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Principles of Dynamic Covalent Chemistry

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1.1 Introduction

1.1.1 What is Dynamic Covalent Chemistry?

A key feature in supramolecular chemistry is its dynamic nature. The weak non-covalent bonds utilized are labile and reversible, and supramolecular systems spontaneously organize into the thermodynamically most preferred composition. However, the same inherent instability of supramolecular assemblies precludes their use in many applications where a higher degree of robustness is required. Thus, a demand for a set of reactions that combine the dynamic properties of supramolecular chemistry with the stability and robustness of covalent bonds arose. To meet this requirement, dynamic covalent chemistry (DCvC) was developed.\(^1\) This chemistry is based on reversible covalent bonds and extends traditional supramolecular chemistry into the molecular domain. The resulting combination gives rise to constitutional dynamic chemistry (CDC), a type of chemistry where the molecular constitution of a chemical system may undergo changes over time or in response to stimuli (Figure 1.1).\(^4\) In this context, the generation of mixtures of interconverting constituents can lead to compound collections, representing a sub-field of CDC normally termed dynamic combinatorial chemistry (DCC).\(^2,5\)

Dynamic covalent chemistry is not a new concept and its origins can be traced back to the roots of chemistry.\(^6\) Fundamental discoveries in the field were made by, for example, Williamson, Schiff, and Fischer, and the concept of reversible covalent bonds was also discussed by Werner during investigations of metal–ligand coordination. An early application of the concept in template synthesis was reported in the 1920s by Seidel, where macrocyclization of 2-aminobenzaldehyde in the presence of ZnCl\(_2\) resulted in an unidentified structure that was later identified as a tetrameric macrocycle (Scheme 1.1).\(^7,8\)

The field of DCvC has, however, evolved rapidly in recent years and today reversible covalent bonds are utilized in a plethora of applications (Figure 1.2).\(^9,10\) DCvC has

*To avoid confusion with DCC, and in congruence with Zhang’s proposed nomenclature, dynamic covalent chemistry is abbreviated DCvC in this chapter.
Figure 1.1 Overview of the structural order of dynamic chemistry.

Scheme 1.1 Template-assisted macrocyclization of 2-aminobenzaldehyde under thermodynamic control.

Figure 1.2 Selected applications of dynamic covalent chemistry.
found extensive use in, for example, materials science, nanochemistry, catalysis, surface chemistry, chemical biology, and analytical sensing.\textsuperscript{[11–16]}

In this chapter, the underlying features of dynamic covalent chemistry are described, followed by a short exposé over the toolbox of reversible covalent reactions available today. Furthermore, some of the analytical challenges in DCvC are briefly highlighted.

1.1.2 Importance of Dynamic Covalent Chemistry

Dynamic covalent bonds are ubiquitous in nature, and they are continuously being utilized in biotic settings to provide a wide range of functions. For example, reversible disulfide chemistry controls protein folding and thus the self-assembly of polypeptides into ternary structures, dynamic imines are integral for human vision, reversible thioesters are key players in our metabolic pathways, and dynamic covalent enone chemistry is a reason why red peppers are so pungent.\textsuperscript{[17]}

Furthermore, DCvC provides an entry into the design of complex systems capable of continuous adaptation and evolution. Creating function by design is a central objective in chemistry, and dynamic covalent bonds provide access to systems capable of self-sorting, replication, adaptation towards selection pressures, self-healing, and the construction of highly complex molecular architectures. Some macrocyclic/cage molecules synthesized through DCvC approaches are displayed in Figure 1.3. The Solomon link (left), prism (middle), and nanocapsule (right) all represent structures that would be difficult to access without DCvC.\textsuperscript{[18–20]}

Since dynamic covalent chemistry operates under thermodynamic control, it allows a system of components (building blocks) and/or constituents (products) to settle into its thermodynamically most favorable state. Thus, the information stored in the molecular components of a system can be expressed with high precision and a high degree of “proof-reading”, giving access to the optimal molecular architectures for a given setting. In comparison with “static”, non-dynamic chemistry, DCvC thus relies on the inherent molecular information in the system. Since any constituent created during a synthesis utilizing reversible covalent bonds is eventually reprocessed, DCvC acts as a sort of error-correction, where non-optimal intermediates are recycled to form the thermodynamically more stable products.

1.1.3 Basic Concepts

Large dynamic systems (Figure 1.4) of interconverting molecular entities can be generated using DCvC. These systems undergo continuous exchange towards an equilibrium point through the information contained in either the molecules themselves or their surroundings.

