1
History and Principles of Dynamic Combinatorial Chemistry

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1.1
Introduction

Dynamic combinatorial chemistry (DCC) [1]—combinatorial chemistry under thermodynamic control—is a tool for the efficient synthesis of libraries of complex structures whose individual properties may be explored through the library's response to the stabilizing influences of external stimuli. A dynamic combinatorial library (DCL) is generated by combining building blocks, functionalized such that they can react with one another either through reversible covalent reactions or specific noncovalent interactions, to form a mixture of interconverting library members. As the exchange of building blocks between library members takes place, the product distribution moves towards equilibrium—the thermodynamic minimum of the system.

The concentrations of the different species in a library will be dependent upon the intrinsic stability of the various library members. However, the library composition is not fixed and the introduction of any external stimulus that can alter the relative stability of a library member will influence the product distribution. In particular, stabilization of a particular library member through noncovalent interactions with an added template will alter the positions of the equilibria governing the system (Figure 1.1). Such a shift in equilibrium position will ideally lead to an increased production—an "overexpression" or "amplification"—of the stabilized library member at the expense of the other species in the mixture. In this way, a library may be probed for species with affinity for a given target molecule.

While amplification of a library member in the presence of a template is usually a good indication of a favorable interaction between that species and the template, one has always to be alert to the possibility of counterintuitive "systems" behavior by the library [2]. The equilibrium distribution is determined by the sum of the total thermodynamic stabilities of all species in the library. Since all the components of a library are linked through a set of equilibria, the stabilization of one library member will be felt by the others and in some circumstances the most amplified species may not be the one that in isolation binds most strongly to the

Dynamic Combinatorial Chemistry. Edited by Joost N. H. Reek and Sijbren Otto

ISBN: 978-3-527-32122-3

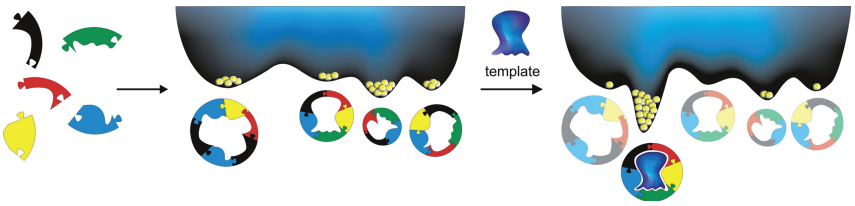


Figure 1.1 A DCL is formed from the different combinations of several building blocks. Ideally, addition to the library of a template will alter the library distribution to amplify the receptor that forms the most stable complex with the template.

target. With careful design of the experiment, however, such misleading amplifications may be minimized [2] (see Chapter 2).

Identification and synthesis of receptors for small molecules has been one of the most popular early uses for DCC (Chapter 3). However, its application now extends beyond this. DCC has been used to generate effective ligands for biomacromolecules (Chapter 5), to identify foldamers stabilized by self-recognition through intramolecular noncovalent interactions (Chapter 6), and to find stable aggregates formed due to interactions between combinations of library members [3]. It has found application in the synthesis of catalysts (Chapter 4), sensors (Chapter 7), and dynamic materials (Chapter 6). Furthermore, stabilization of components in a library need not necessarily be through interactions with a chemical template. Variation of environmental conditions, such as temperature, pH [4], light [5], and electric fields [6], or removal of solvent to induce a phase change [7–9], can be used to influence library distribution and to probe the properties of the species formed in the library.

In conventional synthesis, chemists typically aim to prepare a single target species in each reaction. Reversible reactions are frequently avoided to ensure that the intended products, once synthesized, do not revert to the starting materials or convert to different products. The formation of multiple products is viewed as undesirable, given that the target compound would inevitably be produced in lower yield and would require separation from the various side products. The formation of unexpected products is often viewed not as fortuitous, but indicative of a lack of understanding or foresight in the design of the synthesis.

In conventional combinatorial chemistry, large libraries of related compounds can be generated quickly, and then efficiently screened and tested for desirable properties [10]. In theory, if not always in practice, the larger the library generated, the higher the probability of discovering a useful compound from among the many products. DCC embraces diversity and complexity as an efficient means to discover new molecules or supramolecular assemblies with unanticipated recognition properties. While many chemists would consider a mixture of multiple constantly interconverting compounds an overwhelming mess, in DCC these "libraries" are rather seen as a complex system of compounds whose potential properties and uses are awaiting discovery. There is the prospect of discovering not only new

receptors, catalysts, inhibitors, sensors, or materials, but also hitherto unsuspected (or unexplored) interactions and systems behaviors.

1.2 History

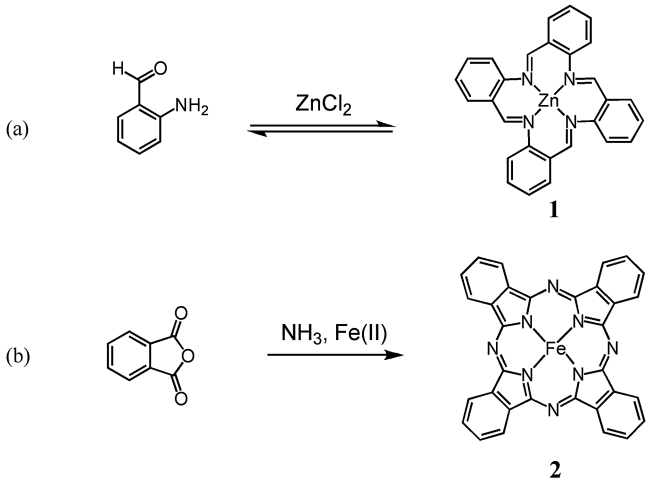
The basic principles of DCC, developed in the 1990s, stemmed from the realization that the task of constructing effective receptors capable of specific molecular recognition – a task that biological systems have accomplished only over millions of years of evolution – is very difficult to address using a straightforward synthetic design approach. A new, more efficient, and general approach was devised that captured the combinatorial, selection, and amplification elements exhibited by the mammalian immune system. The guest molecule would be allowed to select its own, most effective host from among a mixture of possible hosts. Selection from an equilibrium mixture of potential hosts would lead to a shift in the equilibrium position and amplification of the "best binder". Another attraction of this approach would be that, in principle, it minimizes synthetic effort, in that a small number of building blocks can lead to a wide range of large, complex products.

Although this concept was only recently articulated as a general approach to the synthesis of chemical species exhibiting molecular recognition capabilities, many of the principles and practices that characterize DCC had been in place for several decades. DCC may be viewed as the intersection of two pre-existing approaches to synthesis: thermodynamically controlled templated synthesis and combinatorial chemistry.

1.2.1 Thermodynamically Controlled Templated Synthesis

Thermodynamic control in organic synthesis is very familiar, for example, in the synthesis of esters, acetals, or imines. Specific product formation can be favored by shifting the equilibrium position, through the removal or addition of water, the choice of solvent, the use of excess reagents, or by controlling the temperature and pressure of the reaction. Templates may be used in thermodynamically controlled synthesis to guide the system towards the production of a desired product that "fits" the template.

