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# Dynamic Molecular Networks: From Synthetic Receptors to Self-Replicators

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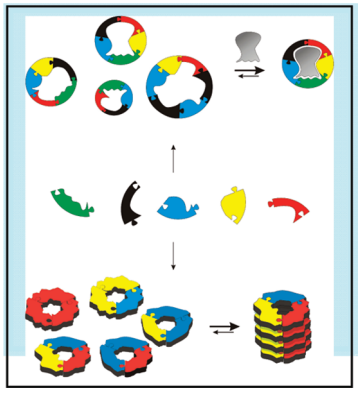
## CONSPECTUS

Dynamic combinatorial libraries (DCLs) are molecular networks in which the network members exchange building blocks. The resulting product distribution is initially under thermodynamic control. Addition of a guest or template molecule tends to shift the equilibrium towards compounds that are receptors for the guest.



This Account gives an overview of our work in this area. We have demonstrated the template-induced amplification of synthetic receptors, which has given rise to several high-affinity binders for cationic and anionic guests in highly competitive aqueous solution. The dynamic combinatorial approach allows for the identification of new receptors unlikely to be obtained through rational design. Receptor discovery is possible and more efficient in larger libraries. The dynamic combinatorial approach has the attractive characteristic of revealing interesting structures, such as catenanes, even when they are not specifically targeted. Using a transition-state analogue as a guest we can identify receptors with catalytic activity.

Although DCLs were initially used with the reductionistic view of identifying new synthetic receptors or catalysts, it is becoming increasingly apparent that DCLs are also of interest in their own right. We performed detailed computational studies of the effect of templates on the product distributions of DCLs using DCLSim software. Template effects can be rationalized by considering the entire network: the system tends to maximize global host-guest binding energy. A data-fitting analysis of the response of the global position of the DCLs to the addition of the template using DCLFit software allowed us to disentangle individual host-guest binding constants. This powerful procedure eliminates the need for isolation and purification of the various individual receptors. Furthermore, local network binding events tend to propagate through the entire network and may be harnessed for transmitting and processing of information. We demonstrated this possibility in silico through a simple dynamic molecular network that can perform AND logic with input and output in the form of molecules.

Not only are dynamic molecular networks responsive to externally added templates, but they also adjust to internal template effects, giving rise to self-replication. Recently we have started to explore scenarios where library members recognize copies of themselves, resulting in a self-assembly process that drives the synthesis of the very molecules that self-assemble. We have developed a system that shows unprecedented mechanosensitive self-replication behavior: depending on whether the solution is shaken, stirred or not agitated, we have obtained a hexameric replicator, a heptameric replicator or no replication, respectively. We rationalize this behavior through a mechanism in which replication is promoted by mechanically-induced fragmentation of self-assembled replicator fibers. These results represent a new mode of self-replication in which mechanical energy liberates replicators from a self-inhibited state. These systems may also be viewed as self-synthesizing, self-assembling materials. These materials can be captured photochemically, converting a free-flowing fiber solution into a hydrogel through photo-induced homolytic disulfide exchange.

## Introduction

Complexity and emergence are subjects that are becoming increasingly topical in chemistry.[1−4] In some sense, chemists have some catching up to do in these areas, since in many surrounding disciplines complexity research is considerably more developed than in chemistry. At the same time, of all disciplines, chemistry is probably the richest and most powerful when it comes to developing complex systems, since it deals with the smallest of components that can still be manipulated relatively easily: molecules. Furthermore, inspiration on what may be achieved by complex chemical systems (i.e., systems chemistry[2,4]) is never far away; simply



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look at the stunning diversity of life forms that surround us everywhere. And life is only *one* manifestation of what may be achieved by complex chemical systems. Once we learn how to design emergent function in chemical systems, a huge unexplored world will open up. At present, we are only starting to scratch the surface and only just beginning to learn how to deal with complexity in chemistry. This Account describes our foray into the fascinating new area of systems chemistry. It starts off with a description of dynamic combinatorial libraries (DCLs),[5−9] which are networks in which molecules are generated by linking subunits together using reversible covalent reactions. The composition of such networks can respond to molecular recognition. Recognition can occur with other species that are not part of the dynamic network, leading (in our case) to host−guest systems, or between the members of the network, giving rise to systems of interdependent self-assembly and self-replication processes.

## Molecular Networks Containing Synthetic Receptors

Making molecules that bind other molecules through noncovalent interactions still remains highly challenging, whether it involves new inhibitors for proteins or synthetic receptors for small-molecule guests. The modest success of traditional design approaches to these subjects has led the groups of Sanders, Lehn, and others[10] in the mid-1990s to independently develop dynamic combinatorial chemistry as a new approach to the (reductionistic) problem of how to efficiently produce molecules that effectively bind other molecules. In dynamic combinatorial chemistry, simple building blocks are made that combine with each other through reversible (often covalent) bonds. This leads to a dynamic molecular network in which all constituent molecules continuously exchange building blocks. The product distribution is governed by thermodynamics: the population of the individual network members is dictated by their relative stabilities. This renders such networks inherently responsive to any influence that alters these stabilities. Such influences may be physical[11−13] but also chemical, including molecular recognition. For example, a dynamic molecular network (or DCL) of potential synthetic receptors will respond to the introduction of a guest molecule that binds to any of these receptors. The host−guest complexes that are thus formed can be thought of as generating an additional well in the free-energy landscape of the system with a depth that is influenced by the strength of the host−guest interaction. If the well is deep enough (i.e., if the host−guest interactions are strong enough), then