As mentioned, when the intrinsic dynamic nature of CDC is applied to large systems with collections of molecular entities, dynamic (DCLs) or virtual combinatorial libraries (VCLs) can be created, the latter representing situations where constituents remain unexpressed in the absence of stabilizing entities.\textsuperscript{[21–23]}

A dynamic covalent bond is reversible and can be broken and reformed to eventually reach a thermodynamic equilibrium. Once this has been established, the molecular status quo can be disturbed if the system is perturbed by stimuli. For example, the constitution of dynamic systems can respond to changes in chemical environment (complexing entities, etc.) or physical conditions (temperature, mechanical stress,
Figure 1.3 Examples of complex macrocyclic/cage structures created through dynamic covalent chemistry.
1.2 The Dynamic Covalent Bond

1.2.1 Requirements for Dynamic Covalent Bonds

The most important criteria for dynamic covalent bonds are the covalent nature and the bond strengths. For some systems, a lifetime of each bond in the range $1 \text{ ms} < \tau < 1 \text{ min}$ has been proposed to yield connections that are stable and detectable with most analytical methods, yet dynamic enough to allow swift adaptation. This translates into equilibrium times in the order of hours to days for large dynamic systems. The upper limit of the equilibration time for a DCvC application is also related to the degradation
stability of the components and constituents in the system, as equilibrium must be attained before the system starts degrading.

As covalent connections are intrinsically more stable than supramolecular interactions, dynamic covalent bonds are typically much more robust but also slower to exchange than the corresponding supramolecular interactions. Thus, most dynamic covalent bonds require some type of catalysis in order to promote exchange (discussed further in section 1.2.2).

For dynamic covalent bonds, mild reaction conditions are beneficial for preserving the integrity of the bond and to maintain delicate non-covalent interactions of interest in the system. The reactions should also be compatible with the application of interest, and resistance to moisture and oxygen is of general importance. For biological applications, a dynamic covalent bond should exchange readily in water or water/organic solvent mixtures, although only a few bonds obeying such criteria have been discovered. Note that a tradeoff between equilibration rates and stability is often observed, with more reactive dynamic covalent bonds leading to lower system stabilities and more difficult analyses.

1.2.2 Catalysis of Exchange

The majority of the dynamic covalent bonds in use today require catalysis to facilitate equilibration. Although this introduces additional operations and increases the complexity of the systems, it also provides several benefits. Primarily, catalysis allows control of the system's progress towards the thermodynamic equilibrium. Manipulations of the catalyst can, for example, be used to halt equilibration prior to analysis or toggle exchange on or off if such switchability is important for system function (see section 1.2.3). Ideally, a catalyst should only modulate the system exchange rate and not the component distribution, but high catalyst loadings can lead to altered equilibrium positions due to complexation effects. Although the energetics of dynamic systems is governed by many response factors, it is preferred to work with lower catalyst concentrations where the catalyst acts fully “innocent”.

The catalyst activity and turnover is of critical importance in DCvC applications. The catalyst needs to remain active over many cycles, and a catalyst that is easily deactivated can lead to a situation where the component distribution remains static as a result of catalyst degradation rather than system equilibration. For this reason, it is often necessary to probe if equilibrium has been reached (see section 1.2.5) when working with dynamic bond exchange reactions that require sensitive catalysts.

A widespread selection of bond exchange catalysts has been developed for DCvC purposes, ranging from buffered acid or base solutions to complex catalysts assembled through multistep syntheses. Progress has also been made in the use of immobilized catalysts, for example with solid-supported enzymes or Grubbs metathesis catalysts.

1.2.3 Halting Equilibration

“Freezing” of the equilibration process is commonly desired in order to facilitate analysis of the systems. Dynamic equilibration can, for example, be halted by temperature changes, removal of light input or catalyst, or changes in pH. For some bonds, such as imines or hemithioacetals, irreversible derivatization is required to fully “freeze” the equilibrium. In such a case, the freezing reaction needs to be very rapid in relation to
the dynamic exchange reaction, lest the system equilibrates during derivatization. For imine bonds, some ways to freeze an equilibrium without scrambling are highlighted in Scheme 1.2. Reduction of imines to amines with no formation of the scrambling products can be completed with NaBH$_4$ in less than 1 s under certain conditions.$^{[27]}$ Also, other derivation reactions such as the Ugi reaction with isocyanides to create Ugi adducts have been used to halt dynamic equilibration.$^{[28]}

### 1.2.4 Exchange Symmetry

A key feature of dynamic covalent bonds is the bond exchange symmetry. Three main categories of symmetry classes can be discerned: symmetric, unsymmetric, and trans-symmetric bonds (Figure 1.6). Symmetric exchange indicates that both exchange partners undergo interchange through the same functional group, while unsymmetric exchange means that two different types of functional groups build up the dynamic covalent bond. The latter thus leads to directionality of the bond type. Trans-symmetric exchange represents a combination of both exchange modes, where two connected reversible reactions work in concert so that a functional group in an unsymmetric reaction is reversibly transformed into the other.$^{[29]}

The exchange symmetry of the bonds has implications for the complexity of dynamic systems. For symmetric connections, there is full symmetry in the exchanging bond, no directionality exists, and the combinations R–R′ and R′–R are mutually commutative. Self-exchange is thus always occurring, as well as oligomerization if multidentate building blocks are used. For unsymmetric exchange, the two functional groups constituting the exchanging reaction are different and self-inert. The advantage is that one can introduce complementary functionalities on each building block. By varying the substituents on one of the functional exchanging groups while keeping the other constant, screening towards cooperativity or optimizing ligand scaffolds becomes more straightforward. On the other hand, it is harder to access all compound combinations within the system.