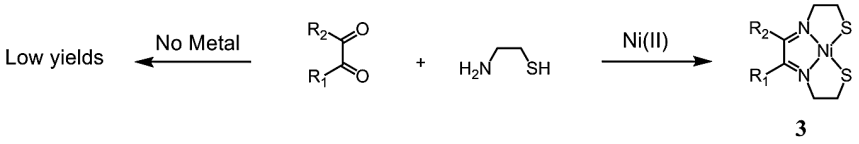
This approach can arguably be traced back to the nineteenth century, and the studies of Emil Fischer on carbohydrates and of Werner on coordination complexes. When Watson and Crick discovered the DNA double helix in 1953 they realized immediately that its replication involved a templated synthesis [11]. In retrospect, it is clear that the metal-ion-templated synthesis had been achieved as early as 1926 when Seidel reacted 2-aminobenzaldehyde with $ZnCl_2$ [12]. An imine-based macrocycle bound to zinc was formed, but was not identified until much later (Scheme 1.1a) [13]. A few years later, Fe(II) phthalocyanine was formed



Scheme 1.1 (a) Imine-based macrocycle synthesis templated by $ZnCl_2$ [13]. (b) Fe(II)-templated synthesis of a phthalocyanine [14].

through an unexpected iron-templated reaction between phthalic anhydride and ammonia (Scheme 1.1b) [14].

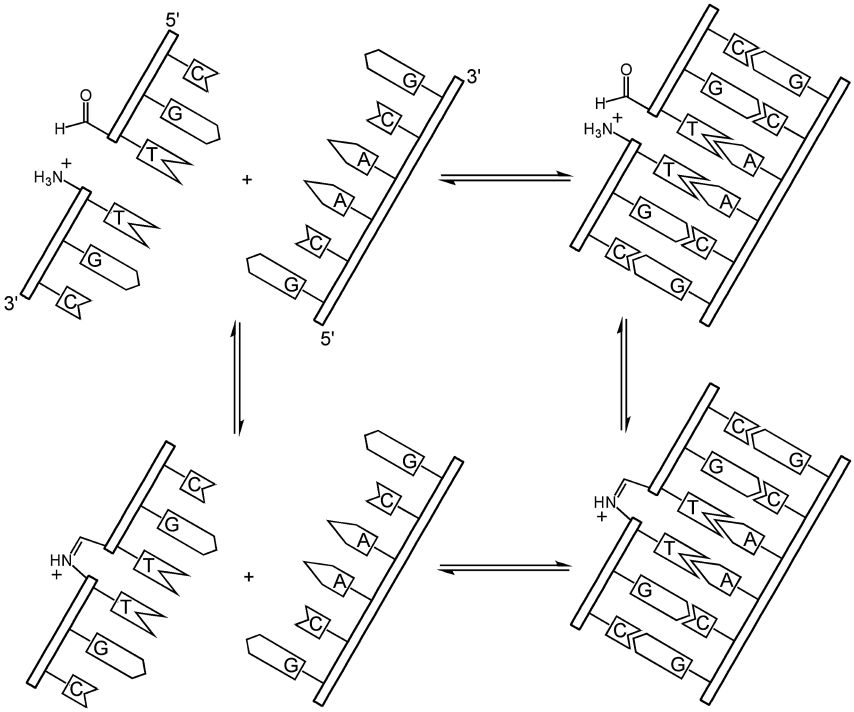
It is through the pioneering work of Busch in the 1960s that the role of templates in synthesis, both kinetically and thermodynamically controlled, was clarified and developed [15]. Busch wrote that "a chemical template organizes an assembly of atoms with respect to one or more geometric loci, in order to achieve a particular linking of atoms" [16]. Kinetic templates operate on irreversible reactions by stabilizing the transition states leading to the desired product [17]. In thermodynamic templating, the template is added to a reaction mixture under equilibrium conditions where it binds to a particular desired product and then shifts the equilibrium to favor the formation of that species. Busch's Ni(II)-templated bis-imine macrocycle **3** synthesis is probably the first published example to clearly articulate the role of a template in stabilizing a desired product from a complex equilibrating mixture (Scheme 1.2) [18].



Scheme 1.2 Synthesis of a bis-imine macrocycle **3** directed by Ni(II) templation [18].

Subsequently, thermodynamic templated syntheses developed along parallel and largely noncommunicating organic, inorganic, and biochemical tracks. A notable contribution by Goodwin and Lynn features reversible imine-mediated

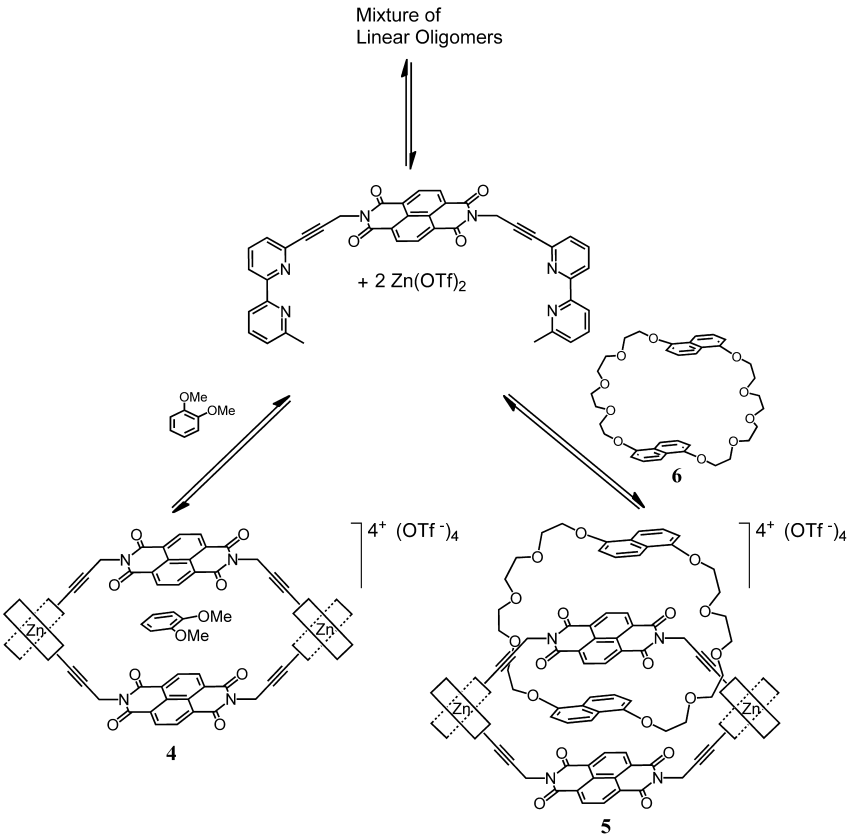
synthesis on a DNA template (Scheme 1.3) [19]. Prior attempts to exploit template-directed synthesis in polymerization reactions sought kinetic differentiation of product distribution. DNA and RNA polymerases employ reaction reversibility and sophisticated proofreading mechanisms to ensure high fidelity in template translations. In Goodwin and Lynn's approach the role of the template is to shift the equilibrium position. By controlling this equilibrium, they both demonstrated unique chemistry on a DNA template, and achieved the first chain-length and sequence-specific template-directed polymerizations.



Scheme 1.3 Thermodynamic cycle showing Goodwin and Lynn's reversible imine-mediated synthesis on a DNA template [19].

1.2.2
Early DCLs

In 1995, Hamilton *et al*. described one of the first examples of a combinatorial approach to synthetic receptors using reversible coordination around a metal ion [20]. In the same year Harding *et al*. described the guest-induced amplification of a metallo-macrocycle **4** and metallo-[2]catenane **5** from a mixture (Scheme 1.4) [20, 21]. Although not described as such, these examples employed the basic principles of DCC – template-stabilized selection of effective synthetic receptors from among an equilibrating library of potential receptors.



