template concentrations is general.[24] A large theoretical study has been carried out aimed at identifying the optimal experimental conditions (template and building block concentrations) for performing dynamic combinatorial experiments.[24] The conclusion is that libraries are best explored in two steps: First a library is analyzed at comparable building block and template concentrations (for example 10 mM each). For those libraries that show interesting amplification effects, a second screening is performed at reduced template concentrations (for example, 1 mM) while keeping the building block concentration unchanged. The latter experiment is likely to give an acceptable correlation between binding affinity and amplification factors, while the former gives the largest probability of finding new template effects.

An important parameter in the design of dynamic combinatorial experiments is the library size. Most literature examples of DCLs feature relatively small libraries, containing only a handful of library members, and there are relatively few published examples of larger libraries that go up to ∼10 000 compounds.[25,26] Of course, larger libraries, made from more building blocks, have a higher probability to contain a species having a very strong affinity for the target. However, for large libraries it is not possible to detect all library members. This prompts the question: Is there an optimal library size? To answer this question, a set of libraries containing from 65 to 4828 compounds was simulated under a range of different building block and template concentrations.[27] In these libraries, template binding affinities were assigned randomly from a normal distribution. Reasonable experimental detection limits of LC-MS analyses were considered in the analysis of the simulated libraries. Within these constraints the larger libraries yielded the strongest binders, suggesting that it should be advantageous to work with libraries that are larger than the vast majority reported thus far.

The objective of many DCC experiments is to find new synthetic receptors or ligands for biomolecules. In many cases, hits obtained in dynamic combinatorial screening experiments are isolated (or resynthesized), and their binding properties evaluated in separate assays. However, it is often possible to evaluate the ligand−receptor binding affinity directly from the distributions of the DCLs. The product distributions of DCLs vary in response to changes in the concentrations of the building blocks and guest molecules. Based on this data, ligand−receptor binding constants may be obtained using a multivariable fitting procedure. We have developed DCLFit software specifically for this purpose.[28] The method has been validated by simulating DCL compositions for a set of 12 different experimental conditions (different ratios of three building blocks and different template concentrations) with known ligand−receptor affinities using DCLSim.[29,30] After introducing random errors into this data, reflecting those encountered in real experimental data, it was used as input data for DCLFit. The fitted binding energies and the original values are compared in Figure 2 and show good agreement for the

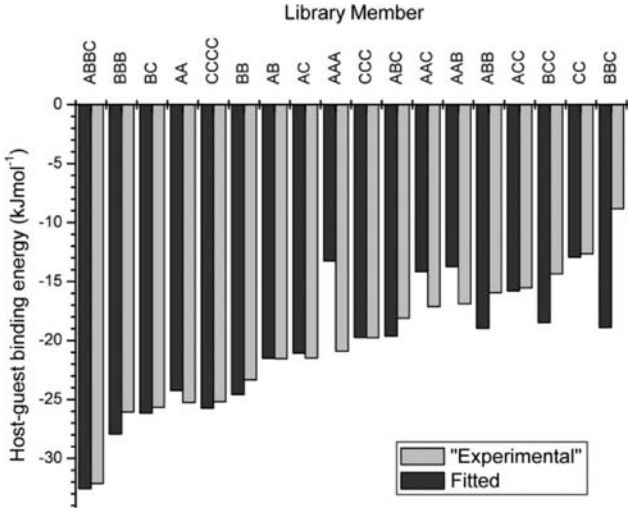

Figure 2. Comparison of "experimental" and fitted values for the host−guest binding energies in a simulated 31-component DCL.

stronger binders. Thus, from a global analysis of product distributions of DCLs it is possible to obtain a wealth of binding data with relatively little effort. This constitutes an efficient but still underutilized approach to investigating structure−property relationships.

3. EXTERNAL TEMPLATING OF DCLS

Producing highly selective receptors for either small molecules or ligands for biomacromolecules still remains challenging. The conventional approach to such molecules is through rational design and synthesis; a stepwise and iterative procedure that is time-consuming and can be frustrating. From the mid-1990s, the groups of Sanders, Lehn, and others have started using DCC as a new method to address this problem. In this section, we will highlight some examples of synthetic receptors for small

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molecules (anions and neutral molecules) and ligands for biomacromolecules (proteins and nucleic acids) that have been developed using DCLs.

3.1. Synthetic Receptors for Small Molecules. DCC has been successfully used to target synthetic receptors for anions,[31−35] cations,[36−43] and neutral (but often ionizable) molecules.[44−46] Some particularly relevant examples will now be discussed.

A compelling illustration of the power of DCC in the discovery of synthetic receptors involves one of the most challenging systems to recognize: anions in water.[47] This work also led to the discovery of a new mechanism for achieving high binding affinities in synthetic receptors: reinforced molecular recognition. In collaboration with the group of Kubik, we developed a highly efficient family of anion binders. In a first study[48] a library was prepared by dissolving **6** and **a**−**f** in a 2:1 (v/v) mixture of acetonitrile and water. Exposing this DCL to KI or K_2SO_4 induced the amplification of three different receptors (**6a**−**c**). ITC measurements showed that **6c**, in particular, is an efficient receptor for both iodide ($K = 5.6 \times 10^4$ M^{-1}) and sulfate ($K = 6.7 \times 10^6$ M^{-1}). Further studies,[49] based on an X-ray crystal structure of the sulfate complex of **6b** and an analysis of the solvent dependence of complex stability, demonstrated that the high affinity exhibited by this system is a consequence of reinforced recognition.[50] The binding is not only due to the direct interactions between receptor and guest but also due to interactions within the receptor that do not directly involve the guest. Subsequent work targeted receptors in which the two cyclopeptide rings are connected via two linkers (**7**, **7a**−**c** in Figure 3).[51] Receptors **7b** and **7c** are both

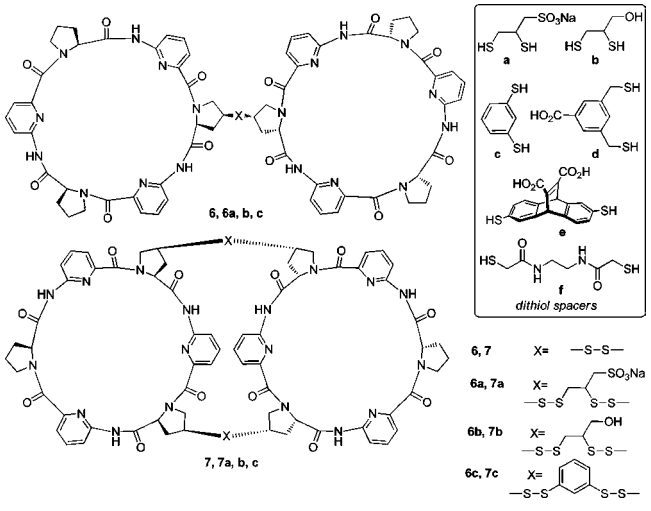

Figure 3. Building blocks and anion-amplified receptors in cyclopeptide DCLs.

strongly amplified by KI, Na_2SeO_4, and Na_2SO_4. ITC measurements showed an exceptional affinity and selectivity for sulfate ions in aqueous solution (log $K_a = 8.67$ in a 2:1 (v/v) mixture of acetonitrile and water); currently the world record for anion binding by a neutral receptor in aqueous solution.

Where most synthetic receptors are macrocyclic structures, recently, Sanders and co-workers have used DCLs to develop linear receptors in preference to competing macrocyclic hosts.[52] These linear receptors contain up to nine building blocks of three different types and were identified from a hydrazone DCL based on a valine-modified ferrocene. The receptor binds $H_2PO_4^-$ ions cooperatively ($K_1K_2 = K = 8.0 \times 10^5$ M^{-2}, $K_1 \ll K_2$) in $CHCl_3$/MeOH (96/4) as a solvent (Figure 4).

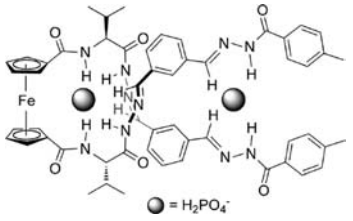

Figure 4. Linear hydrazone-based receptor for $H_2PO_4^-$ that binds cooperatively in a 2:1 fashion.

Another long-standing challenge in supramolecular chemistry is the recognition of sugars in water.[53−56] Ravoo and co-workers have used a dynamic combinatorial approach to identify biomimetic carbohydrate receptors.[57] They used disulfide exchange to prepare DCLs from a set of tripeptides under physiological conditions. The tripeptides contained N- and C-terminal cysteine residues to mediate the disulfide exchange reaction. Arg, Asp, Glu, Gln, His, Ser, and Thr were selected as the second residues because of their potential hydrogen-bonding interactions with carbohydrates; GABA (γ-aminobutyric acid), Phe, Trp, and Tyr provide hydrophobic and aromatic moieties, and Gly was introduced as an inert residue (Figure 5). In a DCL composed of three tripeptides

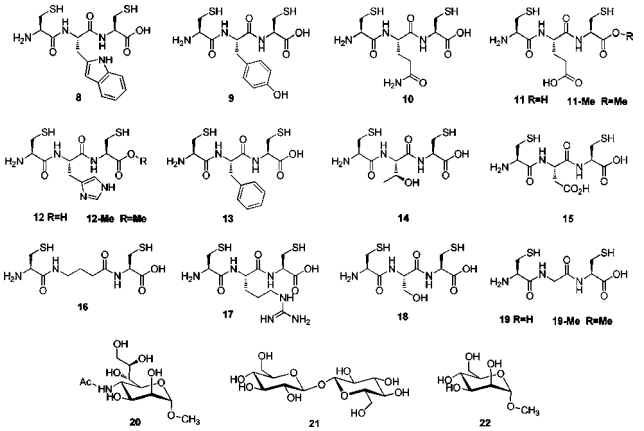

Figure 5. Tripeptide building blocks (**8**−**19**) and carbohydrate templates (**20**−**22**) for DCLs aimed at recognizing sugars in water.

(**11-Me**, **12-Me**, and **19-Me**), the cyclic dimer His-His (**12-12**) was amplified by neurotransmitter NANA (**20**). His-His and NANA formed a cooperative 1:2 complex ($K_1 = 72.7$ M^{-1}, $K_2 = 7.76 \times 10^3$ M^{-1}). In a DCL of six tripeptides (**8**−**13**), a selective 1:1 interaction of the cyclic dimer Tyr-Tyr (**9-9**) with trehalose (**21**) was found ($K = 2.85 \times 10^3$ M^{-1}), and in a DCL of five tripeptides (**14**−**18**), a selective 1:1 interaction of cyclic dimer Thr-Thr (**14-14**) with α-D-methylfucopyranoside (**22**) was identified ($K = 4.0 \times 10^3$ M^{-1}).