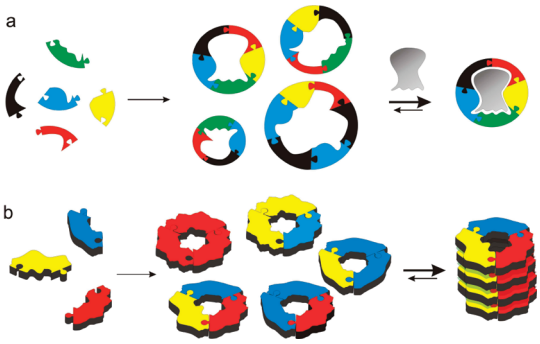


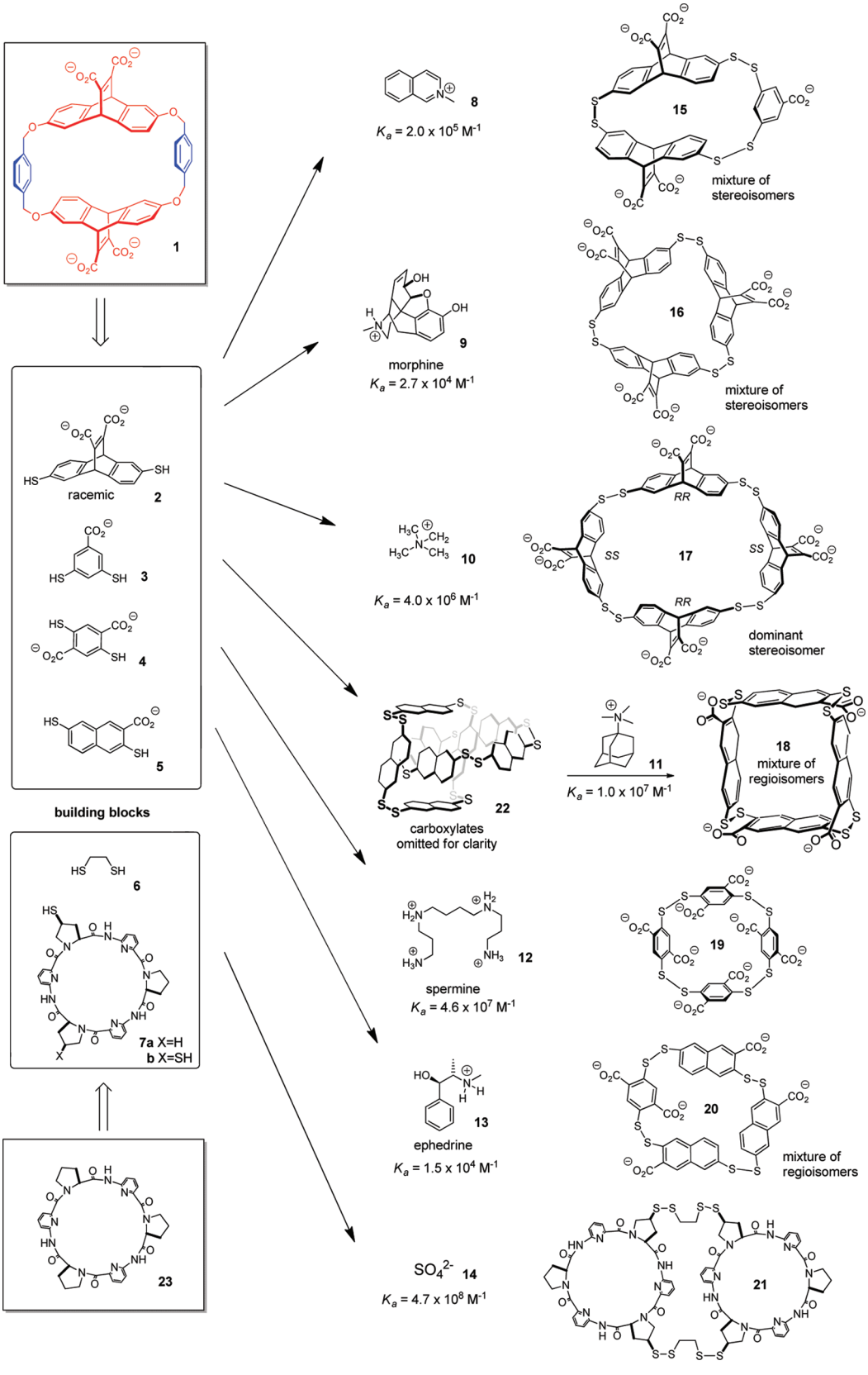

**FIGURE 1.** Mixing a set of bifunctionalized building blocks gives rise to a DCL of macrocycles. (a) Exposing the library to a guest molecule shifts the equilibrium in the direction of (ideally) the best receptor. (b) Self-assembly of one of the macrocycles shifts the equilibrium in the direction of the very molecule that self-assembles.

the equilibrium of the system will shift toward the formation of (ideally) the best receptors, at the expense of the other members of the network. This guest-induced (or, in more general terms template-induced) amplification of the best binders is shown schematically in Figure 1a.

Implementing dynamic combinatorial chemistry relies on the ability to make reversible connections between building blocks, which is most conveniently achieved through reversible covalent chemistry. The most commonly used reversible reactions involve disulfide, hydrazone, or imine bonds.[7] Inspired by the work by Regen on nearest-neighbor recognition in bilayer membranes,[14] we have adapted disulfide chemistry for constructing dynamic molecular networks.[15] Among the attractive features of these linkages are the small size, the good accessibility of thiol precursors, the simple and clean conversion of thiols to disulfides by oxidation in air under neutral conditions in aqueous solution, the possibility to cleanly reverse this process by addition of a mild reducing agent, the reliable (albeit sometimes slow) exchange of the disulfides in the presence of catalytic thiolate anion and the ability to switch off the exchange process by adding acid or upon complete oxidation of the thiols. Disulfide chemistry may be combined with other reversible chemistries, including reversible thioester,[16] hydrazone,[17] or imine and metal−ligand chemistry.[18]