Scheme 1.4 An electron-rich dimethoxybenzene template was used to direct the synthesis of a naphthalenediimide-based macrocycle **4** [21]. Addition of dinaphtho-crown ether **6** led to the formation of [2]catenane **5** [22].

The first papers clearly articulating the concept of DCC appeared in the mid-1990s, the idea being conceived and developed independently in both the Sanders and Lehn groups. In the Sanders group, early experiments employed base-catalyzed transesterification to generate libraries of macrocycles formed from steroid-based building blocks [23]. A proof-of-principle study demonstrated modest amplifications of specific macrocycles in the presence of alkali metal ions [24].

Lehn developed the dynamic combinatorial approach as a result of his work on metal helicates, observing that the major product in a dynamic mixture of helicates was determined by the nature of the counterion that binds in the center of the helicates [25]. Huc and Lehn then extended their work to include templating of a ligand by a protein, describing the inhibition of carbonic anhydrase by a library of imines created *in situ* [26]. This work was preceded by a publication by Venton *et al*. who used nonspecific proteases to prepare and degrade a set of peptides

reversibly, with a view to amplifying the sequences that bound most strongly to fibrinogen [27]. In 1997, Miller *et al*. described the first dynamic combinatorial approach to DNA-binding compounds [28]. In the same year, Sasaki *et al*. published an elegant "self-adjusting" metal-centered ligand for lectins [29], and Eliseev and Nelen used light-induced alkene isomerization as a reaction to drive chemical evolution in an equilibrating mixture of simple arginine receptors [30]. The first disulfide exchange work to articulate a version of the dynamic combinatorial idea was probably that of Hioki and Still in 1998 [31], although the reversibility of thiol–disulfide exchange had been known and exploited for many years.

1.3
Exercising Control over a DCL to Influence Species Distribution

1.3.1
Selection through Molecular Recognition of an External Template

One of the most appealing applications of DCC is the possibility to determine from a complex mixture the "best binder" of a given target molecule. Upon addition of the template molecule to the library, the means of identifying an efficient binder is through its overexpression in the library. Therein the advantage of the approach is clear – not only is the desired molecule identified, but it is synthesized in preference to library members with a lesser affinity for the target molecule. In a particularly effective library, the addition of a template to the mixture may induce all the library material to convert to just one favored species.

Since the first examples of DCC appeared in the literature, external templating has been by far the most extensively developed means of directing a library's distribution. The template may be either the guest or the host molecule. In the first instance (see Chapter 3), building blocks may combine to form a receptor, often a macrocycle, that may be stabilized by binding to a small guest molecule (Figure 1.2a). Alternatively, the building blocks may come together to form a species that binds within a cavity or a ligand that stabilizes a macromolecule (Figure 1.2b). A detailed discussion of ligands for biomolecules identified using DCC can be found in Chapter 5.

1.3.2
Selection through Self-Templating

Internal templating refers to the self-selection of library members through intramolecular or intermolecular stabilizing noncovalent interactions. Intramolecular self-templating is observed when the species formed in a DCL are capable of folding upon themselves (Figure 1.2c). The library members that are best able to form favorable noncovalent interactions within themselves will be amplified in the library. DCC has therefore been used to study the folding of peptides, nucleotides, and synthetic polymers (Chapter 6). It can be used to direct the reversible

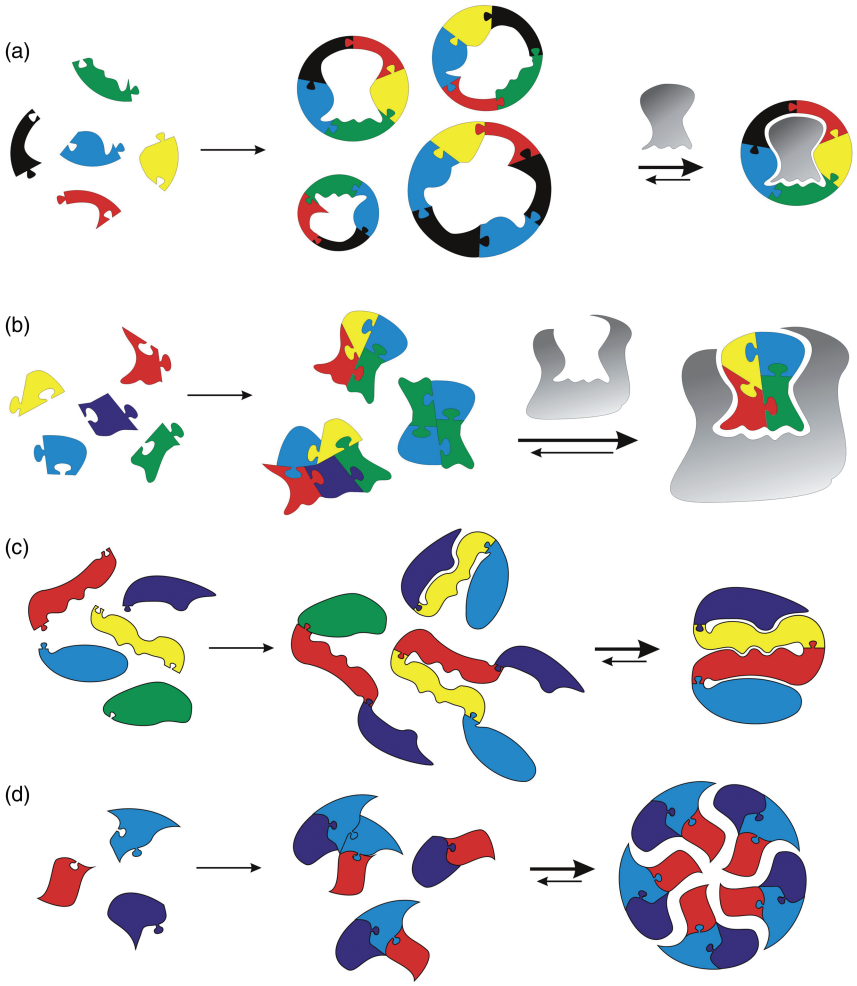
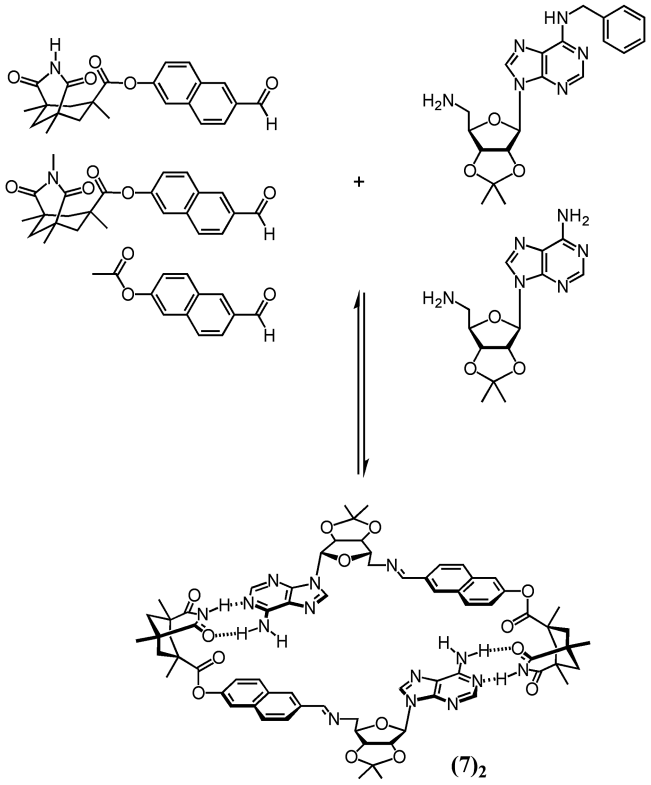


Figure 1.2 The different ways in which molecular recognition can exert control over library distribution: selection may be through external templating by an added (a) guest or (b) host molecule, or though self-templating that is either (c) intramolecular or (d) intermolecular.

synthesis of foldamers by amplifying the formation of the most stable from among a library of oligomers [32].