Another example of the use of DCC for developing binders for a neutral target was focused on a molecule of much current environmental significance: CO_2. It is well established that ammonium carbamates form reversibly through the reaction of carbon dioxide with primary or secondary amines. This reaction is responsible for CO_2 transport in the respiratory process. Under appropriate conditions of temperature and/or pressure, the carbamate can decompose to release CO_2 and the

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associated amine (Figure 6a). Leclaire and Fotiadu have reported a DCL in which carbon dioxide receptors are

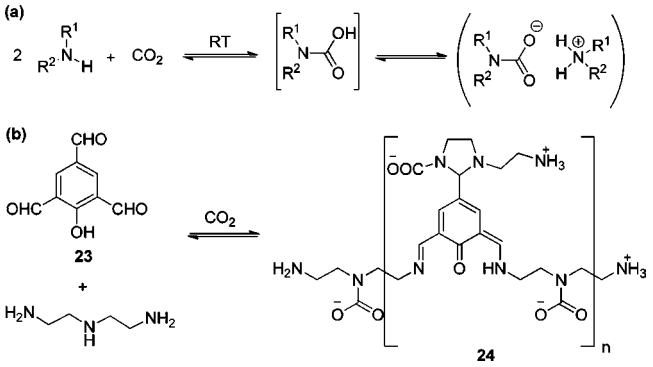

Figure 6. (a) CO_2 capture by reversible ammonium carbamate formation. (b) Possible structure of the oligomer **24** formed upon reaction of **23** and at least 3 equiv of diethylenetriamine in the presence of CO_2.

produced by a strategy of combining two reversible covalent bonds: imines and carbamates.[58] The DCLs were prepared by mixing polyamines and polyaldehydes. Addition of CO_2 to a library started from trialdehyde **23** and diethylene triamine led to the formation of a carbamate (as confirmed by NMR), although a shift of the transimination equilibrium could not be detected. Carbamate formation was accompanied by precipitation of **24** from the library. This compound is an oligomer of **23** and diethylenetriamine, and its possible structure is shown in Figure 6b. Refluxing **24** in methanol led to release of CO_2, and a re-equilibration of the library back to the composition before CO_2 was added. This result demonstrates that the CO_2 capture process is fully reversible. Characterization of the solid by powder X-ray diffraction and ^{13}C CP-MAS, ^{15}N CP-MAS, and $^{1}H-^{13}C$ and $^{15}N-^{13}C$ correlations solid-state NMR, suggested that it has a repeating unit similar to that shown in Figure 6b, featuring a complex arrangement of reversible imine bonds, carbamates, and N-acetals (imidazolidines).

3.2. Ligands for Biomacromolecules. Creation of ligands that recognize biomacromolecules, such as proteins and nucleic acids, paves the way for applications as therapeutic agents as well as diagnostic biosensors for rapid monitoring of imbalances and illnesses.[59] However, biomacromolecules are challenging templates to work with in DCC. Most reversible chemistries are best operated at millimolar concentrations. The limited solubility or availability of biomolecules then makes it difficult to use stoichiometric quantities of the biomolecule relative to the library members. Furthermore, the conditions for reversible chemistry need to be compatible with the stability of biomolecules that are often sensitive to pH, temperature, and chemical agents.[13,14] Nevertheless DCC has produced some promising results also in this area.

One example involves the development of molecules capable of detecting post-translational modifications of proteins. Post-translational modifications are important regulatory mechanisms in biology but hard to study due to the subtle structural variations involved. Thus, there is a need for additional assays. Inspired by our earlier work on ammonium ion receptors,[15] the Waters group has developed a small molecule receptor that is able to distinguish trimethyllysine from lower methylation states.[60] This receptor was obtained from a DCL made from building blocks **1** and **2** using dipeptides Ac-LysMe_n-Gly-NH_2 (n = 0−3) as templates. They found that the amplification of both $\mathbf{1}_2\mathbf{2}$ diastereomers depended on the extent of methylation, with ∼10-fold amplification with $LysMe_3$ and <2-fold amplification with Lys, suggesting significant selectivity. However, they did not find selectivity in the library made from **1** and **25**, although **25** is an isomer of **2** (Figure 7). Both

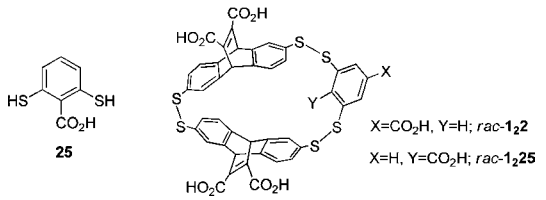

Figure 7. Structures of building block **25**, *rac*-$\mathbf{1}_2\mathbf{2}$, and *rac*-$\mathbf{1}_2\mathbf{25}$.

$\mathbf{1}_2\mathbf{2}$ isomers were purified, and the dissociation constants were determined for binding of *rac*- and *meso*-$\mathbf{1}_2\mathbf{2}$ to a peptide consisting of residues of the histone 3 protein (H3 K9Me_n), using fluorescence anisotropy measurements. The H3 K9Me_3 peptide was found to bind both isomers of $\mathbf{1}_2\mathbf{2}$ with binding affinities (K_d = 25−30 μM) comparable to that of the HP1 chromodomain, the native protein receptor for lysine 9-methylated histone H3.

In 2006, Greaney, Campopiano and co-workers reported the discovery of glutathione *S*-transferase (GST) inhibitors using DCC based on the reversible Michael addition.[61] The GSTs are potential drug targets in parasitic diseases, such as malaria and schistosomiasis, and for cancer therapy, where resistance to chemotherapeutic drugs has been directly correlated with the overexpression of GSTs in tumor cells. In a first study a DCL was prepared from glutathione (GSH) and three other thiol-containing tripeptide analogues and the Michael acceptor ethacrynic acid (EA), a known inhibitor of the GST class. Addition of *Schistosoma japonicum* GST (SjGST) dramatically amplified the glutathione-ethacrynic acid (GS-EA) Michael adduct. Subsequently a larger library was prepared using a single thiol GSH and 14 EA analogues, in order to identify the best hydrophobic acceptor for binding to the GST active site. Two new inhibitors for the GST enzyme were identified. Encouraged by these results, a new system using hydrazone chemistry was developed.[62,63] Ordinarily, hydrazone exchange requires a pH lower than 4.0, which is incompatible with most protein targets. However, following work by Dawson,[64,65] they used aniline as a nucleophilic catalyst, which allowed for conducting reversible hydrazone chemistry at pH 6.2. In the library templated by human pi class GST (hGST P1−1) or SjGST, two isoform-selective binders were amplified (Figure 8). Yet there is no amplification in the presence of bovine serum albumin, compared with the library without any

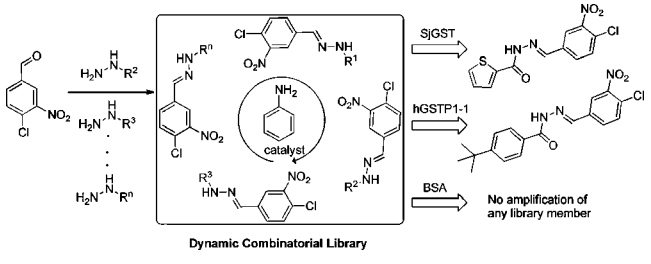

Figure 8. An aniline-catalyzed acylhydrazone DCL and the influence of protein targets on its composition.

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templates. Conjugating a glutathione moiety to the aldehyde enhanced the solubility of the resulting library members and led to the selection of compounds with significant binding ability. Interestingly, a catalytically inactive SjGST mutant selected the same library member as its active counterpart, confirming that the catalytic activity of the enzyme was not critical to the selection process. Subsequent binding studies confirmed that the selected compounds were indeed the most potent members of the library.

The above examples are from protein-directed libraries (further examples can be found in refs 66−71). Nucleic acids (DNA/RNA) are another class of important biomacromolecules whose recognition is fundamental to many biochemical processes related to transcription, regulation, and gene expression. Interestingly, they may exhibit a diversity of secondary structures due to their flexibility. These features make it both attractive and challenging to develop synthetic molecules capable of binding to nucleic acids. DNA and RNA have been successfully targeted with DCC systems in several studies.[72−77] Again, we only present some selected examples in more detail.

Distamycin-like polyamides can bind to the minor groove of double-stranded DNA with an affinity similar to natural DNA-binding proteins in a sequence-specific manner. Based on this finding, Balasubramanian and co-workers designed three building blocks **26**−**28** in a dynamic combinatorial approach to screen for a good binder for duplex DNA (Figure 9).[78]

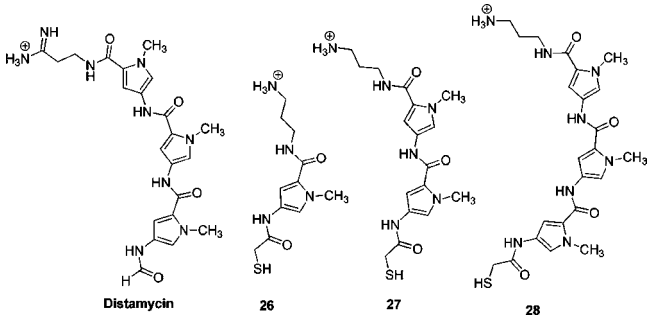

Figure 9. Structures of dithiol-functionalized polyamides designed to mimic distamycin.

Comparing the library distribution with and without duplex DNA, they found that the disulfide dimers **27**−**28** and **28**−**28** were amplified. The binding between the selected compounds and DNA was confirmed by thermal melting studies.

Later, they used the same dynamic combinatorial strategy to explore binders for a quadruplex DNA.[79] They prepared two groups of libraries by mixing **L1** and derivatives of *p*-benzylic cationic thiols (**G1**) or neutral carbohydrate derivatives (**G2**; Figure 10). The DCL made from **G1** was screened against two intramolecular quadruplex forming sequences (c-Kit21, c-Myc22) and a 22-mer duplex DNA for comparison. In the **G1** library with quadruplex, the two guanidinium disulfides **L1**−**29** and **L1**−**30** were amplified. However, in the same library with duplex DNA, no amplification was observed. In the case of carbohydrate building blocks (**G2**), **L1**−**31** was most strongly amplified by c-Kit21 and binds it with a K_d value of 9.1 ± 1.1 μM. This disulfide as well as the disulfide **L1**−**32** bound to c-Myc22 with similar K_d values of 24.4 ± 4.8 μM and 21.1 ± 3.7 μM, respectively.