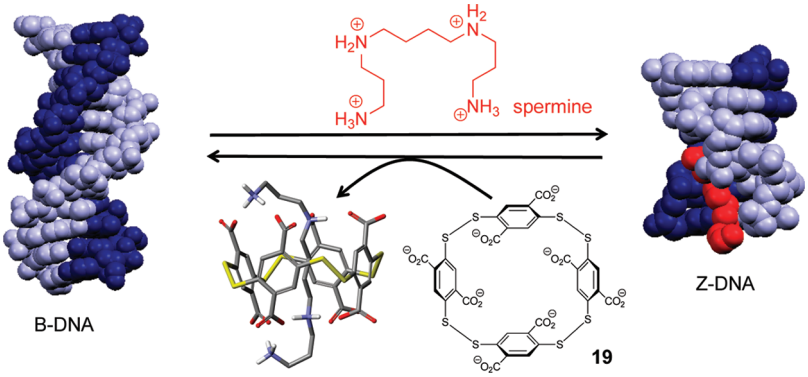
When we entered the field of dynamic combinatorial chemistry, it was still unclear whether molecular recognition was a sufficient driving force to achieve useful changes in product distribution in DCLs. Inspired by synthetic receptor **1** developed by Dougherty (Scheme 1),[19] we synthesized dithiol building blocks **2** and **3** (Scheme 1), which, upon oxidation, gave rise to a DCL containing macrocyclic receptors.[20] We reasoned that exposing this molecular network

**SCHEME 1.** Dithiol Building Blocks **2**–**7** for Constructing DCLs Were Inspired by Synthetic Receptors for Cations and Anions, Described by Dougherty[19] and Kubik,[21] Respectively; Dynamic Combinatorial Experiments with These Building Blocks Led to the Identification of Synthetic Receptors **15**–**21** for Guests **8**–**14**[a]




[a]Values of the host–guest binding constants ($K_a$) in aqueous solution are indicated.

**SCHEME 2.** The Change in Helicity of DNA Induced by Binding of Spermine Is Reversed Following Sequestration of Spermine by Receptor **19**[22]




to guests known to bind to the Dougherty receptor should give rise to amplification of analogous disulfide macrocycles. We indeed observed such amplification, but the amplified macrocycles were different from the one we expected. Guest **8**, which is one of the best guests for the Dougherty receptor **1**, resulted in the amplification of receptor **15**, with one instead of two phenyl linkers. Using a larger guest (morphine; **9**) gave a bigger receptor (**16**), which is even more different from the expected disulfide analogue of **1**. The observed amplifications were large enough to allow the new disulfide receptors to be produced in 60−95% yield. These results established dynamic combinatorial chemistry as a powerful tool for discovering and preparing synthetic receptors.[20]

In further work that illustrates the generality of the dynamic combinatorial approach to receptor development, we succeeded in preparing synthetic receptors for a wide range of guests, including cationic species such as spermine (**12**)[22] and ephedrine (**13**)[23] and anions, such as sulfate[24−26] (Scheme 1). These studies led to a number of interesting observations.

*First, the dynamic combinatorial approach allows one to identify new receptors that are unlikely to be obtained through rational design.* For example, tetramethylammonium iodide induced the amplification of tetrameric receptor **17**, formed from four units of racemic building block **2**.[27] A remarkable result given that this guest is much smaller than morphine, which amplified the corresponding trimeric receptor **16**.[20] Even more remarkable is the fact that amplification of tetramer **17** is stereoselective; the stereoisomer with alternating *RR* and *SS* building blocks is amplified preferentially. In contrast, trimer **16** is obtained as a close to statistical mixture of isomers. This unexpected behavior is due to tetramer **17** binding its small guest in a collapsed conformation, which requires adjacent building blocks to have opposite chirality. Such receptors that bind their guests through induced-fit are notoriously difficult to design.

*Second, DCLs have the highly attractive characteristic of revealing interesting structures even when these are not targeted.* A clear example of this behavior is the unexpected discovery of catenane **22**, which forms quantitatively upon oxidizing naphthalene building block **5**.[28] Exposing this species to adamantane-derived guest **11** opens up the catenane to produce receptor **18**. Interestingly, also in other work on DCLs, catenanes, designed[29,30] or otherwise,[31] reveal themselves remarkably often.

*Third, the dynamic combinatorial method is leading to receptors with remarkably high affinities, even in highly competitive aqueous environments.* For example, receptor **18** is able to bind its guest with submicromolar affinity in water.[28] The structurally analogous tetrameric receptor **19** shows even higher affinity for its preferred guest spermine (**12**).[22] Affinities this high are starting to compete with those typically exhibited by biomolecules and should enable biological applications of the receptors. As a first step in this direction, we have shown that receptor **19** can be used to interfere with the interaction between spermine and DNA.[22] Scheme 2 shows how spermine can change the helicity of certain DNA sequences from normal right-handed B-DNA to left-handed Z-DNA. Addition of receptor **19** to the spermine−Z-DNA complex results in the sequestration of the spermine and the return of the DNA to its original right-handed helicity. Another example of exceptional binding efficiency is anion receptor **21**, which we have developed in collaboration with the Kubik group.[26] We were inspired by cyclopeptide **23**, developed previously by Kubik, which binds to inorganic anions by forming a 2:1 peptide−anion sandwich complex.[21] Our strategy to improve the efficiency was to link the two cyclopeptide rings covalently via one[24,25] or two[26] spacers that were selected through a dynamic combinatorial approach. Thus, DCLs were made starting with cyclopeptide derivatives containing one (**7a**) or two (**7b**) thiol groups.