Selection and amplification of a molecule in a library is also possible where it is stabilized through intermolecular noncovalent interactions with one or more of the same or different library members (Figure 1.2d). Such interactions would necessarily have to be strong enough to outweigh the significant entropy cost associated with such an aggregation process. The first example of this type of system was recently published [3] by Xu and Giuseppone – a library was formed



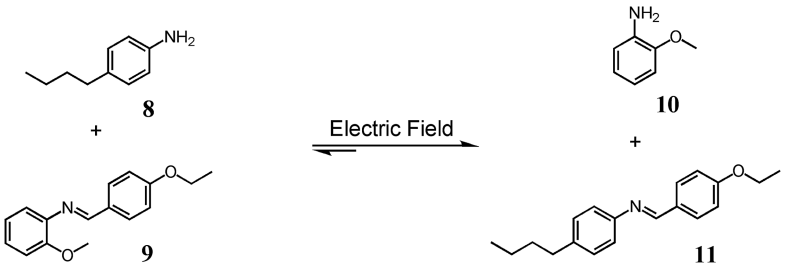
Scheme 1.5 The combination of these three aldehydes and two amines leads to the formation of a library of six imines. Imine **7**, the dominant species formed, is selected through intermolecular self-templation [3].

from the condensation of Kemp's imide-based aldehydes and adenosine-based amines (Scheme 1.5). Imine **7** was amplified from this mixture because it was capable of forming stable dimers through a complementary hydrogen bonding motif.

1.3.3
Selection Directed by External Physical Stimuli

Dynamic materials are being developed that can undergo constituent exchange, reorganization, and selection in response to external physical stimuli. In a DCL where the distribution changes upon variation of external conditions, amplification of a particular species within the library is indicative of its greater stability, relative to the other library members, when acted upon by an external physical stimulus.

Giuseppone and Lehn have recently investigated how the distribution in a DCL of imines can be directed by variation of the temperature and pH [4]. They have also shown that electric field modulation can be used to dictate component evolution in a DCL containing liquid crystals [6]. A simple library was formed from the interconversion of two imines (**9** and **11**) and two amines (**8** and **10**) (Scheme 1.6). When exposed to an electric field, imine **11**, which exhibits liquid crystalline behavior, and which coupled most to and was thus best stabilized by the electric field, was amplified. Ingerman and Waters recently reported a DCL in which irradiation with appropriate wavelengths of light allowed photochemical control over library distribution [5]. An azobenzene building block was incorporated into hydrazone-based libraries with the goal of developing macrocyclic hosts whose binding properties could be modulated by irradiation.



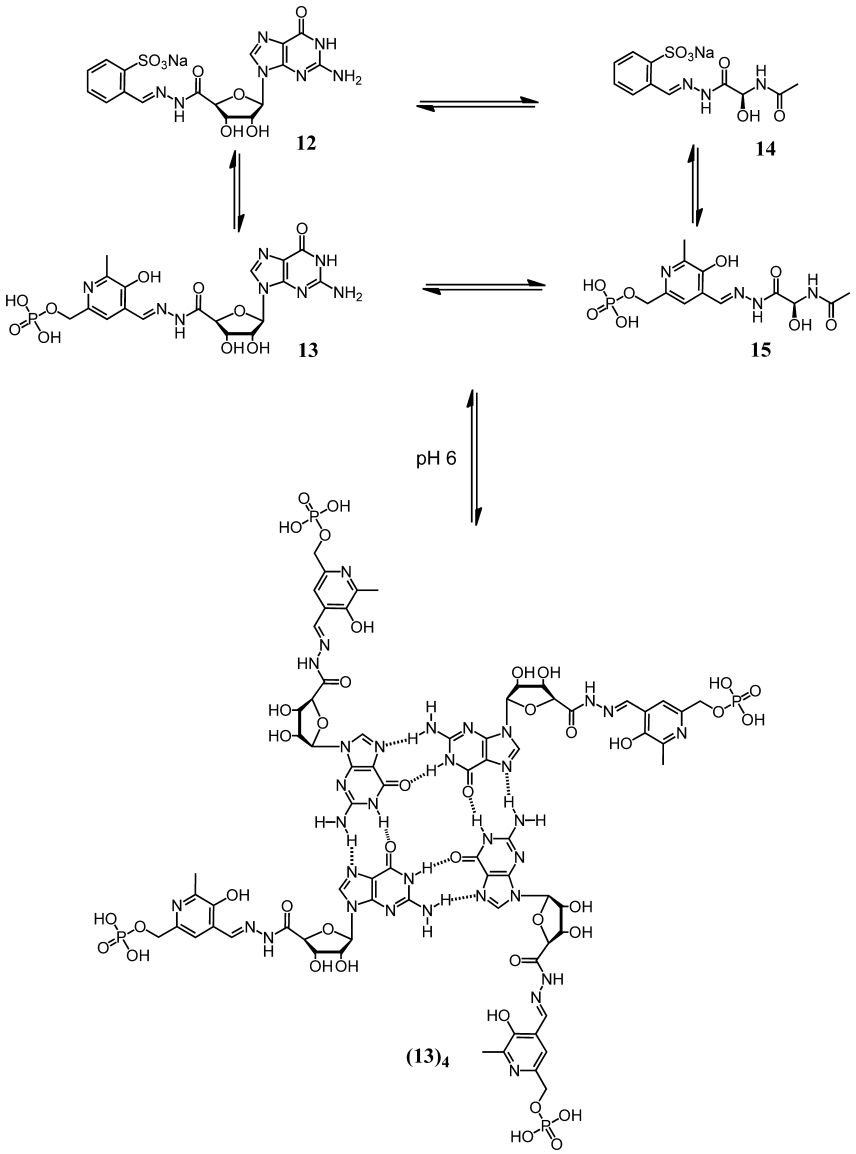
Scheme 1.6 In the presence of an electric field, the equilibrium in this small DCL shifts to increase the production of the liquid crystal **11** [6].

1.3.4
Selection Through a Stabilizing Phase Change

Component evolution in a DCL may be directed by the self-selection of library members that lead to the formation of the most highly organized and stable phase. This concept has been applied to both gelation and crystallization.

Sreenivasachary and Lehn have described a hydrazone DCL in which selection is driven by the formation of a stable gel (Scheme 1.7) [7]. Hydrazide-functionalized guanosine and serine building blocks were reacted with two different aldehyde building blocks in sodium acetate buffer at pH 6 to form a library of four interconverting hydrazones (**12–15**). Hydrazone **13**, which is capable of forming a stable gel based on the G-quartet motif, was amplified in the mixture; here, the distribution of components in the library was determined not by the relative stabilities of the individual hydrazones, but rather by the formation of the insoluble fibers that create a stable gel.