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**Scheme 1.2** Methods to freeze imine systems by reduction or derivatization to Ugi adducts.

**Figure 1.6** Examples of common dynamic covalent bonds within each symmetry class.
with unsymmetrical exchange, limiting the structural diversity. This limitation is, however, overcome with trans-symmetric connections, where the directionality of the linkage can be reversed, resulting in higher complexity.

### 1.2.5 Methods to Confirm Reversibility

Once a dynamic covalent system has been generated, there is usually a need to confirm that equilibrium is reached. Two methods, both illustrated in Figure 1.7, are commonly employed. The first method is termed dual entry-point analysis. Here, a dynamic system is being generated from two different systemic starting compositions while maintaining the overall ratio of the building blocks. Pathway-independence is the defining characteristic of a system at equilibrium. Thus, if the same component distribution is obtained regardless of entry point, it provides evidence that the system is under thermodynamic control. This type of test constitutes the most robust and well-utilized application for testing new dynamic systems and dynamic covalent bonds.

Another useful way to probe equilibration is the stationary state perturbation method. Here, an initial dynamic system is generated under the conditions of interest and allowed to evolve until a point is reached where the system composition no longer changes. Thereafter, another exchange partner is added and the system is again allowed to settle into equilibrium. If the new partner has been incorporated into the dynamic system and the initial component distribution has changed, it provides a good indication that the system originally was at equilibrium. For practical purposes, a large excess (typically 5–10 equivalents) of the perturbing compound is usually added so that effects are more clear-cut and easily interpreted. This methodology is advantageous when acquisition of compounds from both “directions” of a dynamic system is difficult (i.e., if one or more of the necessary molecules are commercially unavailable, expensive or difficult to handle).

Finally, it can also be mentioned that a change in the physical properties of the system (i.e., temperature, solvent, concentration, pressure, etc.) commonly produces an equilibrium response, which in specialized applications can be used to test whether a given system is at equilibrium.

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**Figure 1.7** Methods to probe if equilibrium has been reached.
1.3 Dynamic Covalent Reactions

The following sections will focus on expanding the theory of dynamic covalent bonds into more concrete examples. These include descriptions of most of the reversible covalent reactions, along with their characteristics.

1.3.1 Dynamic Polar Reactions

A majority of all reversible covalent bonds belong to the class of dynamic polar reactions, which means they pass through charged reactive intermediates during the exchange process. The following reactions are sorted by the main type of bond that is formed or broken during the exchange process.

1.3.1.1 C–N Bonds

The most well-utilized family of bonds in DCvC is C–N bonds. A summary of the available C–N bond exchange reactions can be found in Figures 1.8 to 1.12.

The most prominent example of a reversible C–N bond is the imine, the most extensively used dynamic covalent bond since the inception of DCvC. Dynamic imines have been applied in a remarkable variety of applications, including formation of complex molecular architectures, self-sorting systems, switches and molecular motors.[30] Imines are formed through condensation of the respective aldehyde and amine. Exchange occurs either through a hydrolysis/recondensation pathway or, if water is unavailable, through so-called transimination or imine metathesis mechanisms (Figure 1.8a–c). The exchange mechanisms have been studied in great detail and are discussed in depth in a recent review.[31] Exchange of imines occurs under neutral conditions without additives, but to accelerate the equilibration process one can use Brønsted acid, Lewis acid or nucleophilic catalysis.

Lewis acid activation of imines has been known for decades.[32] The transimination pathway have also been studied in detail by Lehn and coworkers, who discovered that the Lewis acid Sc(OTf)₃ is a highly efficient transimination catalyst.[24] It was also demonstrated that the equilibrium composition of the system depends on the basicity of the amine, with the most basic amine forming the most stable imine. Using amines of similar basicity resulted in the highest equilibration rates. Furthermore, it was demonstrated that Lewis acids were more efficient catalysts than Brønsted acids due to a lower degree of deactivation of the nucleophile and catalyst. The last type of imine exchange acceleration is through nucleophilic catalysis with primary amines, shifting the imine exchange reaction to a transimination type mechanism.[33]

\[ \text{C-N exchange with imines} \]

(a) Imine formation/exchange

\[ \text{R}_1\text{NH}_2 + \text{R}_2\text{CHO} \rightleftharpoons \text{R}_1\text{N} = \text{R}_2 + \text{H}_2\text{O} \]

(b) Transimination

\[ \text{R}_1\text{N} = \text{R}_2 + \text{H}_2\text{NR}_1 \rightleftharpoons \text{R}_1\text{N} = \text{R}_1 + \text{H}_2\text{NR}_2 \]

(c) Imine metathesis

\[ \text{R}_1\text{N} = \text{R}_2 + \text{R}_2\text{N} = \text{R}_1 \rightleftharpoons \text{R}_1\text{N} = \text{R}_1 + \text{R}_2\text{N} = \text{R}_2 \]