The best results were obtained with the latter in combination with spacer **6**, affording the macrobicyclic receptor **21**, which binds potassium sulfate with nanomolar affinity in 41 mol % acetonitrile in water. At present, this affinity is the highest known for any neutral synthetic receptor in aqueous solution. The very high binding efficiency is a result of a delicate balance between rigidity and flexibility, which would have been difficult to achieve in a design approach. Another important contributor to the high binding energy of this system are hydrophobic interactions between different nonpolar parts of the receptor that occur in the conformation in which the anion is bound.[24,32] Such reinforced recognition, in which intrareceptor interactions accompany receptor–guest interactions, has been postulated to be important in proteins[33] but has not previously been recognized in synthetic receptors.

*Fourth, receptor discovery is possible in large DCLs.* For example, receptor **20**, which binds ephedrine in water with modest affinity, was discovered from a DCL in which we effectively screened on the order of 10 000 compounds (Figure 2).[23] Analysis of the product distribution relied on LC-MS but did not require complete separation of all components by HPLC. While the use of libraries of this size in dynamic combinatorial chemistry remains uncommon, we have recently shown that it should nevertheless be advantageous to screen large DCLs. Using our DCLSim software,[34] we performed a series of computer simulations and found that upon increasing the number of building blocks in a DCL, the probability of forming strongly binding library members rises more rapidly than the probability of detecting them falls off.[35] Our results suggest that it is most practical to use large libraries even under conditions that most of the expected compounds remain below the detection limits, since strong binders are overrepresented in the set of compounds that are within detection limits.

*Fifth, when a transition-state analogue is used as a guest, it is possible to identify receptors with catalytic actitivity.* Any structure that is able to bind to (and thereby stabilize) a transition state of a reaction is a potential catalyst. Thus, it should be possible to screen a mixture of compounds for catalysts by assessing the affinity of these compounds for molecules that resemble the transition state of a given reaction (transition-state analogues). We tested this hypothesis focusing on the Diels–Alder reaction shown in Scheme 3a, which features a transition state that closely resembles the product. Thus, we simply used the product as the transition-state analogue and used it to screen a DCL made from building blocks **2** and **3**. This led to the amplification of receptors **15** and **16**, of which the latter was able to catalyze the Diels–Alder

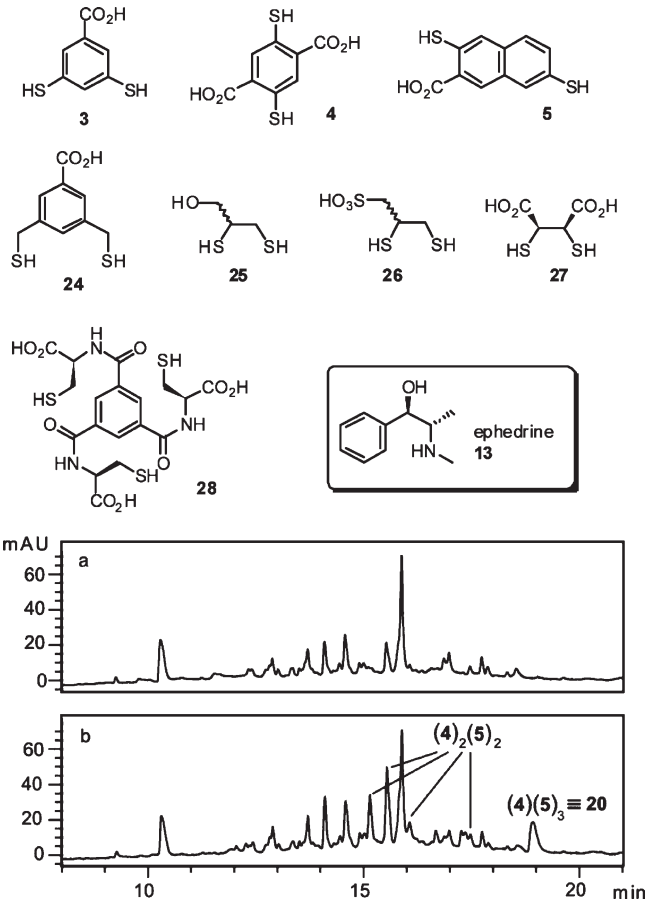



**FIGURE 2.** HPLC chromatograms of DCLs made from building blocks **3**–**5** and **24**–**28** (a) in the absence of template and (b) in the presence of ephedrine **13**, showing the amplification of (among others) receptor **20**.[23]

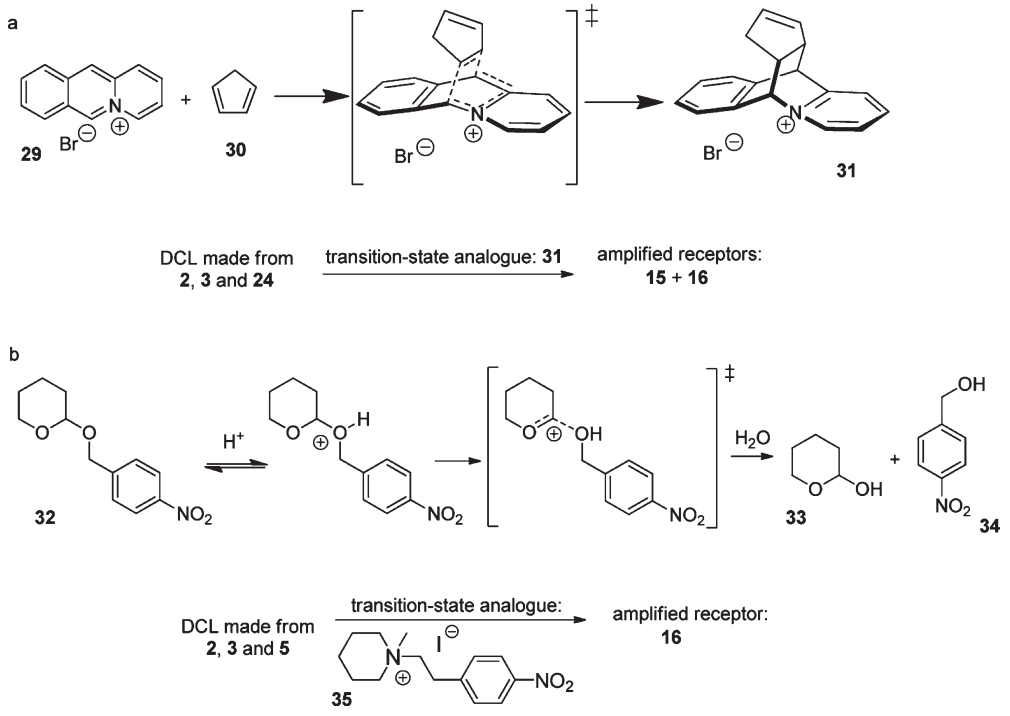
reaction.[36] Not surprisingly, some product inhibition was observed, but since the catalyst binds starting material and product with similar affinity, turnover was still feasible.