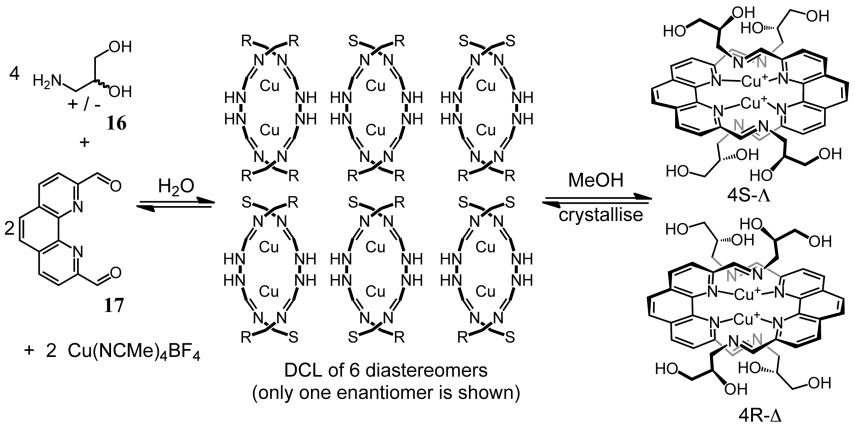
Dynamic polymers ("dynamers"), formed by linking monomers through reversible reactions, have emerged as a means to generate adaptive materials [33]. It has been possible to direct the distribution of different dynamers from within a DCL



Scheme 1.7 In this DCL, the formation of a stable gel gives rise to the selection and amplification of hydrazone **13** [7].

by altering the environmental conditions to stabilize or destabilize the mesoscopic states of the dynamers. Removal of solvent leads to preferential formation of the dynamer that gives the most ordered and stable crystalline phase [8].

In a related example, sorting of a DCL during crystallization has led to the selection of a pair of enantiomers from a complex library of diastereomers



Scheme 1.8 Selection via crystallization of a single pair of enantiomeric Cu(I) helicates from among a complex library of diastereomers [9].

(Scheme 1.8) [9]. A library of six pairs of enantiomers of different diastereomers of metal helicates was generated from the reaction of a racemic mixture of amine **16** with dialdehyde **17** in the presence of $Cu(NCMe)_4BF_4$. Imine exchange and metal–ligand exchange ensured that thermodynamic control of the library was maintained. During crystallization, a single pair of enantiomers was selected as a result of its lower solubility. The consequent continuous removal of this racemate from the solution drives the exchange of all other helicates in the solution toward this one "selected" product.

1.4 Designing a Dynamic Combinatorial System

In DCC, an element of design is sacrificed in order to efficiently obtain a diverse range of products, thus allowing for the possibility of generating unexpected molecular structures with unanticipated properties. However, this does not mean that building blocks are chosen at random. There is a broad spectrum of approaches to the synthesis of supramolecular entities spanning from very carefully designed templated thermodynamic synthesis, such as the construction of three interlocking molecular Borromean rings published by Stoddart *et al.* [34], to the mere mixing of arbitrarily chosen building blocks. DCC lies somewhere in the center of this continuum.

To set up a DCL, a reversible chemistry must be chosen and then suitable building blocks selected or synthesized. To generate a useful DCL the design of the building blocks may be very important. Although an increase in the proportion of the building blocks that have been specially designed may make the outcome of equilibration more predictable, it may also increase the probability that one or more of the library members formed will respond to external influences upon the library.

1.4.1 Building Block Design

The design of building blocks will necessarily require the incorporation of suitable functional groups at one or multiple positions that are capable of reacting reversibly when combined with other building blocks. The remainder of the molecule may then be designed to fit the purpose for which the library is intended, making sure that it does not contain functional groups that will interfere with the exchange reaction.

One of the most common design features in building blocks is the inclusion of functionalities likely to aid in molecular recognition. For building blocks designed to be used in libraries in organic solvents, the incorporation of hydrogen bond donors and acceptors could be important. In aqueous solution, motifs allowing for the possibility of forming hydrophobic pockets when combined with other building blocks might be useful. Charged building blocks may be chosen for recognition of anions or cations. Electron-deficient and electron-rich aromatics may be included where donor–acceptor interactions with an added template or between building blocks are anticipated. Where other external stimuli, such as light, temperature, and pH, are intended to direct the evolution of the library, building blocks may need to be designed such that the species they form under equilibrium conditions will respond to such stimuli.

The overall shape of the building blocks may also be chosen to suit a particular purpose. Where bifunctional building blocks capable of forming oligomers are reacted together in DCLs, it may be desirable to design them either with curved or linear structures, to encourage macrocyclization or polymerization, respectively. In the design of DCLs for the generation of receptors, the relative rigidity or flexibility of the building blocks should be considered. If the building blocks are excessively rigid, then the range of macrocycles that can form may be limited. One might expect to form a library with a narrow distribution, dominated by homo-species resulting from the self-sorting of the building blocks [35]. Rigidity may be useful in designed thermodynamic synthesis, where a single product is sought, but the same does not apply to DCC, where the aim is to form a diverse mixture of products. On the other hand, excessive flexibility is equally undesirable – too great a flexibility may allow the building blocks to collapse on themselves and form stable cyclic monomers rather than a range of higher oligomers. It appears that a balance, or a combination of rigidity and flexibility, is required to produce libraries with a broad distribution of oligomers and maximum chance of diversity.

Other considerations in the design of building block scaffolds might include the incorporation of solubilizing groups, chromophores, or other reporter groups. Analyzing the composition of a library is frequently the most challenging aspect of DCC, and therefore all building blocks should ideally have unique masses and/or spectroscopic signatures. In general, building blocks should be simple, easy, and inexpensive to synthesize, and straightforward to analyze. The idea is that

DCC should be an efficient approach to the generation of sophisticated molecular and supramolecular systems – diversity and complexity are obtained not through complicated synthesis, but through different combinations and permutation of simple building blocks linked by reversible reactions.

1.4.2 Exchange Reactions

The reactions responsible for the formation of DCLs from simple building blocks must necessarily be reversible, allowing for the exchange of building blocks between different library members. To establish a useful and efficient DCL the reaction chosen should meet several criteria.

First, the reaction must be reversible on a reasonable timescale, which implies that the forward and reverse reactions should ideally be fast. It is preferable that a large number of library members be relatively isoenergetic to avoid library mixtures in which there is a strong bias towards certain species, and a high energy cost and long equilibration time required to alter the library distribution to favor a different stabilized species. Where a library is dominated by one cyclic species, it is often a good indication that the intramolecular ring-closing reaction is exceptionally fast relative to any intermolecular reactions. Exchange, therefore, will be slow and the time required to reach equilibrium will be very long, even though the reversible reaction might be intrinsically fast.

In a true DCL, equilibration and selection need to take place simultaneously so the reaction conditions required for reversibility must also be compatible with the noncovalent interactions employed in the selection process. If basic conditions, for example, are required for exchange to take place, then certain recognition groups may be deprotonated and the building blocks negatively charged under library conditions. The reaction conditions should ideally be mild, so as not to disturb the delicate noncovalent interactions involved in molecular recognition.

Exchange reactions used in DCLs include reversible covalent reactions, metal–ligand coordination, and noncovalent interactions (in particular, hydrogen bonds). Of these three exchangeable linkage types, reversible covalent reactions have been by far the most extensively used in DCC. While the typically weaker, and more labile, hydrogen and coordinative bonds allow for fast exchange and short equilibration times, the supramolecular structures formed are inherently less stable, and more difficult to analyze and isolate.