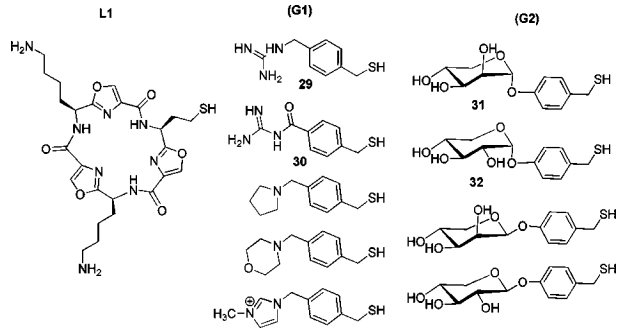

Figure 10. Structures of oxazole-based peptide macrocycle **L1**, cationic (under the conditions of the experiments) benzylic thiols (**G1**), and neutral carbohydrate benzylic dithiols (**G2**).

Unlike for DNA, for RNA there is not yet a canonical set of "rules" which one can follow that relate nucleotide sequence to the design of a selective binder. Miller's group used a novel resin-bound DCC (RBDCC) strategy to target RNA binding by a library with a theoretical size of 11 325 members from 150 resin-attached, cysteine-containing building blocks and an identical set of solution-phase building blocks.[80] They targeted the MBLN1 splicing factor, which is implicated in myotonic dystrophies, which are human diseases in which the accumulation of toxic RNA (CUG or CCUG) repeats in the cell causes sequestration of splicing factors, including MBNL1, leading to clinical symptoms, such as muscle wasting and myotonia. Dimers formed from three of the building blocks were identified as possible RNA target-binding compounds. They synthesized the pure disulfide dimers and found that **33** (Figure 11) showed high affinity and sequence selectivity for

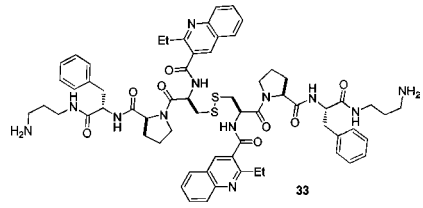

Figure 11. Structures of dimer **33** which showed high affinity constants and sequence selectivity for $(CUG)_n$ repeat RNA.

$(CUG)_n$ repeat RNA. Importantly, it is the first example of a compound able to inhibit the (CUG) repeat RNA-MBNL1 protein interaction. Four library members were identified which inhibited the interaction of $GGG(CUG)_{109}GGG$ RNA with MBNL1 *in vitro* with low micromolar K_i values, consistent with measured K_d values. Very recently, they have reported transformation of these compounds into structures with activity *in vivo*.[81] These discoveries demonstrate that DCC can serve as a discovery tool for high-affinity sequence-selective RNA or DNA binding compounds with desirable biological activity *in vitro* and *in vivo*.

4. CAGES AND CAPSULES FROM DCLS

Three-dimensional molecular and supramolecular cages receive increasing attention due to their intriguing properties, such as guest encapsulation and controlled release, catalysis, and chiral separation.[82−85] Traditionally, two main approaches have been followed to obtain capsular architectures: (i) self-assembly through noncovalent interactions under thermodynamic control and (ii) formation through covalent bonds under

kinetic control. However, these two methods both have disadvantages. The covalently synthesized cages are often accompanied by the formation of side products, and they may be too robust to allow release of trapped guests. Noncovalent cages are often too labile and dynamic. DCC is an attractive alternative approach to molecular encapsulation by giving access to capsules that are connected through more robust covalent bonds, while the final products are thermodynamically controlled. Moreover, many reversible covalent bonds can be cleaved under mild conditions, allowing for controlled release of the contents of the capsules. However, achieving diversity and selection in DCLs of covalent capsules turns out to be surprisingly difficult. We reported an early example of dynamic combinatorial cages, with only limited functionality.[86] Since then, a number of new and more appealing examples have been published.[87−92] We will now highlight some leading examples.

Using building blocks **34** and **2** that had been described previously,[86] Sanders and co-workers have discovered a series of cages capable of binding polyamine templates using DCC (Figure 12).[93] In the absence of template the library was

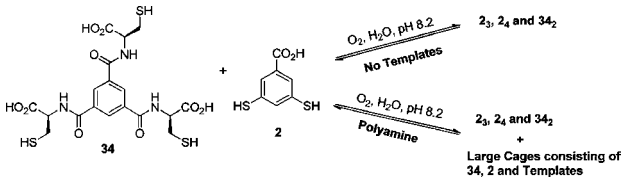

Figure 12. A DCL of water-soluble multicomponent cages generated upon templating by a protonated polyamine at the expense of macrocycles ($\mathbf{2}_3$ and $\mathbf{2}_4$) and smaller cages ($\mathbf{34}_2$).

dominated by three species: the cyclic trimer ($\mathbf{2}_3$) and tetramer ($\mathbf{2}_4$) of building block **2** and the dimeric capsule $(\mathbf{34})_2$ of **34**. To promote the emergence of larger architectures from the library, they screened a set of morphologically and structurally diverse positively charged polyamines as potential templates. In the spermine-templated library, at least six different cage structures were generated. These remarkable purely organic architectures consist of up to 11 components connected together by disulfide bonds. Decrease in polyamine length results in either smaller or total absence of amplification.

Metal coordination cages are an interesting and popular class of architectures in supramolecular chemistry. Nitschke's group has developed an extensive body of work combining reversible imine chemistry with metal−ligand coordination.[94] One particularly appealing recent example involves a capsule that is capable of structural reconstitution on receipt of a signal (the presence of perchlorate) to create a tight binding pocket for another anion (chloride).[95] The complex, barrel-like structure of the chloride receptor is templated by five perchlorate anions. First, they set up a library (**A**) of coordination complexes by the reaction of *p*-toluidine, 6,6′-diformyl-3,3′-bipyridine and Co-$[N(SO_2CF_3)_2]_2 \cdot H_2O$ in acetonitrile. When they used Co-$(SO_3CF_3)_2 \cdot 6H_2O$ instead of the triflimide salt, tetrahedral product $Co_4L_6^{8+}$ (**B**) was obtained almost exclusively (Figure 13). The ^{19}F NMR spectrum of the solution confirmed the encapsulation of a triflate ion (OTf^-) within **B**, suggesting that this anion acted as a template for the formation of the tetrahedral cage. Indeed, the addition of sodium triflate to **A** was found to template **B**·OTf^-, while the addition of lithium perchlorate to either **A** or cage **B** resulted in the transformation into a unique product: the $Co_{10}L_{15}^{20+}$ pentagonal prism **C**.

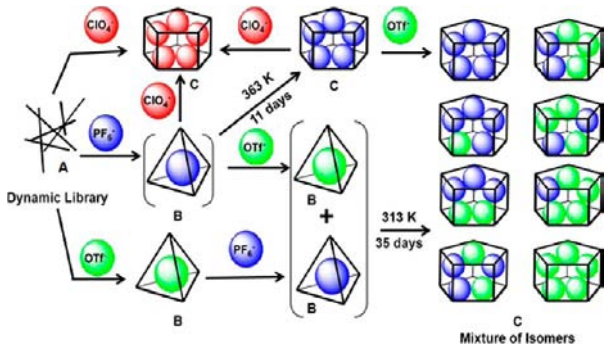

Figure 13. Chemical network showing the effects of sequential addition of anions.

Mass spectrometric analysis of **C** reveals that a single chloride anion was bound, even though it was not added purposely. Interestingly, the authors did not succeed in removing the chloride anion, not even by the addition of silver perchlorate, which reveals the high affinity between chloride and **C**. The addition of KPF_6 to **A** initially yields **B**·PF_6. However, after heating this sample at 363 K for 11 days, they obtained a new product **C**·$(PF_6)_5$, which is isomorphous to **C.** The mixture of **B**·OTf^- and **B**·PF_6 rearranged into host **C** after heating at 313 K over 35 days. By ESI-MS, complex **C** was found to encapsulate different combinations of the two anions. These results reveal that one anion triggers a structural reorganization that allows the newly formed structure to function as a highly efficient binder of another anion. Such processes start to mirror how biological systems are able to manifest complex responses to environmental stimuli.

5. INTERLOCKED STRUCTURES

The propensity of DCLs to easily give thermodynamic products with high yields and selectivities is also reflected in libraries where the template molecule is also a part of the library (internal templating). Such self-templating behavior can be successfully exploited to create topological bonds. The reversibility of the reactions used to form a catenane, rotaxane, or knot is crucial for achieving high selectivity, since they provide an error-correction mechanism which allows for the conversion of the misassembled kinetic products to the thermodynamic ones. With this mechanism, the unlikeliness of the threading events necessary for the formation of the desired products is no longer an obstacle.

The remarkable efficiency of this principle has been recently employed by the Stoddart group to synthesize a series of oligorotaxanes (Figure 14),[96,97] building on their previous work on imine DCLs of simple rotaxanes stabilized by the

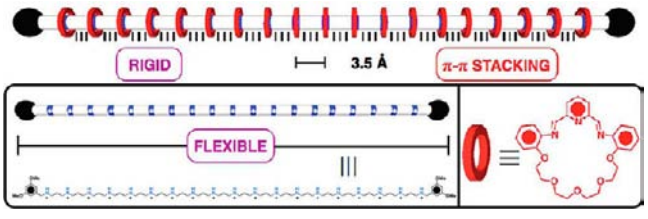

Figure 14. A rigid [20]-rotaxane formed from 19 equiv of a dynamic macrocycle cooperatively assembling around the flexible template rod. Reproduced with permission from ref 97. Copyright 2012 American Chemical Society.