A similar library was screened against the transition-state analogue **35** of the acetal hydrolysis reaction shown in Scheme 3b, leading, again, to the amplification of receptor **16**, which was also able to catalyze the acetal hydrolysis.[37]

## A Systems View of Dynamic Combinatorial Libraries

In the section above, DCLs were used with the reductionistic view of identifying new synthetic receptors or catalysts. However, the DCLs that contain the receptors or catalysts are of interest in their own right.[9] The libraries are molecular networks that exhibit fascinating and sometimes counterintuitive properties. Interesting systems-level behavior was revealed upon analyzing the relationship between amplification and binding energy. One might naively have expected that a straightforward correlation exists between these two

**SCHEME 3.** Exposing a DCL Containing Building Blocks **2** and **3** to the Transition-State Analogues of (a) a Diels–Alder Reaction[36] and (b) an Acetal Hydrolysis Reaction Led the Amplification of Receptors That Were Able To Catalyze These Reactions[37]




parameters. In reality such correlation is only found under rather special circumstances, while under most experimental conditions, library behavior is more complex. In order to obtain a better understanding of the systems behavior of DCLs, we have simulated libraries that were based on an arbitrarily chosen number of seven building blocks, which were allowed to form all possible cyclic library members up to tetramers, resulting in a DCL of 322 library members. Each of these was assigned a binding affinity for the template that was drawn randomly from a normal distribution. The mean value for log(*K*) was set at 2 (i.e., the average binding constant was 100 $M^{-1}$) and the standard deviation for log(*K*) was 1. We simulated DCLs using a range of building-block and template concentrations and assessed the correlation between host–guest binding energy and the amplification factor.[34] For each set of experimental conditions, a graph comparable to those shown in Figure 3 was obtained.

The results show considerable variability from one run to the next, even when the only difference is the random assignment of binding affinities to library members. A particularly clear-cut example is shown in Figure 3a,b, which shows the behavior of DCLs run at 10 mM template and 10 mM building block concentrations. Where the DCL in Figure 3a gives a good correlation between binding affinity and amplification factor, the one in Figure 3b gives a particularly poor correlation, with no amplification at all for the best binder. When one is performing dynamic combinatorial experiments, it is not known *a priori* how the binding constants are distributed over the various library members, so it is a matter of chance how well the binding affinities will correlate with amplification factors for a given set of experimental conditions. In order to obtain more clarity, we repeated the simulations of the type of Figure 3 50 times each for a range of experimental conditions. This allowed the quality of the correlation between amplification factor and binding affinity (as quantified by the mean correlation coefficient $R^2$) to be assessed as a function of template and building block concentrations. The resulting two-dimensional graph (Figure 3d) shows that setting up DCLs of the type simulated here using a template to building block ratio of 1:10 ensures satisfactory correlations.[34]

Returning to the problem case of Figure 3b, when we resimulated this library at a 10-fold reduced template concentration of 1.0 mM (corresponding to the 1:10 template to building block ratio), the correlation improved markedly. However, the magnitudes of most of the amplification factors are reduced (Figure 3c).[6] This may be undesirable, so particularly when screening new DCLs, it may be better to use a modest excess of template to increase the likelihood of detecting any template effects. A second round of screening

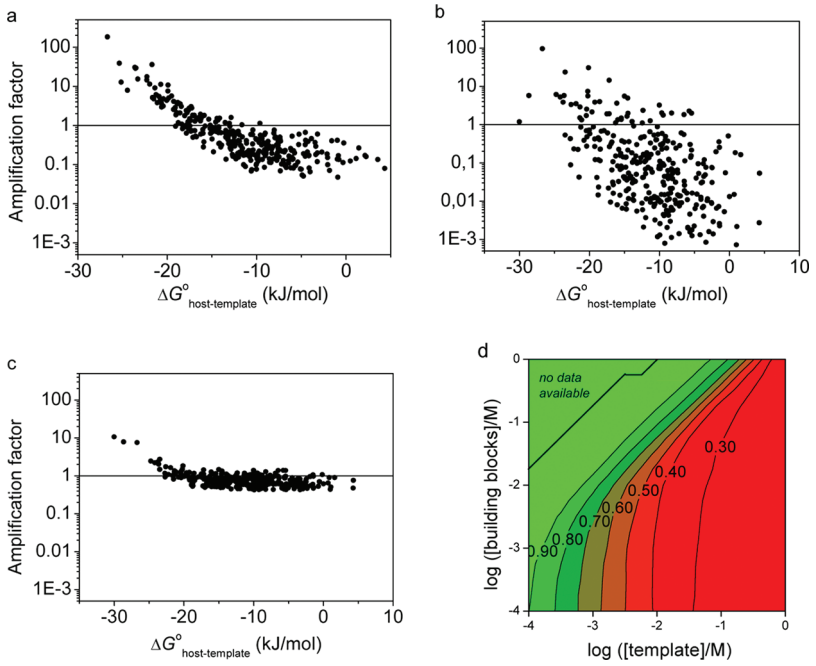



**FIGURE 3.** (a, b) The relationship between amplification and free energy of binding for all binders in two randomly generated DCLs that differ only in the way the binding constants are distributed over the various hosts. In both DCLs, the total concentration of the building blocks and the concentration of the template is 10 mM. (c) The library of panel b simulated at a reduced template concentration of 1.0 mM. (d) Correlation between binding affinity and amplification in simulated DCLs as a function of template and total building block concentration. The numbers indicate the correlation coefficient ($R^2$).[34]

can then be performed using a smaller amount of template to assess whether the observed template effects are indeed pointing to the better binders in the system.