Figure 1.8 C–N bond formation by reversible exchange of imines.
Beside the aldehyde and amine components, there are several intermediates involved in imine exchange. Due to their low stability, they can be considered virtual constituents of a system. Labile intermediates like hemi-aminals can only be stabilized through unusual measures, such as complexation inside a synthetic cavitand. An example of reversible hemiaminal and more stable aminal constructs (Figure 1.9a), stabilized by \textit{N}-methyl pyrrolidone, have been demonstrated in dynamic covalent networks formed from diamines and formaldehyde. Due to the reversible nature of this reaction, the polymeric networks formed are recyclable and have self-healing properties, while maintaining high rigidity.

A second type of intermediates from imine formation are \(\beta\)-amino-enones (Figure 1.9b). The presence of the electron-withdrawing keto fragment makes it possible for the molecule to tautomerize to form an imine/iminium ion. This iminium ion undergoes reversible exchange with other amines. Similar exchange has also been shown previously with iminium ions as electron-withdrawing facilitator. In both cases, exchange could be achieved in the absence of catalysts and can even be run at near physiological conditions.

Recently, imine rearrangement of \(\alpha\)-acidic imines was shown to be fully reversible (Figure 1.9c). In the presence of a quinuclidine catalyst, an “allylic”-type rearrangement takes place. This exchange reaction effectively shifts around carbonyl groups of aldehydes with amine groups of benzylic amines, increasing the dimensions of standard imine systems when coupled to a secondary dynamic reaction such as transimination.

Furthermore, \(C = N\) bond exchange reactions aside from normal imines have seen extensive use. The most common alternative \(C = N\) exchange reactions are summarized in Figure 1.10, each utilizing \(N\)- or \(O\)-substituted amines as nucleophiles. Due to the presence of free electron pairs on the adjacent atom to the reactive nitrogen, these molecules have a higher nucleophilic character. This also increases the stability of the formed imine bond, due to the reduced electrophilicity.

Uncharged hydrazones, acylhydrazones and oximes (Figure 1.10a–c) have been studied extensively due to their compatibility with biological systems. However, the enhanced stability leads to slow exchange kinetics. In comparison to imines, acylhydrazones and especially oximes are very stable and require efficient catalysis for exchange to occur. Oximes can be formed using aniline catalyst, which works most effectively at slightly acidic conditions (pH = 4.5) to protonate the intermediate aniline-derived imine (Scheme 1.3).

For hydrazones and acylhydrazones, a decrease in stability is observed compared to oximes, making exchange more straightforward. For hydrazone exchange, it has been
shown that strong acid catalysis results in decomposition products, but efficient exchange can be obtained using Lewis acid catalyst with loadings as low as 1%.\(^{[41]}\) Due to its resemblance to a peptide bond, the acylhydrazone moiety has sometimes been referred to as a “dynamic peptide” and research has focused on improving the biological compatibility of the exchange process. The dynamic system can easily be frozen by pH modulation and, similar to oximes, exchange can be accelerated using aniline catalysis.\(^{[42]}\) This procedure later was made more compatible with biological conditions by making exchange available at pH values as high as 6.\(^{[43]}\)

Nitrones are the least studied reversible C = N bonds (Figure 1.10d). Their exchange can be directly facilitated using a combination of nucleophilic and Brønsted acid catalysis.\(^{[44]}\) Unlike all the other imine type bonds, the nitrone exchange equilibrium seems to be insensitive to the concentration of acid catalyst utilized.

Besides imine-type exchange, other reversible C–N bonds have been designed. The amide bond (Figure 1.12a) is of high biological importance, and dynamic versions of this connection are thus highly desirable. Efficient exchange of amides could lead to discovery of important applications for dynamic polymers, drug discovery and many other areas. However, the amide bond is chemically robust and requires harsh conditions or specific enzymes to break up. One way to facilitate transamidation is using metal catalysts to activate secondary amides, shown using Fe(III) salts and Al\(_2\)(NMe\(_2\))\(_6\).\(^{[45,46]}\)

### Imine exchange with α-effect nucleophiles

(a) Oxime ligation

\[
\text{H}_2\text{N}^+\text{O}^-\text{R}_1 + \text{R}_2\text{H} \rightleftharpoons \text{R}_2\text{N}=\text{O}^-\text{R}_1 + \text{H}_2\text{O}
\]

(b) Hydrazine formation

\[
\text{H}_2\text{N}^+\text{H}^-\text{R}_1 + \text{R}_2\text{H} \rightleftharpoons \text{R}_2\text{N}^-\text{H}^-\text{R}_1 + \text{H}_2\text{O}
\]

(c) Acylhydrazone formation

\[
\text{H}_2\text{N}^+\text{O}^-\text{R}_1 + \text{R}_2\text{H} \rightleftharpoons \text{R}_2\text{N}=\text{O}^-\text{R}_1 + \text{H}_2\text{O}
\]