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ammonium−crown ether motif.[98] Exceptional yields stemmed from the cooperative effect, caused by stacking interactions between the neighboring rings. It has been shown that a library containing an excess of rods had a highly nonstatistical distribution, with a strong preference toward fully saturated oligorotaxanes, proving the cooperativity. The cooperative behavior was absent when the library components were mismatched, i.e., the distance between the ammonium recognition groups was larger than the optimal 0.35 nm. Similarly, an imine clipping protocol has found application in the thermodynamic synthesis of [c2]-daisy chains with almost quantitative yields.[99] Extension of this approach to polymeric and switchable daisy chains is the next challenge which can integrate motions of nanomachines to meso- and macroscales.[100]

Catenanes have also profited a lot in the recent years from the DCC approach. Building on earlier work by Sanders,[16] the Gagné group has discovered a 56-membered [2]-catenane formed using hydrazone exchange of modified dipeptides to achieve perfect diastereoselectivities thanks to the stabilization of the interlocked structure through hydrogen bonds.[101] Later on, the group has included various mutants of the dipeptide into the libraries to discover that the β-turn conformation was critical for the stability of the catenane.[102] Another approach was utilized by Sanders and co-workers, who focused mainly on aromatic and hydrophobic interactions between library components made from naphthalene diimide (NDI) acceptor and naphthalene donor building blocks (Figure 15). This work has led to the discovery of donor−acceptor [2]-catenanes,[103] showing that unfavorable aromatic interactions can be often overcome by the hydrophobic effect, giving rise to unexpected structures.[104,105] Increased understanding of the delicate balance between various effects stabilizing interlocked structures and fine-tuning of the parameters of the building blocks (linker length, flexibility, chirality) has recently helped to develop DCLs rich in uncommon giant macrocycles and catenanes, with the possibility to control their distribution (Figure 15).[106]

A major advantage of dynamic assembly of interlocked structures is the high degree of responsiveness of such systems. This property can be utilized to stabilize the catenane only upon addition of a template molecule as well as destabilize it in cases when the building blocks forming a catenane can form another molecule with an affinity toward an external guest molecule. The former has been utilized to make [2]-catenanes templated with acetylcholine[16] and [3]-catenanes templated with spermine.[107] The latter approach has been shown to induce the formation of a square tetrameric receptor from its dimeric catenane upon action of an adamantyltrimethylammonium guest[108] and, in a similar mechanism, caused disassembly of a [3]-catenane upon addition of potassium cations.[109]

Mechanical bonds may also lead to the formation of molecules with more complex topologies which involve interweaving one or more long and flexible molecules. Error-correction mechanisms in DCLs based on self-recognizing motifs can lead to the formation of only the best-fitting knots with high selectivities. Chemists have been utilizing this strategy to create such remarkable structures like Borromean rings,[110] Solomon links,[111] and pentafoil knots.[112] In contrast to the structures obtained so far, a recent system containing a trefoil knot reported by Sanders and co-workers involved only purely organic building blocks.[113] The importance of the reversible character of the library is illustrated well by the kinetics of the system (Figure 16), where entropy favors formation of the kinetically controlled dimeric macrocycles, but the hydrophobic effect drives the library toward the formation of the thermodynamically controlled trefoil knot later on.

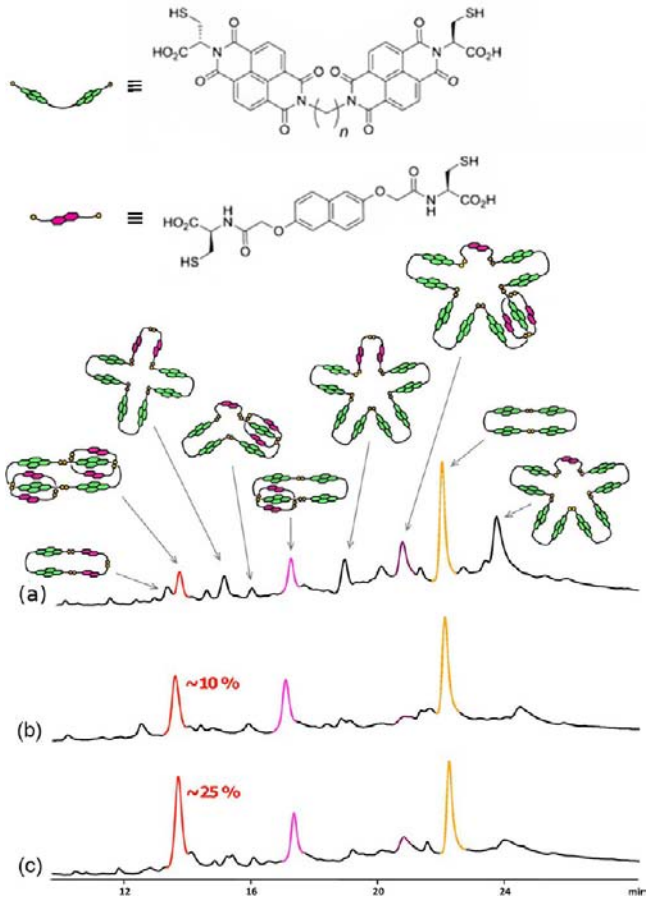

Figure 15. HPLC traces of DCLs formed by donor (red) and acceptor (green) building blocks mixed in ratios: (a) 1:1; (b) 2:1, and (c) 2:1 after stepwise addition of the donor. Reproduced with permission from ref 106. Copyright 2012 American Chemical Society.

6. CATALYSIS IN DCLS

Most chemical reactions in nature are mediated by enzymes, which are usually remarkably efficient catalysts. Supramolecular chemists have taken inspiration from biology in their attempts to design synthetic catalysts. Host−guest interactions have been utilized in supramolecular catalysis for binding a substrate in a cavity containing the catalytically active center.[114−118] Catalytically active cage compounds have been developed that act by bringing substrates together and stabilizing the transition state of the reaction.[119−121] Since catalysis is intimately linked to molecular recognition and DCC is a powerful approach for exploring molecular recognition, it is also a potentially attractive strategy for developing catalysts.[122] Indeed, the first proof-of-principle examples have been reported in this area, but progress has been relatively slow.

In 2003, we reported the first example of a catalyst obtained from a DCL. A transition-state analogue (TSA) was used to screen for compounds that were capable of binding and stabilizing the transition state of a chemical reaction. If such stabilization exceeds initial-state stabilization, then any compounds amplified by the TSA should exhibit catalytic activity. Thus, a DCL of macrocyclic disulfides in water was

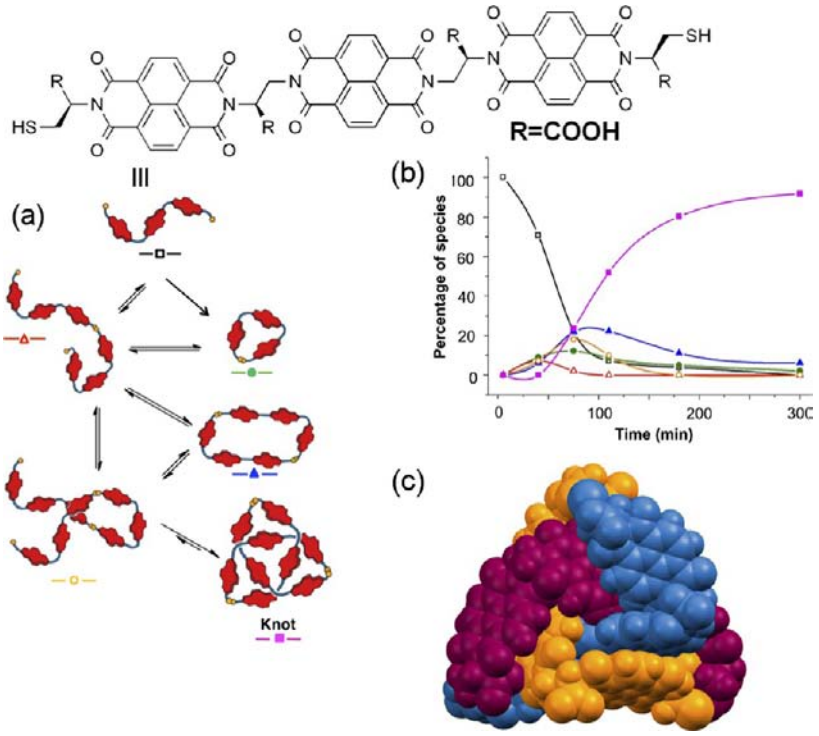

Figure 16. (a) Chemical equilibria and (b) the kinetic profile of the library forming (c) an organic trefoil knot. The lines in the speciation graph correspond to the different library members as indicated by the corresponding symbols below their structures.

made from building blocks **1** and **2** and exposed to a TSA for the Diels–Alder reaction shown in Figure 17a.[123] Since the

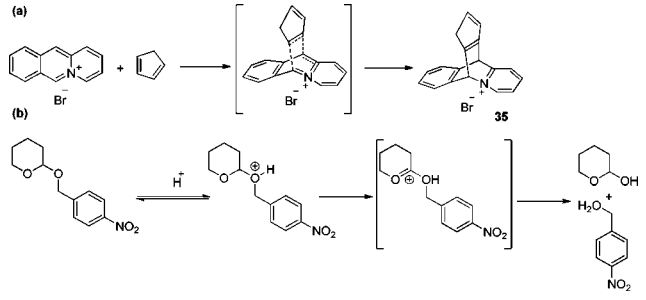

Figure 17. Reactions catalyzed by members from a DCL. (a) Diels–Alder and (b) acetal hydrolysis reactions.

products and transition states of Diels–Alder reactions are generally very similar, the product was used as the TSA. This led to the selection and amplification of hosts **4** and **5** (Figure 1). The selected hosts were isolated and applied as catalysts in separate experiments and **5** was demonstrated to catalyze the Diels–Alder reaction. The reaction was accelerated by a rather modest factor of 10. Since the catalyst can bind the product as well, the latter is expected to inhibit the reaction. Indeed, when the reaction is performed in the presence of the product, it was slower. However, turnover was still observed, indicating that the starting material was able to displace the product from the binding site of the catalyst. In a similar study we also obtained catalysts for the acetal hydrolysis reaction shown in Figure 17b.[124]

Prins, Scrimin, and co-workers have developed a dynamic approach to select the best functional groups to enhance the rate of hydrolysis of a neighboring ester.[125,126] They based their screening on affinity between the functional group and a phosphonate as a TSA for the ester hydrolysis. They started with a 10-component hydrazide library which was screened for components able to interact with the phosphonate target (Figure 18). Changes in the composition of the library were

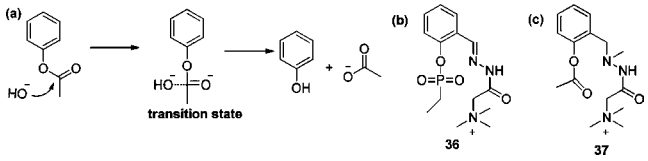

Figure 18. (a) Target reaction; (b) selection of the functional group by the phosphonate TSA; and (c) positioning of the selected group near the target bond.

monitored by $^{1}H-^{13}C$ HSQC by following the characteristic imine signals in the spectrum. The results revealed a surprisingly good correlation between phosphonate-induced amplification (a thermodynamic effect) and the efficiency of the selected functional group to promote the hydrolysis of the neighboring ester (a kinetic effect). The amplified species **36** containing an ammonium group was found to catalyze the hydrolysis of the ester moiety in **37** by a factor of 60.