Thus, with careful experimental design, DCLs may be used with some confidence for identifying strong binders through comparing the amplification factors of the various library members. However, in isolation, amplification factors cannot be relied on for assessing absolute affinities. Traditionally determining binding requires isolating the receptors, followed by host–guest titrations. This is often a labor-intensive process. We have recently shown that it is possible to obtain host–guest binding affinities without the need for isolation of any of the library members.[38] Instead, library distributions were determined for a set of different experimental conditions (template and building block concentrations). Equilibrium constants for host–guest interactions can then be fitted to this data. We have developed dedicated DCLFit software for this purpose.[38] An impression of how well the fitted values of the equilibrium constants for host–guest interactions approach the real values was obtained by using a series of simulated DCL compositions generated using DCLSim and based on known binding constants as the input. DCL compositions for a set of 12 different experimental conditions (different ratios of the three building blocks and

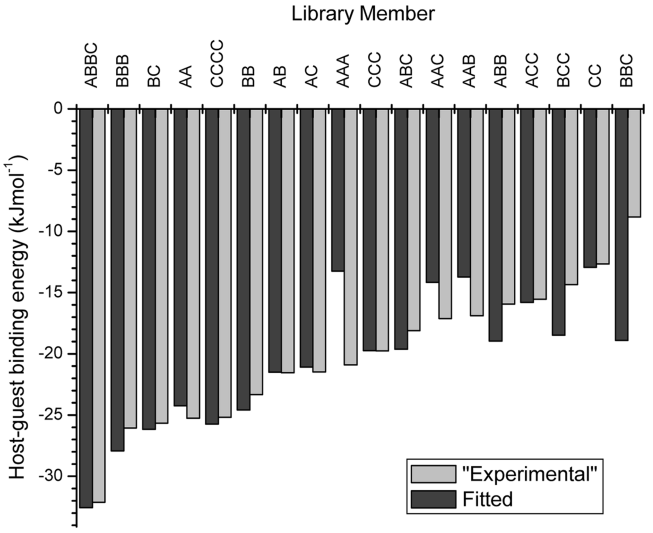



**FIGURE 4.** Comparison of "experimental" and fitted values for the host–guest binding energies in a simulated 31-component DCL.[38]

different template concentrations) were simulated. After introducing random errors into this data (similar to those expected for a true experimental data set), it was used as input for DCLFit, which produced the data represented by the black bars in Figure 4 as output. The predicted binding energies for the stronger binders are in good agreement with the real values (gray bars in Figure 4).

The fitting approach allows multiple host–guest binding constants to be estimated in parallel, illustrating that taking a global "systems" view of molecular networks has important advantages over the reductionistic approach of focusing on individual host–guest interactions.

The highly interconnected nature of dynamic molecular networks causes recognition events to propagate through the entire network; that is, binding of a guest by one receptor will cause a shift in the equilibrium that will be felt by many other network members, even if these do not interact with the guest themselves. Thus, such networks have an innate ability to transmit and process information. For example, it should be possible to design logic gates. We briefly explored this application using our DCLSim software.[39] We designed a small in silico molecular network made from building blocks A–E, which we allowed to form all pairwise library members (i.e., A–A, A–B, A–C, etc.). We introduced two template (or effector) molecules, T1 and T2, which were given strong affinities for A–B and C–D, respectively. We then analyzed the product distribution of the small DCL as a function of the concentration of the two effectors. Figure 5 shows how the concentration of library member E–E depends on the concentrations of T1 and T2. Since E is the only building block that is not involved in recognition, its concentration rises when all other building blocks are recruited into forming the receptors for T1 and T2. Thus, this system constitutes an AND logic gate, where input and output are molecules.

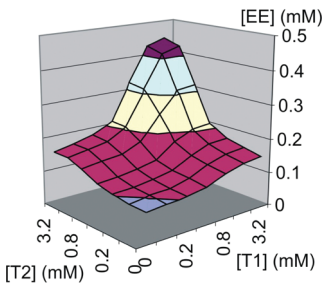



**FIGURE 5.** Concentration of library member EE as a function of the concentration of effector molecules T1 and T2 in a dynamic library made from building blocks A–E in which T1 binds to AB and T2 to BC.[39]