(d) Nitro oxide exchange

\[
\text{R}_1\text{N}=\text{O}^-\text{R}_2 + \text{R}_1\text{N}^-\text{OH} \rightleftharpoons \text{R}_1\text{N}=\text{O}^-\text{R}_1 + \text{R}_2\text{N}^-\text{OH}
\]

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**Figure 1.10** Imine-type bonds with different nucleophiles.
However, both of these procedures require elevated temperatures and organic solvents, making them incompatible with biological systems. Zr(NMe)\textsubscript{4} has also been used, enabling exchange of tertiary amides in organic solvents under ambient conditions.\cite{47} Exchange of tertiary amides is, however, more straightforward, circumventing deprotonation of the otherwise relatively acidic amide protons. This was also used in a method related to native chemical ligation, where efficient amide exchange in peptides was demonstrated.\cite{48} Introduction of an N-(methyl)cysteine residue in the peptide chain shifted the reaction mechanism from intermolecular transamidation to intramolecular amide-thioester exchange (Figure 1.11).

Ureas are structurally related to amides but have been shown to undergo dynamic exchange via the isocyanate (Figure 1.12b).\cite{49} Destabilization of the urea bond by introduction of bulky substituents on the nitrogen facilitated the dissociation/recombination procedure, and the exchange rate and the equilibrium constant could easily be controlled by changing the size of the substituent (Scheme 1.4). Bulkier substituents favored the formation of the isocyanate, while less bulky substituents led to favored urea formation.

The last reversible C–N bond type discussed here is reversible nucleophilic substitution, typically at quaternary nitrogen centres (Figure 1.12c). It has, for example, been shown that paraquat-based macrocycles undergo reversible ring opening and closing under catalysis with iodide ions, allowing efficient access to catenane-type structures.\cite{50,51}

### 1.3.1.2 C–C Bonds

Formation of carbon–carbon bonds is the core of organic chemistry and reversible polar C–C single bond exchange has thus been studied extensively. A summary of the available reactions can be found in Figures 1.13 to 1.16.

A classical reversible C–C bond formation is the aldol reaction (Figure 1.13a). This reaction has not found much application in DCvC, mainly because of challenges with side reactions and finding suitable catalysts. An example of reversible aldol exchange was, however, carried out under enzyme catalysis with N-acetylneuraminic acid aldolase to facilitate exchange between a variety of hexoses and sodium pyruvate.\cite{52} Another example of aldol exchange used a combination of Brønsted base and Lewis acid catalysis, utilizing triazabicyclo[4.4.0]dec-5-ene and Al\textsubscript{2}O\textsubscript{3}, which resulted in relatively rapid formation of aldol products in both aqueous and apolar aprotic conditions.\cite{53} When extending this catalytic system to a full system, an excess of ketone was necessary to facilitate exchange.

In the nitroaldol- (Henry) reaction, nitroalkanes are used as nucleophiles (Figure 1.13b). In contrast to the aldol reaction, this system readily undergoes dynamic exchange under a variety of conditions.\cite{54} A stereocenter is also formed during the addition step, generating an additional level of structural information that can be selectively interpreted or resolved in a selection step.\cite{55}

Cyanohydrins are highly important compounds in both biochemistry and organic synthesis due to their versatility as synthetic intermediates. Cyanation of aldehydes was found to be readily reversible in the presence of a base catalyst, and the exchange process was biocompatible and rapid (Figure 1.13c). Another dynamic C–C bond formation based on cyanide addition is the Strecker reaction, where a cyanide ion adds to an in situ formed imine, yielding an \(\alpha\)-amino nitrile (Figure 1.13d). The dynamic behavior of this three-component reaction has been studied extensively,\cite{56,57} where the cyanation
Figure 1.11 Amide exchange proceeding through intramolecular thioester exchange.
**Scheme 1.4** Tuning of equilibrium position in urea–isocyanate equilibrium by changing the steric bulk of substituents.

**Figure 1.12** Other C–N bond formation reactions.

**Carbon nucleophile additions to carbonyls**

(a) **Aldol reaction**

\[
\text{RC} = \text{O} + \text{RC} = \text{O} \rightleftharpoons \text{RC} = \text{O} - \text{O} \text{H}
\]

(b) **Nitroaldol reaction**

\[
\text{RCH} = \text{O} + \text{NO}_2 \rightleftharpoons \text{RCH} = \text{O} - \text{NO}_2
\]

(c) **Cyanohydrin formation**

\[
\text{RCH} = \text{O} + \text{HCN} \rightleftharpoons \text{RCH} = \text{O} - \text{HN}
\]

(d) **Strecker reaction**

\[
\text{R} - \text{CN} + \text{R}_2 \text{NH}_2 + \text{HCN} \rightleftharpoons \text{R} - \text{CN} + \text{HCN} - \text{H}_2 \text{O}
\]

(e) **Knoevenagel reaction**

\[
\text{RCH} = \text{O} + \text{NC} - \text{CN} \rightleftharpoons \text{RCH} = \text{O} - \text{NC} - \text{CN} - \text{H}_2 \text{O}
\]

**Figure 1.13** C–C bond formation by nucleophilic addition of carbon nucleophiles.
1.3 Dynamic Covalent Reactions

was found to be reversibly catalyzed by Lewis acids like zinc halides. Zinc bromide proved especially efficient in the overall, three-component Strecker reaction, catalyzing not only the cyanide exchange, but also the transamination step.