Another example is from the Nicholas group.[127] They described the catalysis of an ester hydrolysis reaction in a library of imine–zinc(II) complexes via templating with *pro*-TSA **40** or **41** (Figure 19). In the dynamic mixture consisting of Zn(II) complexes of **38** and **39**, the former was amplified by *pro*-TSA **40**. Imine **39** is more active than **38** for the hydrolysis of the pyridyl ester **46**. Investigating a larger library of hydroxyimine–Zn complexes, consisting of **42**–**45**, addition of *pro*-TSA **41** produced a nearly 3-fold amplification of **42**, with attenuation of **43**–**45**. The rate constant for hydrolysis of **46** by **42** is enhanced 10-fold compared to the other library species. These

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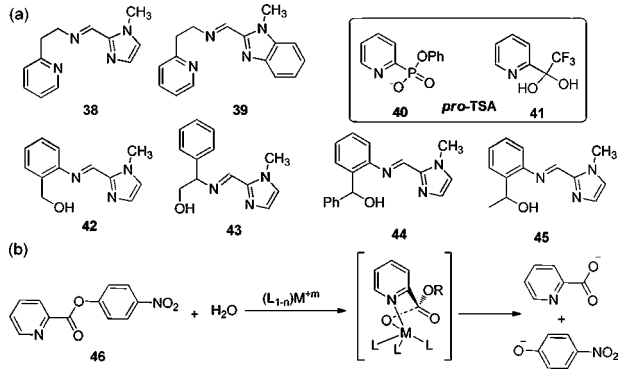

Figure 19. (a) Structures of the library members and *pro*-TSA and (b) proposed mechanism of the ester hydrolysis reaction.

results again confirm that thermodynamic effects (TSA binding) and kinetic effects (catalysis) are correlated.

7. MULTIPHASE DCLS

So far systems highlighted in this perspective were based on homogeneous solutions of DCLs. Introduction of another phase may bring substantial benefits for both the selection and purification of library members with desired properties. In the simplest case, a template molecule can be linked to a solid support, thus simplifying the isolation of good binders. While such an approach has been used since DCC's infancy,[128] this concept has been recently extended by combining it with affinity chromatography[129] to allow for identification and isolation of an optimal host molecule in a library composed of four different dithiols capable of forming more than 140 theoretical members. While various library members are amplified in the library, several of them increase in concentration not because of their high affinity to the template molecule but due to the fact that building blocks constituting them are not involved in the formation of the template binder. Upon elution and washing the resin only macrocycles amplified nonspecifically were recovered, while washing the resin with a solvent that disrupts the molecular recognition (in this case ethanol) eluted library members that have an affinity for the resin-bound template. As we discussed above, the probability of finding a strong binder increases substantially with library size. Using this approach it should be possible to successfully analyze more complex libraries without losing response selectivity, thanks to the selective removal of nonbinding library members.

An interesting alternative approach has been proposed by Miller's group who developed resin-bound DCC (RBDCC).[130] In this case, not the template but the building blocks are attached to a resin support and mixed with free building blocks in the presence of a fluorescently tagged template. After washing unbound library members, inspection of the beads under a fluorescence microscope allows for easy deconvolution of the library. This approach has been successfully implemented in the selection of a (CUG) repeat binder from a library composed of more than 11 000 members.[80] Another application of the RBDCC technique has shown that two orthogonal dynamic chemistries can be carried out simultaneously, expanding the diversity of the libraries beyond dimeric members.[131]

According to the Le Chatelier–Braun principle, the library composition can be affected also by a phase change of one or more library members. In such cases a DCL is enriched in the component that is removed from the solution. For instance, a limited solubility of one of the library components can lead to its crystallization. This principle has been utilized to selectively precipitate macrocycles of various sizes from a boronic ester library by the action of solvents and/or guest molecules determining the solubility of the library members.[132,133] Similar methodology has been applied by Ramström and co-workers to select a diastereoisomerically pure isoindolinone from a tandem DCL by crystallization.[134] Self-sorting behavior of imines is another profound result achieved by addition of water to an ethanolic solution of libraries formed from substituted imines and benzaldehydes.[135]

The same mechanism can be used to drive chemical equilibria toward the release of volatile substances like fragrances and other bioactive molecules.[136−139] Recently Osowska and Miljanić have shown that self-sorting of a DCL can be triggered by distillation of volatile library members.[140] In their dynamic mixtures of different aldehydes and amines, each building block was transformed into a single product, with exceptional purities and high yields (Figure 20).

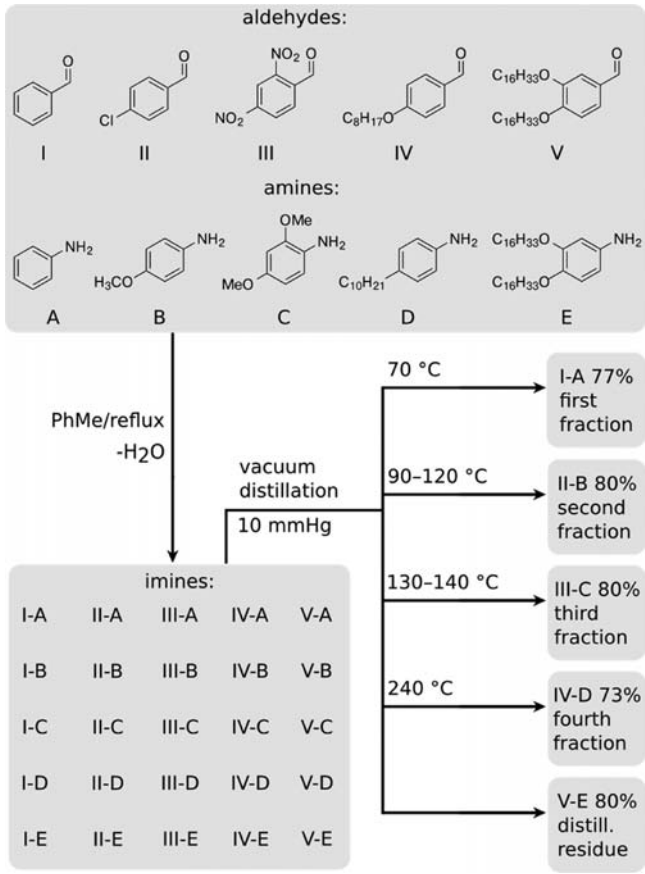

Figure 20. A mixture formed by five different amines and aldehydes comprises of 25 library members. A distillation process triggers self-sorting of the DCL, reducing the library to only five components.

An interesting way of influencing library composition has been recently studied by Hafezi and Lehn, who discovered that upon inducing a liquid/liquid phase separation, building blocks are distributed unevenly between phases, thus changing the library composition in both phases.[141] Remarkable differences in the library composition have been also observed between a library in bulk solution and its counterpart embedded in a lipid

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bilayer membrane.[142] While the latter showed a pronounced preference toward linear species, cyclic ones were predominant in the former.

The adaptive nature of DCL systems gives an opportunity not only to screen for good binders but also for their functions. Sanders and Lüning have created libraries that were capable to bind cargo (spermine and Ca^{2+}, respectively) in the aqueous phase and transport it through an organic phase into another aqueous phase (Figure 21).[37,143] The library members found in

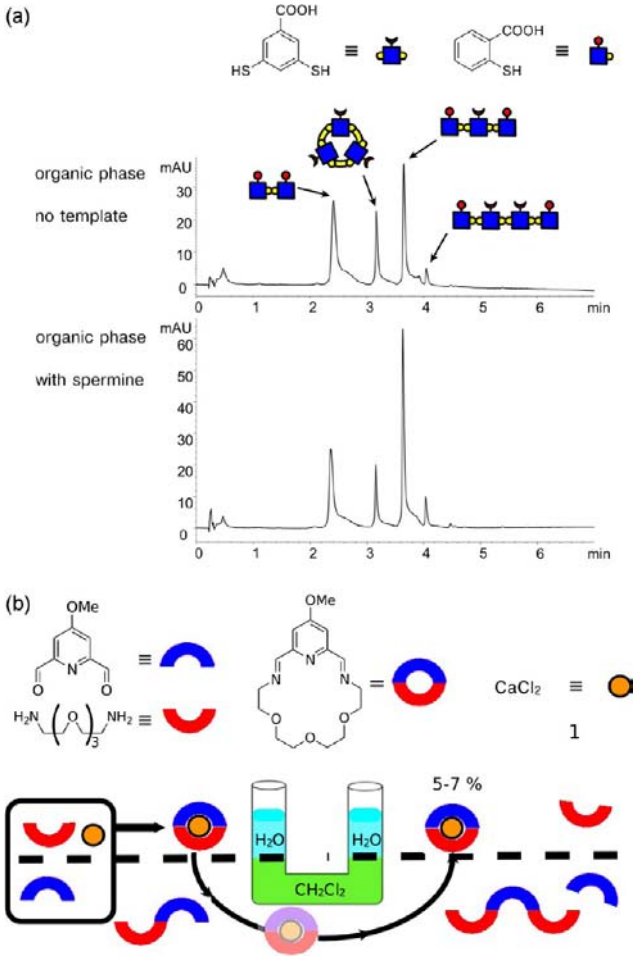

Figure 21. (a) Top and middle: composition of a nontemplated library. Bottom: composition of the organic phase of the library templated with spermine. (b) A calcium ion transport experiment from the left to the right aqueous phase, facilitated by a macrocyclic library member.

the receiving phase were not necessarily the best binders but they were definitely the best transporters. It is also noteworthy that in a similar transport experiment, featuring spermine as cargo, the transport capability of the isolated transporter and the pre-equilibrated library were similar, indicating that isolation of an active compound is indeed not required while studying functions of amplified library members. In order to decrease the time scale required to pass the bulk organic membrane, a supported liquid membrane can be used instead.[144]

Rapid advances in mechanosynthesis have not left the DCC methodology unaffected. Either neat or liquid-assisted grinding has been shown to facilitate exchange between solid disulfides.[145] The outcome of such process can be explained and predicted by the thermodynamic stabilities of the crystalline library members, therefore providing a different outcome than that obtained with libraries equilibrated in solution; while metathesis in a solution gives a statistical mixture, pure heterodimer is obtained by liquid-assisted grinding (Figure 22).

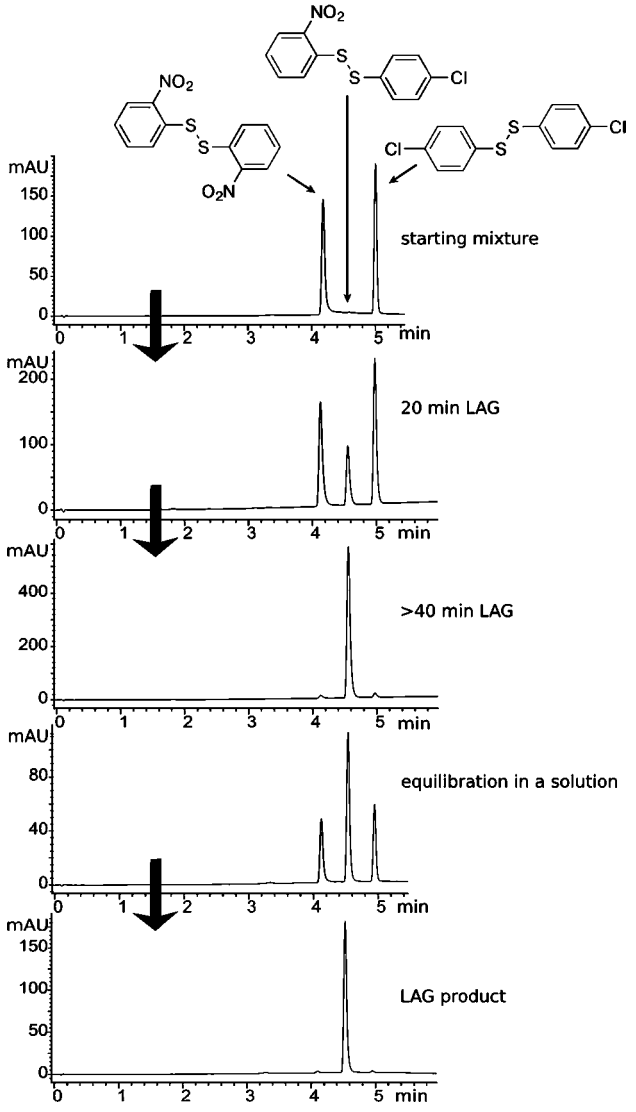

Figure 22. Chromatograms corresponding to libraries equilibrating under liquid-assisted grinding (LAG) conditions or in homogeneous solution.