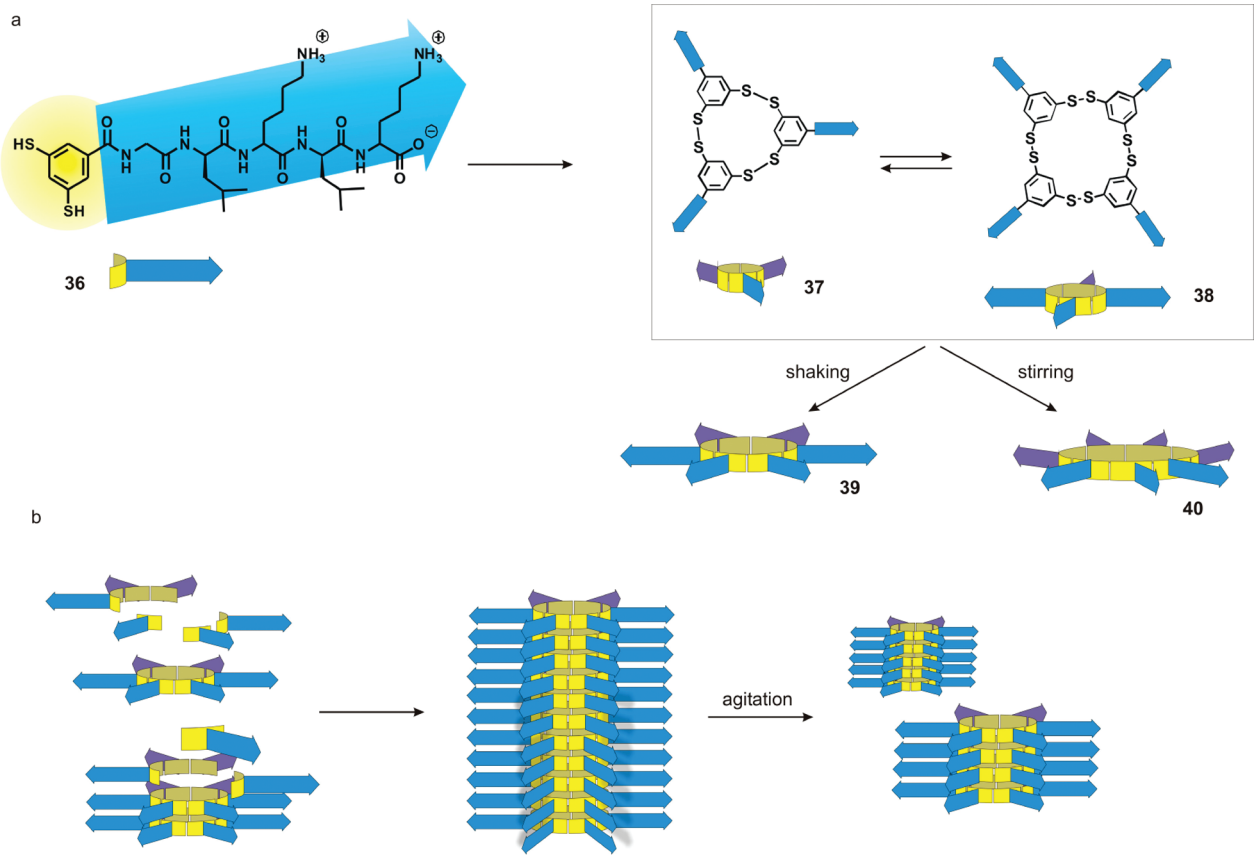



**FIGURE 6.** (a) Oxidation of peptide-functionalized building block **36** initially produces a mixture of macrocycles, dominated by trimer **37** and tetramer **38**. Upon agitation, a conversion takes place to larger macrocycles; shaking gives hexamer **39**, while stirring gives heptamer **40**. (b) Schematic representation of the stacks of the hexamer, held together by $\beta$-sheets formed by the peptide chains. Agitation results in fracture of the stacks, increasing the number of ends from which the stacks grow.[44]

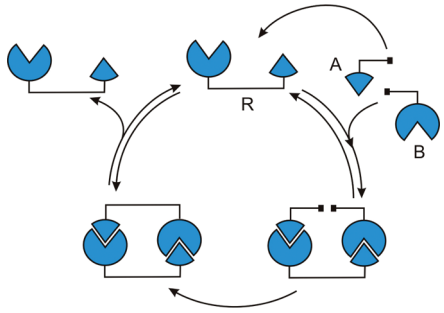
## Self-Replication in Dynamic Molecular Networks

While the majority of research on DCLs has focused on changes in product distributions mediated by *externally* added templates, also molecular recognition within and between library members will induce shifts in product distribution through a process of *internal* templating. When a library member is able to recognize itself, forming a self-assembled structure, this will promote the formation of more of the very library member that self-assembles (Figure 1b). This process can be regarded as a new form of self-replication[40] and may give rise to interesting new materials.[41,42]

We have recently extended our DCLFit software to be capable of dealing with extended assembly processes of the type shown in Figure 1b.[43] These systems were described using a commonly used model in which only the first assembly step leading to the dimer was characterized with a separate equilibrium constant $K_{dim}$. Subsequent stepwise assembly elongation equilibria were described by a single equilibrium constant $K_{elong}$. With DCLFit, it is now possible to estimate values for $K_{dim}$ and $K_{elong}$ from an analysis of distributions at different building block concentrations. Determining these equilibrium constants by traditional methods normally requires a means of quantifying assembled and free monomers. In a dynamic molecular network, this is not required, because the various equilibria associated with the interconversion between covalent library members report on the noncovalent association of these compounds.[43] This demonstrates, again, the power of performing analyses at systems level.

Ironically, we have not yet been able to use DCLFit for the analysis of self-assembly in a real (as opposed to simulated) dynamic molecular network, because the self-assembling system that we developed turned out not to be under thermodynamic control. This is perhaps not altogether unexpected, since assembly into nanostructures may well shield the assembling molecules from the exchange reaction through which they were produced. The system we developed is shown in Figure 6 and is based on building block **3** to which a peptide chain (represented by a blue arrow) was attached to give **36**.[44] The peptide sequence was designed to have alternating hydrophilic and hydrophobic amino-acid residues and is thereby prone to assemble into $\beta$-sheets. While the peptide is too short to assembly by itself, upon thiol oxidation, macrocycles will form that display several peptides. A multivalency effect ensures that assembly should now in principle be feasible at a sufficiently large ring size. Indeed, the formation of micrometer-long fibers constituted from heptamer **40** was observed upon subjecting an aqueous solution of **36** to air oxidation, *but only when the sample was stirred*. A sample that was not agitated showed predominantly trimer **37** and tetramer **38** that did not self-assemble. Surprisingly, when the sample was *shaken* fibers were obtained constituted from hexamer **39**. These results clearly demonstrate the importance of agitation and concomitant fiber fragmentation in the assembly process, which may be rationalized as follows: Fibers grow from their ends, so the rate of fiber growth is proportional to the number of fiber ends, which may be increased by fiber fragmentation (Figure 6b).