Recently, this type of chemistry has been expanded to include Knoevenagel-type products (Figure 1.13e), which exchange readily in the presence of water under catalysis by secondary amines such as L-proline. This type of exchange was also compatible with imine chemistry, leading to connected dynamic systems where several different equilibria operated simultaneously.[58,59]

A second group of C–C bond-forming reactions consists of carbene-based reactions. N-heterocyclic carbenes (NHCs) exist as both monomers and dimers (see Figure 1.14a), and the equilibrium position depends on the nature of the heterocyclic ring and the size of the substituents. It has, for example, been demonstrated that a dicarbene structure can form a mixture of polymers and free carbenes, which changes composition in a reversible fashion based on the amount of heat or chain transfer agent applied.[60] Reversible NHC coupling to isothiocyanates was also shown (Figure 1.14b).[61] This reaction favors the formation of the adduct, but at elevated temperatures the NHC is reversibly released.

Reversible C–C bond formations based on electrophilic aromatic substitutions have furthermore been developed (Figure 1.15). It was discovered that when a Lewis acid catalyzed Friedel–Crafts alkylation between a symmetrical bis-nucleophilic and a symmetrical bis-electrophilic species was performed, a macrocycle consisting of an odd number of starting materials was obtained. Since the starting materials are symmetrical, this phenomenon is only explicable if the reaction is reversible.[62] A variety of Lewis acids like ZnCl₂, FeCl₃, BF₃•OEt₂ and AlCl₃ proved capable of facilitating this exchange at room temperature, with AlCl₃ being the most efficient. Another electrophilic aromatic substitution found to be reversible is the condensation of formaldehyde with electron-rich aromatic rings (Figure 1.15b). It thus was shown that calix[8]arenes undergo reorganization to calix[4]arenes under strongly basic conditions at elevated temperatures.[63] Similarly, it was also demonstrated that reversibility for this reaction can be attained using elevated temperatures and strongly acidic conditions.[64]

The most useful dynamic covalent C–C bond-forming reaction is probably olefin metathesis (Figure 1.16a). Although principally not polar in nature, this reaction allows for exchange of the substituents on a C=C double bond in the presence of a metal catalyst. Proceeding through sequential [2 + 2] cycloadditions via metallacyclic
intermediates, the overall reversibility of the reaction is well known. The reaction has been used extensively, for example, in dynamic combinatorial applications, and for the construction of shape-persistent macrocycles under thermodynamic control.\[26, 65–68\] A wide array of catalysts for the transformation is available, with the Grubbs second-generation catalyst and the Grubbs–Hoveyda catalyst (Figure 1.17) being the most prominent.\[69\]

Olefin metathesis has advantages such as mild reaction conditions, wide functional group tolerance, commercially available catalysts, fast exchange kinetics, and orthogonal reactivity relative to many other dynamic covalent bonds. Most common functionalities can operate simultaneously with olefin metathesis, although strongly coordinating compounds such as amines, nitriles or phosphines sometimes poison the catalyst. Other pitfalls in dynamic olefin metathesis can be found in the reactivity difference between terminal and internal alkenes, rendering the reactions prone to kinetic traps. Also, the catalyst turnover numbers are sometimes inadequate for long-term DCvC applications, and the presence of both E- and Z-alkenes complicates analysis. Lastly, the equilibrium is hard to freeze, and even trace amounts of remaining catalyst during purification can promote further metathesis.\[70\]

Another type of metal-catalyzed dynamic reaction is alkyne metathesis (Figure 1.16b), which initially suffered from stability problems and low turnovers of the catalysts. However, recent development of new classes of Schrock-type Mo(VI) based catalysts has led to significantly decreased moist and air sensitivities (Figure 1.17, bottom), improving the usability for dynamic chemistry.\[71,72\]
1.3 Dynamic Covalent Reactions

1.3.1.3 C–O Bonds

The dynamic exchange of C–O bonds has been extensively studied, although applications in dynamic systems are rather limited. A summary of the available reactions can be found in Figures 1.18 and 1.19.