8. DYNAMIC SURFACES

Marriage between DCC and surface chemistry has started in the middle of the past decade through the reversible patterning of amine-modified self-assembled monolayers (SAMs) with aldehydes, forming imine-functionalized SAMs.[146] The relatively late onset of such combination stems from the difficulty in analyzing libraries formed on surfaces. Because analytical techniques commonly applied to bulk DCLs (NMR, HPLC, X-ray crystallography, etc.) cannot be easily applied, characterization has to rely mostly on the methods used in surface chemistry. Subsequent work in the field has proven however, that accepting the challenge can be remarkably rewarding.

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Directional molecular motion is one of the impressive achievements that have been born in the wedlock of DCC and surface science. Amine-functionalized dendrimers stamped onto aldehyde-patterned glass surfaces were able to move on the surface through simultaneous formation and hydrolysis of multiple imine bonds if immersed in water.[147] While no directionality was observed on a surface with uniform aldehyde concentration, dendrimers were moving along an aldehyde gradient if such was present on the substrate (Figure 23). Interestingly, diffusion rates were proportional to the concentration of the aldehyde on the surface.

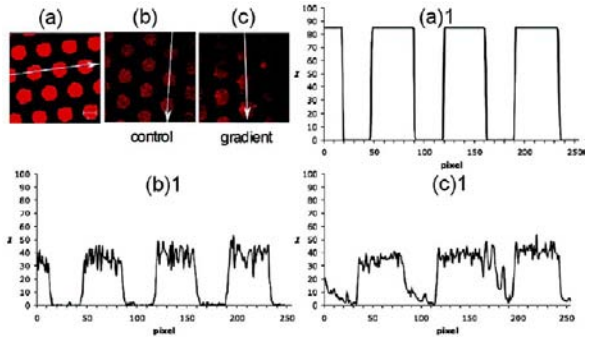

Figure 23. Confocal images of dendrimers: (a) before immersion in water, (b) control, and (c) gradient samples 16 h after immersion. Fluorescence profiles of the samples are shown in (a)1, (b)1, and (c)1, respectively. Reproduced with permission from ref 147. Copyright 2007 American Chemical Society.

Selective patterning of SAMs with various (bio)molecules using reversible covalent bonds (DynaSAMs) has been achieved by Giuseppone and co-workers.[148] They have shown that differences in amine basicities can be utilized to bind various amines to an aldehyde-coated quartz substrate as a function of pH. This property allowed them to establish concentration gradients on the substrates with pH and spatiotemporal control (Figure 24).

Bottom-up approaches toward laterally ordered photosystems have been hindered by the necessity for extraordinarily high templating efficiency. High degree of coaxial alignment is crucial to achieve optimal electron and hole conductance in the opposite directions. Therefore, any mismatch in assembly processes will result in a decrease in the photocurrent.[149] A system that comes close to achieving such high templating efficiencies has been reported by Matile and co-workers, who implemented a hydroxylamine-initiated hydrazone exchange modification of self-organizing surface-initiated polymers (SOSIP).[150] SOSIP is a recently introduced technique to efficiently propagate a 2D pattern into the third dimension using thiol-disulfide exchange.[151,152] Thanks to the narcissistic character of naphthalene diimide (NDI) interactions, the new NDI-containing units are almost quantitatively introduced into SOSIP stacks, nearly doubling the photocurrent generation (Figure 25). High efficiency of postsynthetic modification of the stacks invokes a question if thermodynamic equilibration could be also applied in co-SOSIP polymerization. Since self-templating plays an important role in the process, utilizing the dynamic character of the disulfide bonds used to make the polymer may improve templating efficiencies if the polymerizing system is kept under thermodynamic equilibrium.

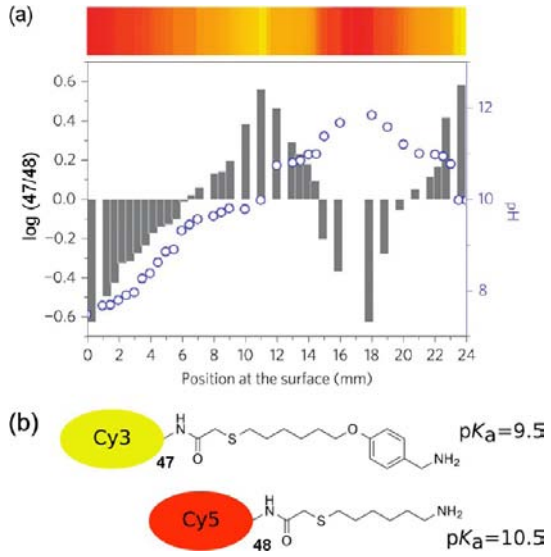

Figure 24. (a) Fluorescence image of the quartz surface functionalized with Cy3 benzylamine and Cy5 alkylamine gradients together with dye ratio logarithms (gray) and pH (blue) which was modulated to achieve the desired composition. (b) Structures of cyanine-modified amines with their corresponding pK_a values and emission colors. Reproduced with permission from ref 148. Copyright 2009 Nature Publishing Group.

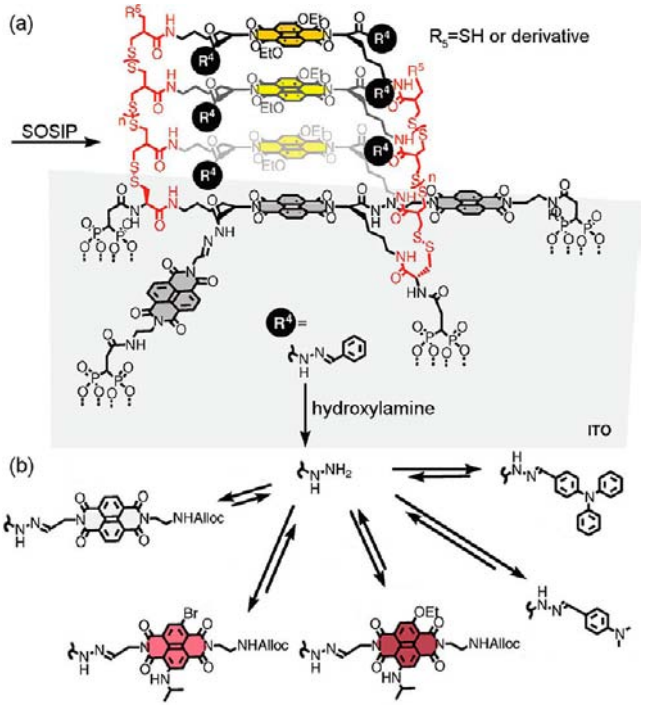

Figure 25. (a) Stacks formed using SOSIP on indium tin oxide and subsequent cleavage of the placeholder hydrazone with hydroxylamine. (b) Modification of hydrazide functionalized stacks with NDI-aldehydes leads to the formation of complementary coaxial π-stacks. Adapted with permission from ref 150. Copyright 2011 American Chemical Society.

9. DCLS OF AMPHIPHILES

An interesting property that can emerge from DCLs consisting of building blocks of different hydrophobicity is their ability to reversibly form supramolecular assemblies composed of

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amphiphilic library members. Such processes can trigger drastic changes in physicochemical properties of the system on the macroscopic scale. Necessary shifts in the DCL composition can be induced by various external stimuli, rendering such responsive systems interesting in biomedical and materials sciences contexts.

One of the first demonstrations comes from the work by Ulijn who used a protease enzyme to mediate the reversible amide chemistry that allowed for the formation of hydrogels. Their work featured a library consisting of dipeptides and Fmoc amino acids.[153] The action of the protease facilitated the formation of amphiphilic peptides that were stabilized by their self-assembly into nanofibers, that were responsible for the subsequent gelation of the aqueous solvent.

Other possible phases that can be created by amphiphiles are lyotropic liquid crystals. The first example of self-assembly of dynamic covalent surfactants was shown by the group of van Esch.[154] While neither amines **50** nor aldehyde **49** alone were able to form micelles, the imines readily self-assembled once their concentration exceeded the critical micelle concentration (CMC), as shown in Figure 26. It is also notable that the

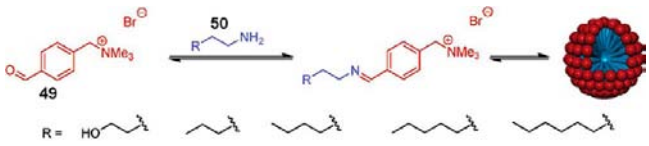

Figure 26. Formation of micelles by dynamic covalent surfactants. Reproduced with permission from ref 154. Copyright 2009 American Chemical Society.

unfavorable equilibrium of imine formation in water can be shifted by the stabilization of the product inside micelles. Upon acidification, stabilization of imines provided by the assembly is no longer sufficient, triggering disassembly of the micelles, making the system responsive to pH. Increase of the temperature induced a similar effect, but in contrast to ordinary micellar systems, the disassembly is caused mainly by the shift of the library composition toward the substrates.

Subsequent work on imine chemistry in water has led to the discovery of other responsive, dynamic surfactants consisting of bolaform[155] and toothbrush-type[156] superamphiphiles, libraries of competing amphiphiles,[157] amphiphiles forming rod-like micelles,[158] and libraries forming self-replicating supramolecular structures (explained in more detail below).[159]

Another successful use of dynamic amphiphiles is their application in binding and transport of molecules through lipid bilayers. Matile and co-workers have developed hydrazone-based DNA binders which, upon reaction with aliphatic aldehydes, were able to act as DNA activators in lipid bilayers.[160,161] Such hydrophobic DNA-counterion pairs can easily cross lipid bilayers, carrying hydrophilic counterions.