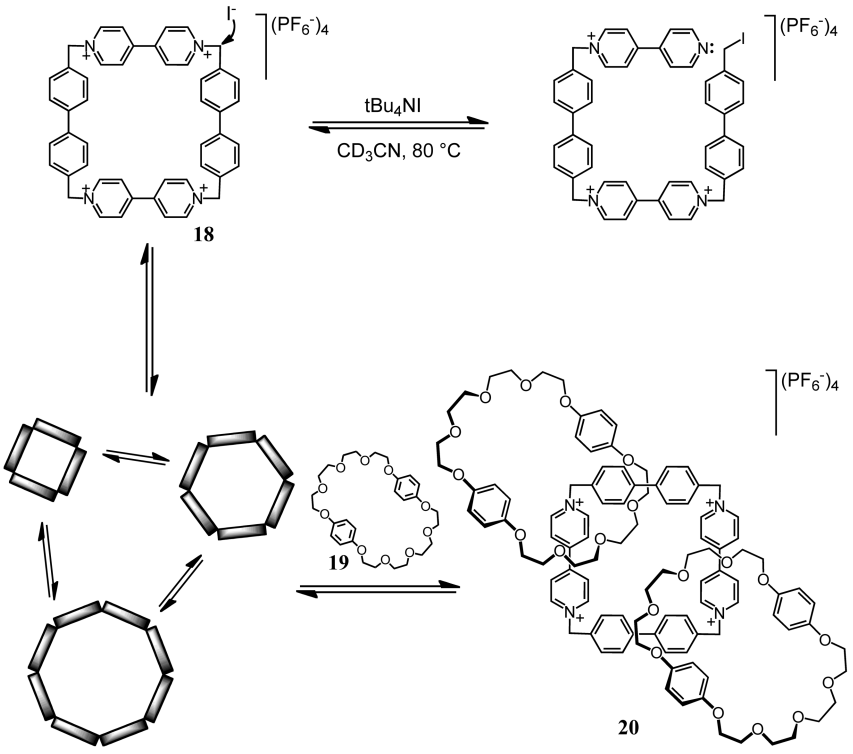
Reversible covalent reactions, although slower, give rise to more robust products. Often requiring a catalyst to ensure reversibility, such reactions are likely to be significantly slowed by removing the catalyst so that exchange may be effectively "switched off," allowing for isolation of selected library members without the complication of further exchange. However, the approach towards equilibrium requires an extremely large number of turnovers. This reduces the utility of reactions where the catalyst has a limited lifetime (e.g., alkene and alkyne metathesis) or where side-reactions occur [36].

1.4.3
Exchange Reactions Currently in Use

The exchange reactions used to date are listed below in Figure 1.3. A comprehensive review of exchange reactions used in DCC was published only recently [1(a)]. Therein the particulars of the reaction conditions required are discussed and relevant examples are provided. An overview of the most commonly used reversible chemistries will be provided in the first part of Chapter 3, discussed in the context of the development of synthetic receptors. We will therefore describe here specifically only the most recent additions to the growing repertoire of reversible covalent reactions that can be used in DCC or dynamic covalent synthesis.

1.4.3.1 Reversible Benzylic Nucleophilic Substitution

Stoddart *et al.* have recently used iodide-catalyzed reversible nucleophilic substitution in the thermodynamically controlled assembly of a donor–acceptor [3]catenane **20** (Figure 1.3l) [37]. Exposure of cyclobis-(paraquat-4,4′-biphenylene) tetrakis-hexafluorophosphate (**18**) to 2 equiv. of bis-*para*-phenylene [34]crown-10 (**19**) in the presence of tetrabutylammonium iodide in acetonitrile at 80 °C led to the formation of [3]catenane **20** in 80% yield (Scheme 1.9). The S_N2 reaction



Scheme 1.9 [3]Catenane **20** has been generated using thermodynamically controlled templated synthesis [37].

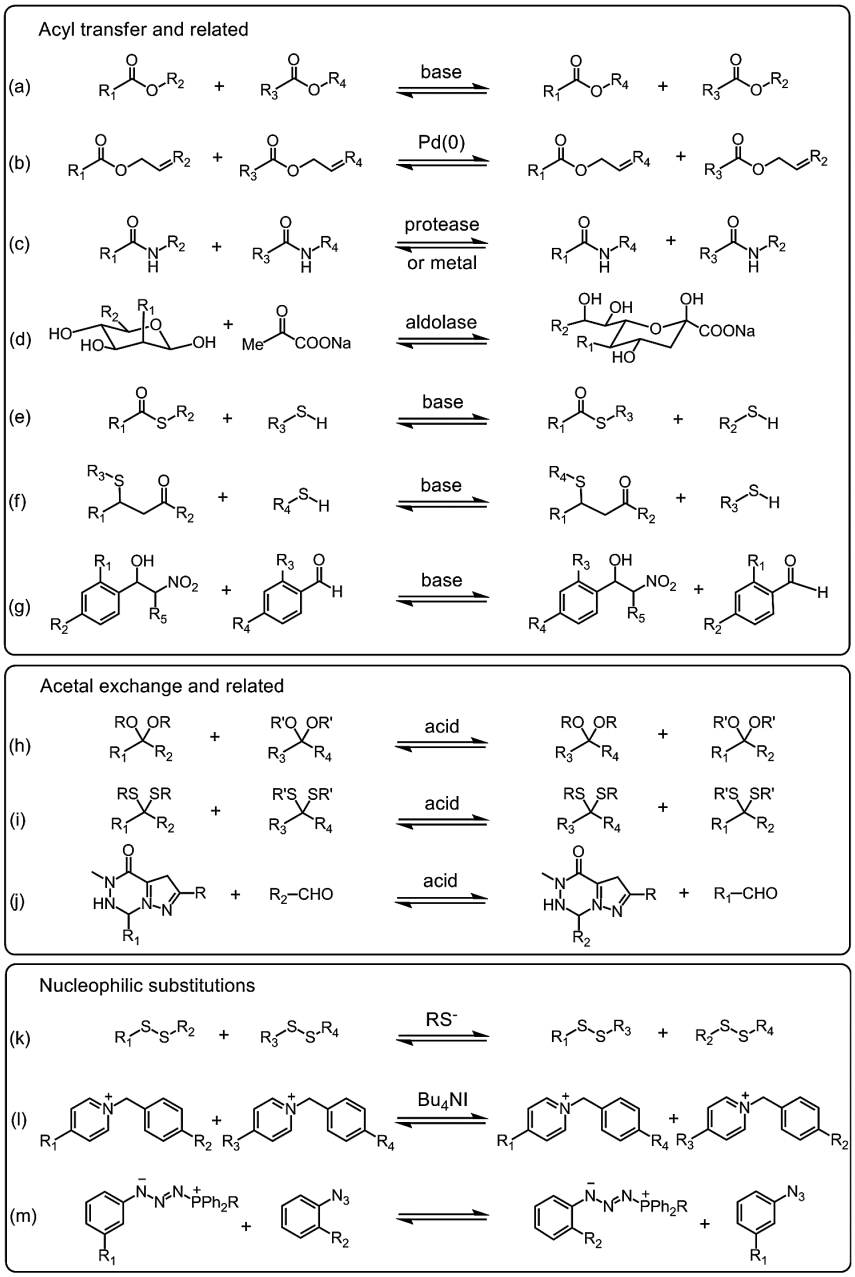


Figure 1.3 Reversible reactions used in DCLs to date: (a) transesterification, (b) transallylesterification, (c) transamidation, (d) aldol exchange, (e) transthioesterification, (f) Michael/retro-Michael reactions, (g) nitroaldol exchange, (h) acetal exchange, (i) thioacetal exchange, (j) pyrazolotriazone metathesis, (k) disulfide exchange, (l) reversible benzylic nucleophilic substitution, (m) phosphazide exchange,