The first class of dynamic C–O bonds are based on nucleophilic additions to C=O bonds. One of the most unstable reversible bonds of this type is hemiacetals (Figure 1.18a). Hemiacetals form readily under basic as well as acidic conditions, but can normally not be isolated due to the unfavorable equilibria. In combination with metal-templating, however, observable hemiacetals can be formed.\cite{73}

Oxygen nucleophile addition to carbonyls

(a) Hemiacetal exchange

\[
\begin{align*}
\text{O} & \quad \text{OH} \\
\text{R}_1 \quad \text{H} & \quad \text{R}_2 \\
\text{R}_1 & \quad \text{O}^{-} \quad \text{R}_2
\end{align*}
\]

(b) Acetal exchange

\[
\begin{align*}
\text{O} & \quad \text{OH} \\
\text{R}_1 \quad \text{H} & \quad 2 \text{R}_2 \text{OH} \\
\text{R}_1 & \quad \text{O}^{-} \quad \text{R}_2 \quad \text{H}_2\text{O}
\end{align*}
\]

(c) Orthoester exchange

\[
\begin{align*}
\text{R}_2 \text{O} \quad \text{O} \quad \text{R}_2 & \quad \text{OH} \\
\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 & \quad \text{R}_2 \quad \text{R}_2 \text{OH}
\end{align*}
\]

(d) Ester exchange

\[
\begin{align*}
\text{R}_2 \text{O} \quad \text{R}_2 & \quad \text{R}_3 \text{OH} \\
\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 & \quad \text{R}_2 \text{OH}
\end{align*}
\]

Figure 1.17 Catalysts for dynamic alkene and alkyne metathesis.

Figure 1.18 C–O bond formation by nucleophilic addition of oxygen nucleophiles to carbonyl groups.
When hemiacetal formation is carried out under acidic conditions, the reaction can proceed further through a dehydration step to form more easily handled acetals (Figure 1.18b).\cite{74,75} The exchange, however, needs to be carried out under dry conditions to avoid hydrolysis of the acetals. Furthermore, alcohol exchange with orthoesters was recently demonstrated.\cite{76,77} Rapid exchange was observed under Brønsted acid catalysis, but, similar to acetal exchange, this reaction is incompatible with aqueous environments, as hydrolysis products dominate the system. However, when considering direct exchange between two distinct orthoesters, the addition of a minimal amount of water aids the reaction by release of alcohols as mediator. This reaction is of significant interest due to the three-dimensional nature, as the tripodal exchange motif is unique in a dynamic chemistry context.

Ester exchange, as shown in Figure 1.18d, is another reaction where the dynamics of C–O bonds are used. In traditional (trans)esterifications, strong acids or bases are commonly utilized as catalysts.\cite{78} However, undesired decomposition of components of the system can occur under harsh conditions, especially during prolonged exchange. Equilibration of esters have also been performed using strong Brønsted bases like NaO\textsubscript{t}-Bu and DBU, or Lewis acids such as Ti(OBu\textsubscript{4}) as catalysts.\cite{79,80} A high excess of base can be necessary to increase the equilibration rates in these cases.

Beside the dynamic C–O bonds that utilize the inherent reactivity of functional groups, some transition metal-catalyzed C–O bond exchange procedures have also been developed (Figure 1.19). For example, another way to utilize alkynes as dynamic linkages aside from alkyne metathesis is to convert them into their corresponding Nicholas ether adducts. These cobalt complexes have recently been demonstrated to be reversible when the ether groups are positioned α to the cobalt carbonyl–alkyne complex (Figure 1.19a).\cite{81} In order for dynamic covalent exchange to proceed rapidly, strong Lewis or Brønsted acids such as BF\textsubscript{3}•OEt\textsubscript{2} or TfOH need to be added, with resulting equilibration times in the order of 3–24 h. The original alkynes can also be efficiently regenerated using cerium(IV) ammonium nitrate. Another type of dynamic C–O bond is reversible transallylesterification, utilizing palladium catalysis to scramble allylic esters under thermodynamic control (Figure 1.19b).\cite{82}

1.3.1.4 C–S Bonds

Dynamic C–S bonds have much in common with C–O bonds, as implicated by the related positions of S and O in the periodic table. Sulfur has a more nucleophilic character, however, and is also a better leaving group. Reversible exchange reactions with C–S bonds thus tend to follow similar reaction pathways as with C–O bonds, but
1.3 Dynamic Covalent Reactions

Characteristics regarding equilibration rates and catalysis are different. A summary of the reactions discussed in this section can be found in Figure 1.20.

Similar to alcohols, thiols can also add to carbonyl groups to generate unstable hemithioacetals (Figure 1.20a).\cite{83,84} When the reaction is conducted with excess thiol and removal of $\text{H}_2\text{O}$, stable thioacetals (Figure 1.20b) can be obtained. The dehydration step is crucial and only acidic conditions give satisfactory equilibration rates. Brønsted acids promote thioacetal formation but not the reverse reaction, whereas the Lewis acid Zn(OTf)$_2$ result in swift forward and reverse reactions.\cite{85}

When comparing ester exchange with thioester exchange (Figure 1.20c), the differences are even more striking. Whereas ester exchange requires harsh conditions and is incompatible with aqueous conditions, thioester exchange does not require any catalysis and can be conducted under mild conditions in water.\cite{86,87} Due to the reactivity of thiols towards thioesters, thioester exchange is also compatible with functionalities present in peptides and nucleic acids.\cite{88,89} In addition, it has been shown that introduction of positively charged residues in the molecule can enhance the equilibration rate by possible stabilization of the negative charge building up in the transition state.\cite{90}

Thiols can also add to other carbonyl-type bonds such as nitrones (Figure 1.20d).\cite{91} However, the equilibrium constants are heavily weighted towards starting materials, and the established equilibria are essentially virtual. Nevertheless, the exchange is rapid and biocompatible, and the formed products can be kinetically trapped to drive the equilibrium away from the nitrone side.