10. REPLICATION IN DCLS

Replication is the basis of all living systems and has likely played a central role in the origin of life. While research on synthetic replicating systems has been gaining significance in the scientific community,[162] synthetic replicators still lack qualities which are essential to biological systems. Living organisms operate under far-from-equilibrium conditions, by constantly making copies of themselves and thus counteracting their continuous decay. If their replication rate is equal to or greater than their decay, they exhibit dynamic kinetic stability (DKS).[163] In contrast to thermodynamically controlled systems, replicator networks subject to continuous growth and decay are divergent in nature, which enables them to evolve (Figure 27). The majority of the replicators so far have been

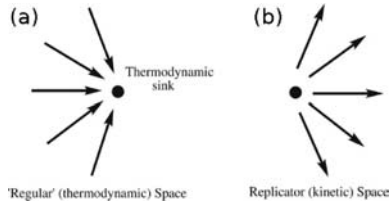

Figure 27. (a) Standard chemical systems are convergent in nature. (b) DKS systems are divergent and therefore able to evolve. Reproduced with permission from ref 163. Copyright 2011 Chemistry Central.

only studied from the replication point of view, which is already challenging enough. Thus, most replicators are the thermodynamic products, i.e. they are more stable than the building blocks (food molecules) used to make them. Furthermore, replication is usually irreversible. Yet, replication that involves a reversible reaction would bring us a step closer to achieving DKS. Combining the principles of DCC with replicator chemistry appears to be a promising way forward.

The first DCL in which the selection process was determined by a replication reaction has been discovered by Sadownik and Philp.[164] The irreversible replication process consumed the food library member from the dynamic reagent pool, thus driving the re-equilibration of the library and determining its fate (Figure 28). Autocatalytic properties have been also found

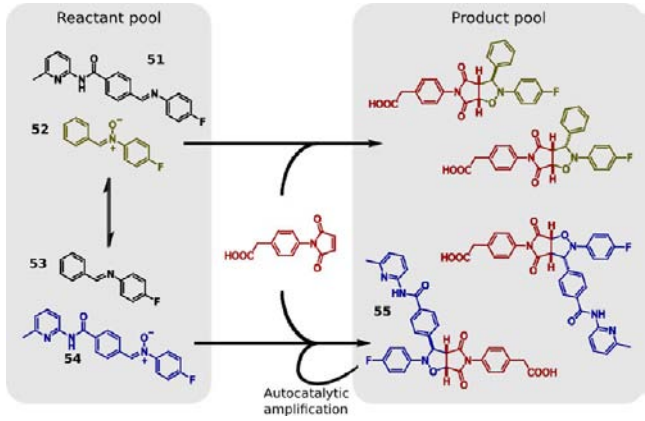

Figure 28. Only the molecule capable of self-replication (**55**) is selected in a system with equilibrating substrates (**51**−**54**).

in related imine libraries in which the replication reaction was actually imine formation, making the replication process itself reversible.[165]

Imine formation has also been implemented to form a dynamic amphiphile capable of reversibly assembling into spherical micelles and cylindrical micelles.[159] Because the imines are stabilized while forming supramolecular assemblies, formation of micelles promotes further imine formation, leading to the growth of the aggregates. Bigger micelles become unstable, leading, in turn, to their division (Figure 29). In such case, the replicating entity is not constituted by a single molecule but by the entire micelle, a process referred to as

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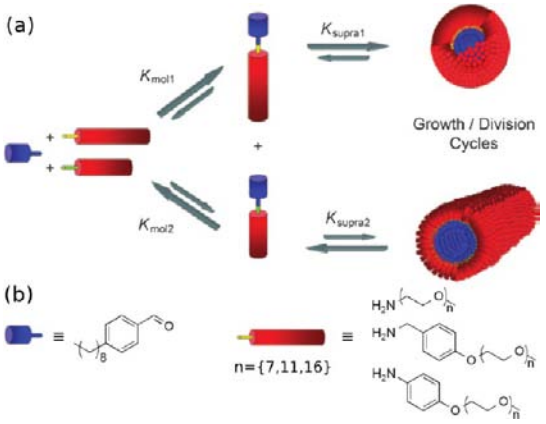

Figure 29. (a) A DCL composed of hydrophilic amines (red) and hydrophobic aldehydes (blue) reacting into imines. Autocatalytic growth of different micelles favors more efficient replicators. (b) Chemical structures of the aldehyde and amines. Reproduced with permission from ref 159. Copyright 2009 John Wiley & Sons, Inc.

autopoiesis.[166] Remarkably, small DCLs composed of different amine building blocks showed a pronounced preference toward incorporation of one of them into imines, therefore showing selection of a more efficient replicator.

A conceptually similar approach has been used to create a self-replicating network composed by dithiol-functionalized peptidic building blocks.[17] These building blocks first form a mixture of macrocycles, some of which then form fibers thanks to the propensity of the peptide chains for beta-sheet formation. When the fibers grow long enough, they become susceptible to shear stresses and break, duplicating the number of catalytically active fiber ends (Figure 30). Because macrocycles of various sizes can be formed in the library, different self-replicating fibers can, in principle, exist. Competition for food molecules between replicators leads to selection of one of them, where the selected macrocycle size may depend on the agitation method. Furthermore, the resulting fiber solutions formed a hydrogel upon irradiation with a UV lamp.[167] Irradiation of the library causes disulfide bond exchange within the fiber, creating strong, covalent bonds between the stacked macrocycles. The ability of replicators to form useful materials may render them interesting not only for studies on *de novo* life but also hold promise for self-synthesizing materials.

Replication facilitated by coiled−coil peptide self-assembly of food molecules has been also employed by Ashkenasy and coworkers in order to form replicating binary networks under partial thermodynamic control.[168] The system was doubly responsive, in a way that the outcome of the replication could be influenced by both chemical and physical inputs (templates and light, respectively).

Watson−Crick DNA base pairing constitutes a reliable way of templated information transfer into a complementary strand, which in turn can be used for building cross-catalytic systems. In nature however, a polymerase enzyme is required to synthesize a complementary copy, and the reaction itself is irreversible. On the other hand, the DCC methodology has allowed for enzyme-free functionalization of an oligomer, based on nucleobase pairing.[169] Reversible thioester bond formation between thioester-functionalized nucleobases and oligocystein provides a possibility to keep the system at the thermodynamic equilibrium and influence its composition by introduction of an oligonucleotide template (Figure 31). In contrast to enzymatic

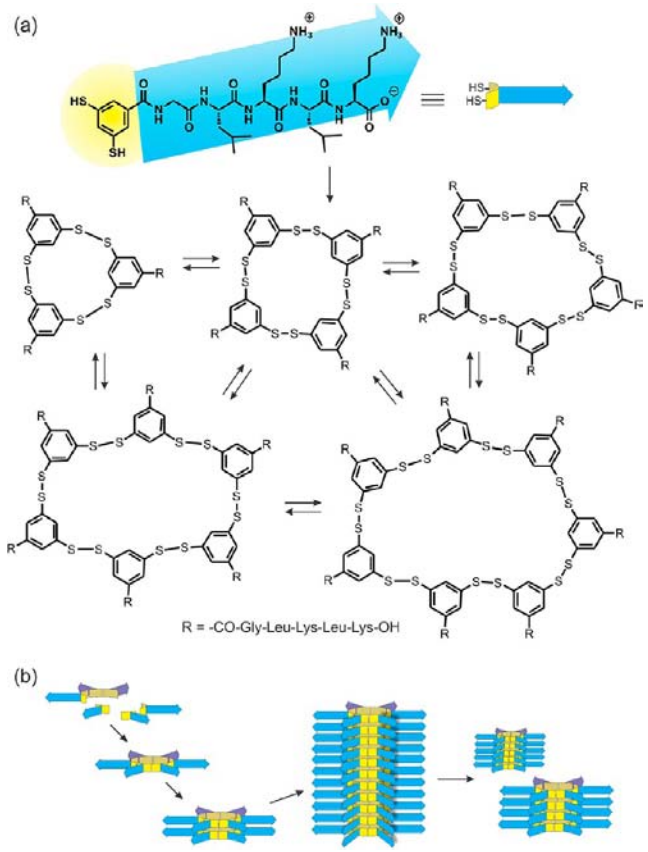

Figure 30. (a) A dithiol-functionalized peptide is oxidized into hexameric macrocycles which are able to stack and form fibers. (b) Mechanical breakage of the fibers duplicates the number of replicators. Reproduced with permission from ref 17. Copyright 2010 The American Association for the Advancement of Science.

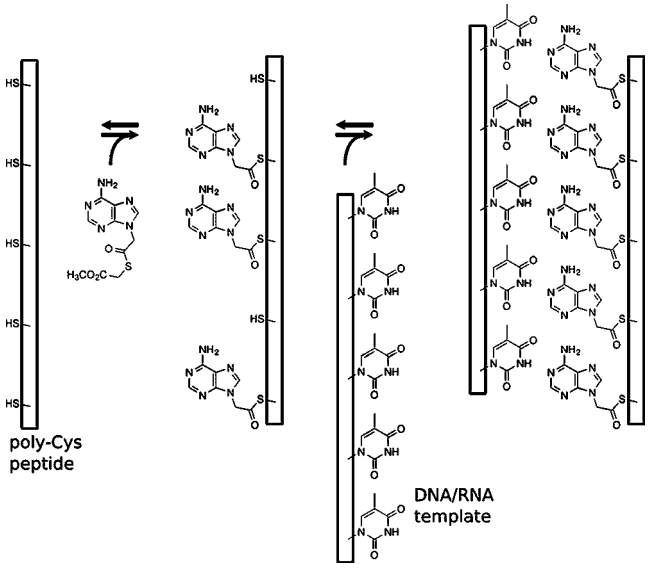

Figure 31. A statistical configuration of nucleobases on a polypeptide is efficiently templated to form a complementary strand.

DNA polymerization, this process is reversible, allowing for error correction and relatively high fidelity, compared to other enzyme-free polymerizations. While no autocatalytic processes have been investigated, this study constitutes an important step toward cross-replication of information rich polymers.

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11. MACHINES AND INFORMATION PROCESSING

In this final section we highlight some examples which at first glance may appear rather remote from the concepts of DCC, as originally conceived, and which are not aimed directly at achieving diversity. However, these systems share another characteristic of DCLs: they exploit dynamic covalent bonds to steer the composition of the systems by the means of external physicochemical stimuli and use these changes to extract either work or information. We have chosen to include these systems as they illustrate which functions may be achieved using this chemistry. Hence, targeting similar functions through a molecular network/dynamic combinatorial approach may well be possible.