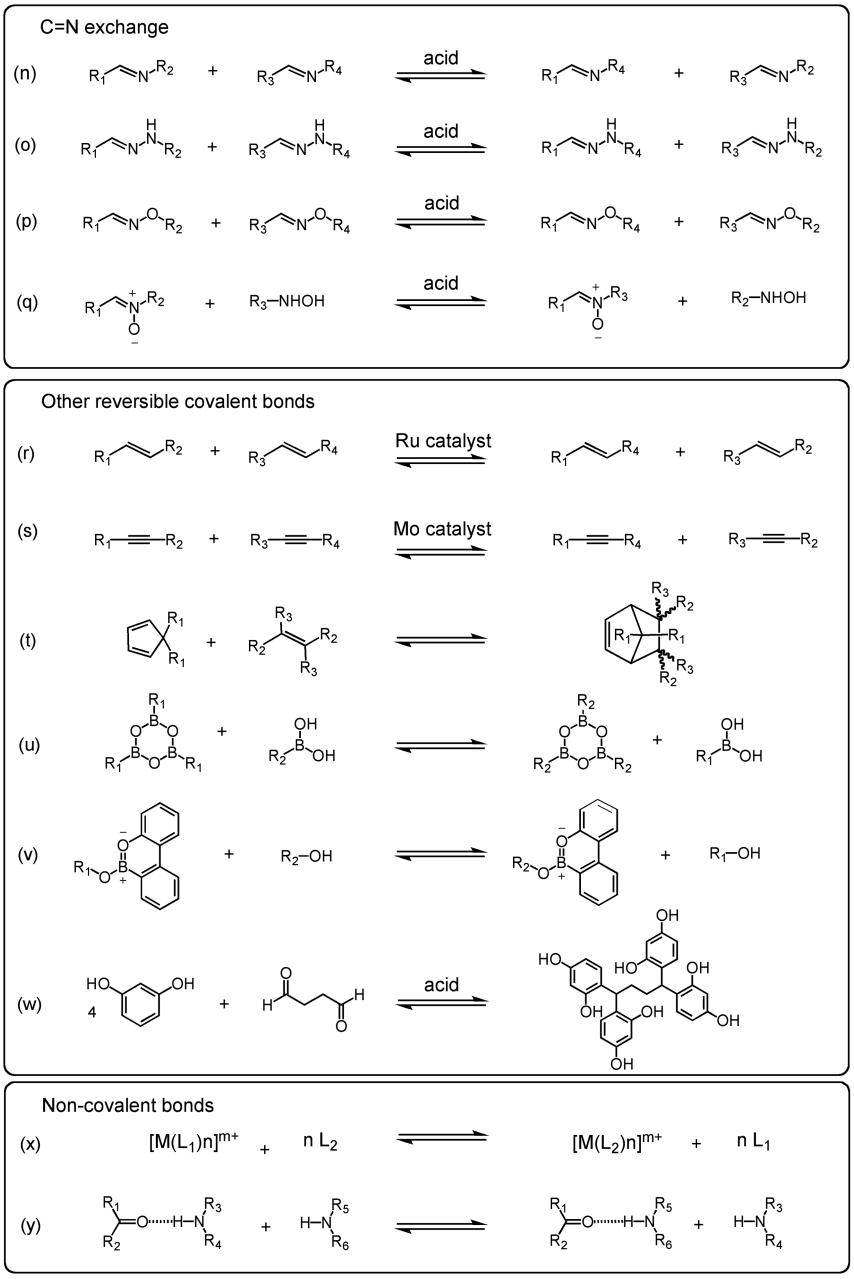
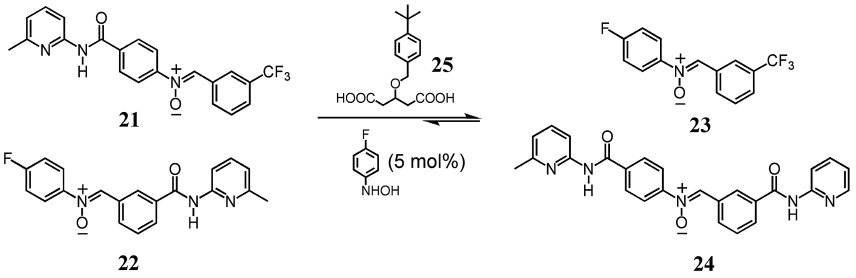


Figure 1.3 (*Continued*) (n) imine exchange, (o) hydrazone exchange, (p) oxime exchange, (q) nitrone exchange, (r) alkene metathesis, (s) alkyne metathesis, (t) Diels–Alder/retro-Diels–Alder reactions, (u) reversible boroxine formation, (v) transboroxoaromatic esterification, (w) reversible resorcinol and 1,4-butanedial condensation, (x) metal–ligand exchange, and (y) hydrogen bond exchange.

at benzylic carbons has traditionally been viewed as reversible, with the nucleophiles alternatively acting as leaving groups and vice versa. However, it is only very recently, employing tetrabutylammonium iodide as a catalyst, that the reaction reversibility has been optimized for use in dynamic covalent synthesis.

1.4.3.2 Nitrone Exchange

Diaryl nitrones undergo exchange in chloroform under acidic conditions in the presence of a catalytic amount of a hydroxylamine (Figure 1.3q) [38]. Philp *et al.* first utilized this reaction in DCC to generate a small DCL of nitrones at equilibrium after 48 h (Scheme 1.10). Selection and amplification of nitrone **24** was observed upon addition to the library of a dicarboxylic acid capable of binding to two amidopyridine recognition groups. Philp's group have further used nitrone exchange as the basis for their studies of self-templating, extrapolating upon the basic concepts of DCC to investigate replication processes [39].



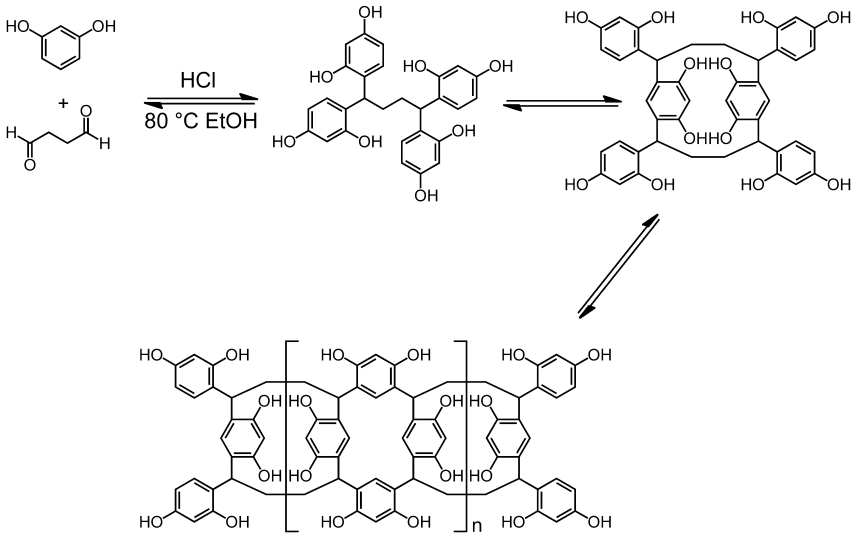
Scheme 1.10 Addition of dicarboxylic acid **25** to this small library of nitrones shifts the equilibrium to favor formation of nitrone **24** that has two amidopyridine recognition groups [38].