**SCHEME 4.** Schematic Representation of the Traditional Self-Replication Mechanism in Which a Replicator R Promotes Its Own Formation by Preorganizing Two Reactive Precursors A and B




But why does shaking produce hexamer and stirring give heptamer? Shaking disrupts predominantly the aggregates of hexamer, conferring on it an advantage over the heptamer in the formation of more aggregates. Stirring fragments both hexamer and heptamer fibers indiscriminately, and now the heptamer fibers win because they have an inherently faster rate of growth.[44]

These results are not just a curiosity; they have some profound implications. First, replication takes place under kinetic control. Whether hexamer or heptamer replicator wins the competition for building block **36** is not determined by the thermodynamic stability of the resulting fibers but by the kinetics of their formation. Thus, while the system is based on two processes that are both reversible (disulfide bond formation and self-assembly), the resulting structure is not (necessarily) the thermodynamic product. Such escape from thermodynamic control opens up a new dimension for dynamic combinatorial chemistry and represents a first step toward the far-from-equilibrium character of life.

Second, the system shown in Figure 6 represents one of the first examples of new replicators emerging spontaneously from a pool of compounds in which they were initially only minor constituents.

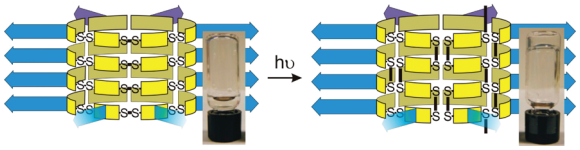



**FIGURE 7.** Photochemical disulfide exchange results in the covalent capture of self-assembled structures obtained from disulfide-based DCLs, causing gelation of the aqueous solvent.[47]

A third important aspect of the present mechanism of self-assembly driven replication is the possibility of solving the self-inhibition problem that thwarts the majority of self-replicating molecules developed to date, which rely on a template-accelerated bimolecular reaction (Scheme 4).[45] In the typical kinetically controlled mechanism, the replicator R has two binding sites on which the two replicator precursors A and B assemble. The reaction between A and B is accelerated as a result of the close proximity of the reactive sites of these precursors. The product of the reaction is a replicator duplex that needs to dissociate before a new round of replication can take place. It is challenging to break up the replicator duplex without adversely affecting the binding of the precursors with the replicator. Yet, duplex dissociation is a requirement for achieving exponential replicator growth. It has been demonstrated that exponential replication is an essential ingredient for Darwinian evolution at the molecular level.[46] In a competition scenario, two subexponential replicators that are self-inhibited will coexist indefinitely, while a competition between two exponential replicators will result in the less efficient replicator going extinct.

In the replication mechanism shown in Figure 6b, the replicator is liberated by mechanically induced fragmentation of the fibers, which may in theory allow exponential growth to be realized. Studies to confirm whether this is indeed the case in our systems are currently ongoing.

The system shown in Figure 6 is not only of interest from the perspective of self-replication, it also represents an interesting new approach to the development of soft materials, where the self-assembly process drives the synthesis of the very molecules that self-assemble. We recently discovered that the disulfide linkages present in the fibers may be used for further stabilization of these structures in a process akin to covalent capture.[47] Upon irradiation (at 365 nm) of a solution containing fibers constituted of hexamer macrocycle **39**, a second round of disulfide exchange took place, resulting in the lateral cross-linking of the fibers (Figure 7). Where the solution was initially free-flowing, after photoirradiation a gel was obtained, presumably because the fibers, which are now built up from oligomers and polymers of **39**, fragment less readily than the fibers made from stacks of hexamer.

These results further underline the versatility of disulfide chemistry. Different product distributions may be obtained through traditional disulfide exchange (mediated by thiolate anions) as compared with photochemical disulfide exchange (proceeding through thiol radicals). The possibility for such photoinduced covalent capture should exist in all self-assembled structures obtained through dynamic combinatorial disulfide chemistry.

## Conclusions

This Account describes a journey of discovery into the world of networks of interconverting molecules. Once the often challenging analytical chemistry was mastered, a wealth of information and many new insights emerged. A very appealing characteristic of dynamic molecular networks is that they reveal directly whether interesting molecular recognition phenomena take place, including those that are not expected, thus providing an extremely fertile ground for new discoveries. After the chemist has mixed together the right ingredients, the molecules lead the way to new receptors, new replicators, and new self-synthesizing materials.

The work summarized herein has featured reversible covalent chemistry, which bridges the fields of organic synthesis and supramolecular chemistry. Indeed, the boundary between these two subject areas fades in systems such as those described in the last part of this Account, where self-assembly instructs covalent chemistry and vice versa. Such systems allow the strength of both fields to be harvested simultaneously.

Finally, the results summarized herein are testimony to the power the systems chemistry approach, where molecules act in concert, leading the observant chemist to species or systems with unique properties. Much has already been achieved, even though we are as yet only beginning to understand how to control chemical systems and how to select the right ingredients and proper conditions. All this suggests a very bright future for the field of systems chemistry.

BIOGRAPHICAL INFORMATION

**Sijbren Otto** obtained his Ph.D. in 1998 from the University of Groningen in the Netherlands working with Prof. Jan Engberts. Following postdoctoral work with Prof. Steve Regen at Lehigh University (USA) and Prof. Jeremy Sanders (University of Cambridge, U.K.), he started his independent research career as a Royal Society

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## FOOTNOTES

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