The orthogonality of reversible hydrazone and disulfide chemistry[170−172] enables the construction of machines of the nanoworld. Leigh's group has brilliantly capitalized on this opportunity by creating a series of walker molecules based on dynamic covalent bonds. In their first system, a bipedal, small-molecule walker has been equipped with hydrazone and disulfide legs, which were attached to the track and could be independently rendered dynamic.[173−175] In this way one of the "legs" is always attached to the "ground", while the other can move freely. By oscillating equilibration conditions, it is possible to cycle between movement of both legs (Figure 32). Of course the walker can make a step both forward or backward (if footholds are available) with probability governed only by the thermodynamic stability of both positions, so that a steady state is achieved after a few cycles. Despite this, it is possible to achieve an overall translation of the walker on the track, when the initial distribution does not correspond to the minimum Gibbs energy distribution.

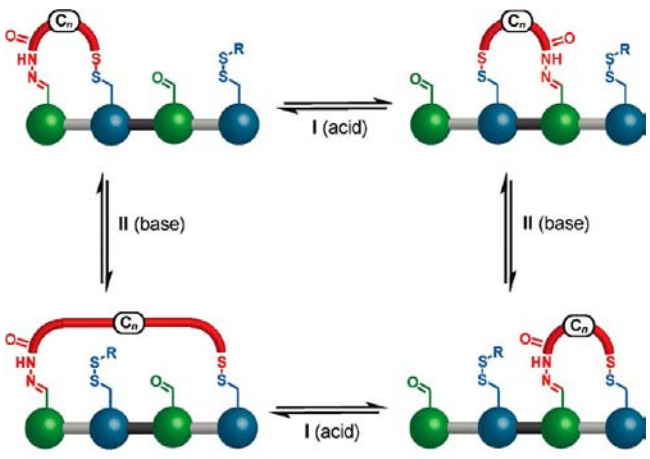

Figure 32. Cycling between acidic and basic conditions enables the walker to make steps with its hydrazide and thiol feet, respectively. Reproduced with permission from ref 173. Copyright 2010 American Chemical Society.

A small modification of this system with a photoswitchable azobenzene group between second and third footholds has provided greater control over the walker movement.[176] By switching the azobenzene at the appropriate part of the cycle, it was possible to bias the movement in a desired direction by utilizing the Brownian ratchet mechanism.

The last walker molecule in the series was able to move on the track spontaneously, without any need for external intervention or changing the conditions.[177] Its translation was based exclusively on a reversible Michael addition between amines on the track and a Michael acceptor on the walker. Similar behavior has been observed by Kovaříček and Lehn in a system composed of a polyamine track and an aldehyde walker capable of movement involving equilibria between imine, aminal, and iminium cation.[178] Unfortunately, the movement of those walkers is again fully random, i.e., the final distribution of the walker is again determined by the relative Gibbs energies of the different states. Designing dissipative systems that can exhibit directional motion on a longer track without the need to constantly cycle between different conditions is a challenging undertaking, requiring coupling consumption of chemical and/or physical energy with motion. Natural protein motors prove that this endeavor is nevertheless manageable.

DCC-based machineries may find applications completely different than translational movement. Recently, dynamic covalent systems have been employed to perform information processing and storage tasks. A doubly dynamic system comprising of imine formation and exchange and metal−ligand coordination has been shown to perform complex logical operation corresponding to reassembly events, triggered by addition of new library members (Figure 33).[179] Intricate interdependencies in the dynamic reaction network highly resemble signaling pathways in nature, however in this case, all of them are under thermodynamic control, thus requiring stoichiometric amounts of signal molecules.

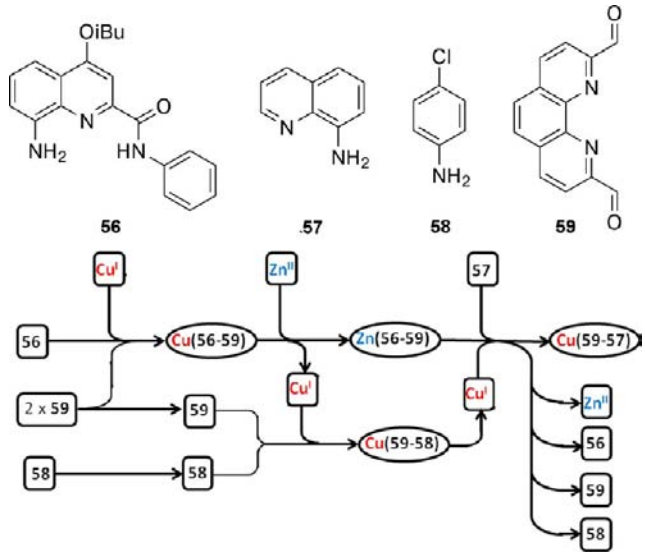

Figure 33. A responsive dynamic system consisting of amines (**56**–**58**), aldehyde (**59**), metal cations and their assemblies.

Lehn's group proposed a dynamic library performing logic operations based not only on chemical inputs but also on thermal and optical signals.[180] Their system incorporates a hydrazone molecule which can not only reshuffle upon treatment with hydrazones but also undergo *E*−*Z* isomerization when irradiated or heated and coordinate metal cations. The three processes are inextricably intertwined, providing the system with memory and allowing it to process simple information. Moreover, constitutional, configurational, and coordinational control is characterized by different kinetics, thus distinguishing between long- and short-term memory.

The capability of processing chemical information by complex DCLs can be also utilized to distinguish between

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different template molecules based on their effect on the libraries. We have used this property to cluster different effector molecules into two subsets based on their library fingerprint.[181] Libraries composed of three dithiol building blocks formed mainly six macrocycles (Figure 34a), which responded

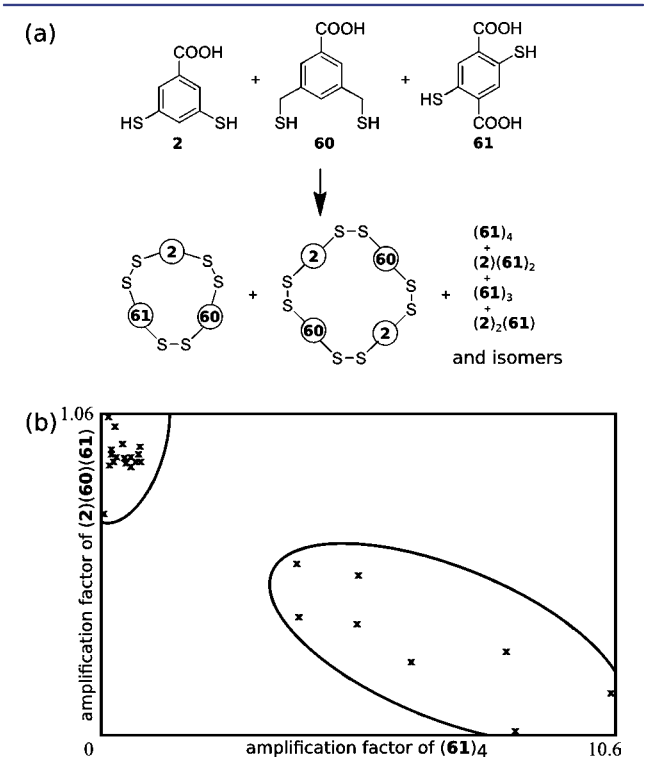

Figure 34. (a) A DCL mainly composed of six library members used to screen various amines and ammonium cations for their similarity. (b) 25 different amines clustered into two subsets based on the response of the library. Reproduced with permission from ref 181. Copyright 2013 Chemistry Central.

differently to different amine effectors. Based on the amplification factors of six different library members, a clustering algorithm showed that the molecular network was able to discriminate between different types of amines (Figure 34b). Afterward, a computer algorithm has been trained to recognize templates featuring an ethylamine moiety based solely on the amplification factors and assign unknown molecules to the correct set with high success rate. It is noteworthy that the library used to assess molecular similarity was composed of only three slightly different building blocks, making us hopeful that more complex networks may be able to predict biological activity.

12. CONCLUSIONS AND OUTLOOK

DCC has matured as a successful field of chemistry over the last two decades. DCC has been extremely successful in discovering receptors for small molecules, capable of competing with natural ones. Their dynamic nature facilitates the recovery of both the guest and the constituting building blocks, as exemplified by the DCC approach to sequestering CO_2. Furthermore, DCL experiments performed directly in analytical setups have provided an opportunity to simultaneously screen for properties of library members, without the typical need to isolate the most potent library member. Therefore a traditional iterative procedure of synthesis, purification, and analyzing function has been effectively reduced to a single step.

DCC has expanded well beyond the applications for which it was originally conceived and is starting to make an impact in self-replicating systems and materials chemistry. Yet, there is still much room for further development. Despite being a seemingly ideal methodology to hunt for new drugs, the use of DCC is still not mainstream in this area, especially when compared with fragment-based drug discovery,[182] a similar, diversity-oriented methodology which, despite a comparable lifetime, has already delivered one drug to the market while several others are currently at the stage of clinical trials. There is hope that developments of new reversible reactions that are compatible with biological conditions and that may be operated at low concentrations will give a further boost to this area.

Many of the successes in DCC have been achieved using DCLs of fairly limited sizes. The field has been reluctant to use larger libraries, despite some precedents and indications that larger libraries should give better results. Researchers might have been put off by the perceived analytical challenges posed by larger libraries. However, modern instruments allow even highly complex mixtures to be analyzed (think only of protein digests from which protein sequences are now routinely established). Furthermore, DCLs may be utilized in which either templates or library members are bound to a solid support, allowing for orders of magnitude richer libraries, without requiring the use of sophisticated analytical instrumentation.

Science is sometimes compared with art. In case of DCC, this statement also rings true. The libraries have crafted molecules possessing extraordinarily interwoven topologies and captivating structures with unrivalled ease.

Early definitions of DCC considered only systems at equilibrium. However, the functional properties exhibited by equilibrium systems are dwarfed by those of far-from-equilibrium systems. An exciting new area is now being uncovered based on DCLs that combine equilibration processes with kinetically controlled chemical or physical steps, including catalysis and autocatalysis. Particularly rich are dissipative systems, in which a sustained supply of energy yields behavior such as (directional) movement, transport, and adaptive self-replication. This trend toward increasing the complexity of not just DCLs but assemblies of their members and experimental conditions has guided the field into the area of systems chemistry,[1−7,20] which focuses on emergent properties of complex (but not necessarily covalently dynamic) mixtures. In this way DCC together with systems chemistry is establishing new connections between chemistry, biology, and nanotechnology. This has been a natural development of the field as it increases its focus on complexity and emergence, complementing a more traditional approach to chemistry where the emphasis is on single and pure compounds.

Future development of the broader field of DCC is likely to be driven by multidisciplinarity and unorthodox approaches. We believe that such development will lead not only to discoveries of new phenomena or solutions to urging problems but also to reinterpretation of existing systems and bridging different as yet poorly connected fields. However, predicting exactly where the field will go from here is beyond us, as one of the most exciting features of DCC, proven time and again, is its ability to deliver the unexpected.[15−17,113]

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Notes

The authors declare no competing financial interest.

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