1.4.3.3 Reversible Nitroaldol Reaction

The reaction between nitroethane and aromatic aldehydes in the presence of triethylamine in chloroform reaches equilibrium within hours (Figure 1.3g). Selection of library members through a subsequent tandem irreversible reaction (i.e., Henry-iminolactone rearrangement) has been demonstrated [40].

1.4.3.4 Reversible Resorcinol and Alkanedial Condensation

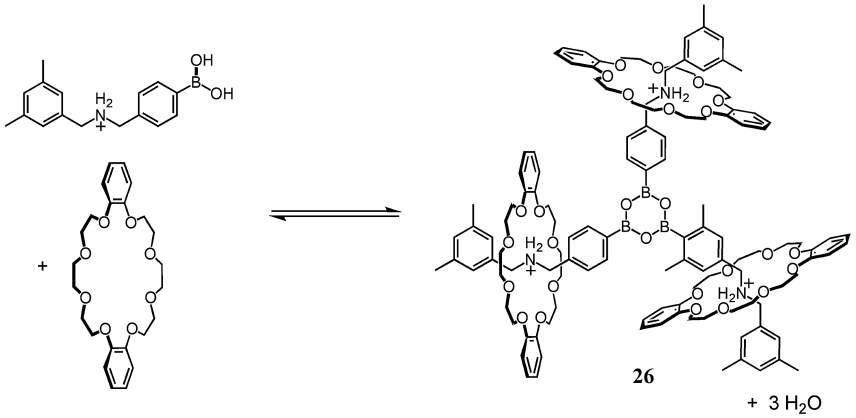
A DCL of short polymers has been generated from the condensation of resorcinol and 1,4-butanedial (Scheme 1.11) [41]. Resorcinol and 2,5-dimethoxytetrahydrofuran (3.3 equiv.) were combined in ethanol at 80 °C in the presence of HCl. Acid-catalyzed decomposition of the 2,5-dimethoxytetrahydrofuran led to the formation of 1,4-butanedial. Each aldehyde then underwent two condensation reactions with resorcinol to form ladder-like polymers containing calixarene moieties under thermodynamic control.



Scheme 1.11 A DCL of ladder-like calixarene containing polymers was generated from the reversible condensation of resorcinol and 1,4-butandial [41].

1.4.3.5 **Reversible Boroxine Formation**

Boroxine formation, through the cyclotrimerization of three boronic acid units, is another reversible reaction recently applied in dynamic covalent synthesis (Figure 1.3u). The forward reaction is entropically driven by the release of water molecules upon condensation and is favored where electron-donating groups in the *para* position are used [42]. To date, this reaction has only been used in the designed thermodynamic synthesis of a C_3-symmetric [4]rotaxane **26**, apparently under thermodynamic control (Scheme 1.12) [43]. However, it could be envisaged that

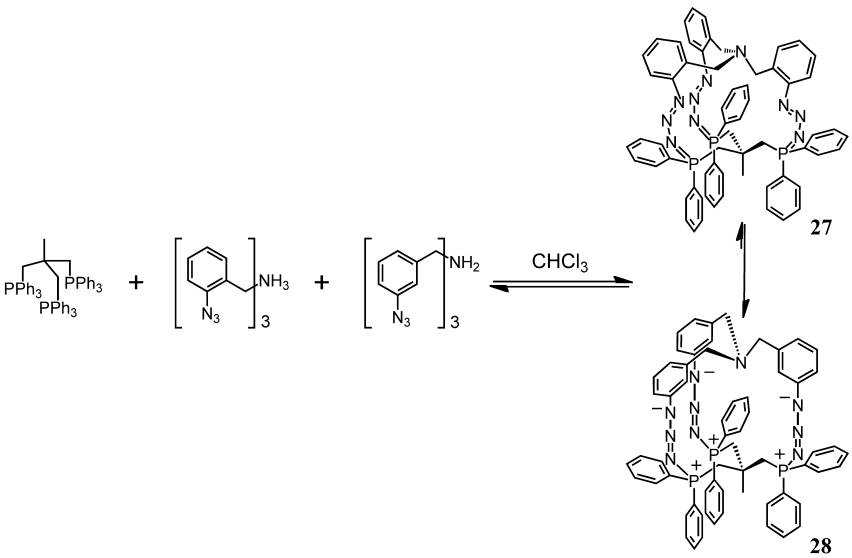


Scheme 1.12 Templated synthesis of a C_3-symmetric [4]rotaxane **26** generated through reversible boroxine formation [43].

diverse DCLs could be generated using building blocks functionalized with two or more boronic acid functional groups.

1.4.3.6 **Phosphazide Exchange**

A new reversible reaction for DCC has emerged from the synthesis of macrobicyclic tri-λ^5-phosphazides (Scheme 1.13) [44]. When carried out in chloroform, the reaction between tris-(*ortho*- or *meta*-azobenzyl)amines and triphos is dynamic and reversible. Selection of the *meta*-substituted triphosphazide from a dynamic mixture was observed as a result of greater stability of this less sterically congested species. In fact, complete triazide exchange was seen when tris-(*meta*-azobenzyl) amine was added to the *ortho*-triphosphazide **27**.



Scheme 1.13 Phosphazide exchange is rapid in chloroform: here the equilibrium favors the more stable *meta*-substituted triphosphazide **28** [44].

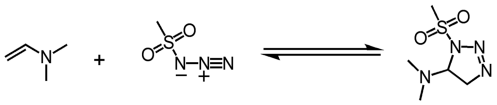
1.4.3.7 **Transboroxoaromatic Esterification**

The transesterification of boroxoaromatic esters is currently being developed for DCC. Thus far, Philp *et al.* have shown that small libraries of diesters can be generated rapidly under thermodynamic control from the reaction of boroxoaromatics with bis-alcohols (Figure 1.3v) [45]. The formation of more complex cyclic superstructures has not yet been achieved due to the low reactivity of the bifunctional boroxoaromatics tested.

1.4.3.8 **Future Reactions**

The search for other reversible reactions that would be suitable for use in DCLs is ongoing. Using computational methods, Houk *et al.* have investigated substitu-

ents effects in thermal azide 1,3-dipolar cycloadditions with a view to optimizing the reversibility of the reaction [46]. These theoretical studies have led to the preliminary prediction that the reaction between methanesulfonylazide and *N*,*N*′-dimethylvinylamine (Scheme 1.14) would be rapid and reversible at low concentrations required for DCLs. However, the instability of the enamine in water is expected to cause practical difficulties.



Scheme 1.14 The reaction between methanesulfonazide and *N*,*N*′-dimethylvinylamine is predicted to proceed rapidly and be reversible at micromolar concentrations [46].

1.5 Conclusions

In just over a decade, DCC has emerged as an efficient and powerful approach for generating and exploring systems reliant upon molecular recognition. It has been shown to offer an attractive route to the synthesis of complex molecules, with useful and unanticipated recognition properties, not easily accessible by other means. Additionally DCLs, viewed as complex networks of molecules, have provided a platform to study the emergent properties of systems. During this short period, the field has expanded to applications far beyond those originally conceived. These are explored in the following chapters.

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