Reversible thia-Michael additions (Figure 1.20e) have also been demonstrated. Due to the presence of surface-centered cysteine residues on many proteins, this type of exchange is of great interest for the design of reversible covalent drugs, a rapidly expanding area.\cite{15} For specific systems, the thia-Michael addition has been shown to be reversible on a short timescale under slightly basic conditions ($\text{pH} = 8$), with a fairly equal distribution between the starting materials and the adducts.\cite{92}

![Figure 1.20](image-url)
Principles of Dynamic Covalent Chemistry

Acidic conditions, equilibration was halted. Using the more electron-poor enone fragments derived from benzalcyanoacetamides, significantly enhanced equilibration rates were demonstrated. Moreover, it was shown that the equilibrium position could be shifted by substituting the aromatic ring with electron-withdrawing groups, reducing the electron density of the enone fragment.

It has also been shown that thia-Michael systems starting from β-sulfido-substituted enone fragments efficiently exchange thiols to form new β-sulfido-substituted enones and β-dithiane carbonyls. In these specific systems, the thioacetal exchange (Scheme 1.5) could be performed under basic conditions, proceeding through a Michael-type instead of hemiacetal-type mechanism.

1.3.1.5 S–S Bonds and Se–Se Bonds

The second most utilized dynamic covalent connection after imines are the disulfides. Other chalcogenic exchange reactions such as selenide–selenide and sulfur–selenide exchange have also been reported, but as the disulfide exchange reaction is of exceptional importance in DCvC the following section will mainly focus on this reaction.

Disulfide chemistry (Figure 1.21a) plays an important role in many biological processes, such as protein folding, and remains ubiquitous in DCvC since its inception. The exchange can be triggered by nucleophilic attack of a thiolate anion on the disulfide bond, creating a new disulfide and regenerating a new thiolate anion. Phosphines have furthermore been shown to catalyze the reaction. As the exchange requires a deprotonated thiol, this reaction is dependent on the pH of the mixture and a pH range around 7–9 is usually adequate to achieve fast equilibration. Not only can addition of thiol catalyze the exchange, but the same thermodynamic equilibrium can be obtained when starting from solely disulfides and adding reducing agent to form a catalytic amount of thiols in situ. Another common method to generate disulfide systems is to simply mix the corresponding thiols and allow the mixture to oxidize in the presence of air, or by addition of other oxidation agents. The exchange can be stopped by either complete oxidation to disulfides or protonating the thiolates by lowering the pH of the mixture. Disulfide exchange can also be performed using thiolate- or transition metal catalysis in organic solvents.

An extension of S–S bond chemistry is found when selenols and diselenides are utilized instead (Figure 1.21b,c). As selenols are more acidic than the corresponding thiols, there will be a comparatively higher concentration of selenolates in the mixture at

Scheme 1.5 Thioacetal exchange through thia-Michael addition.
neutral pH. It has been shown that diselenide exchange in combination with a thiol initiator remains efficient down to a pH of 5.\textsuperscript{[103]} When combining a diselenide building block with a disulfide building block, scrambling of the components and reorganization of the system towards both homocoupled and heterocoupled products could be observed. Because the sulfur–selenide heteroexchange proved to be faster, a small amount of diselenide can be added to disulfide mixtures to facilitate disulfide exchange. Diselenide exchange has also been demonstrated under visible light catalysis,\textsuperscript{[104]} proceeding in a variety of solvents under mild conditions.

1.3.1.6 B–O Bonds
The last of extensively investigated dynamic polar bonds are the B–O bonds. While B–O bonds can be made with monovalent alcohols, the thermodynamic stability of the formed product is low and isolation and characterization is difficult. For that reason, the main exchange reactions involving B–O bonds generally involve diols, which form more stable products (Figure 1.22a).

Due to the reversible interaction of boronic acids with Lewis bases, these compounds have found applications in molecular recognition, sensing and self-assembly of complex molecular architectures.\textsuperscript{[105]} The first type of reversible B–O bond formation are the boronic esters (Figure 1.22a). As reactants for Suzuki couplings, a lot of attention has gone into the synthesis of boronic esters, which similarly to normal esters are formed through dehydration reactions. To achieve efficient exchange of boronic esters at room
temperature, the presence of a nucleophile like water or alcohols is necessary.\textsuperscript{[34,106]} However, the dynamic system is not necessarily restricted to boronic esters, as the boron center still acts as a Lewis acid. Coordination of additional ligands results in formation of boronate esters (Figure 1.22b). Ligands that have been successfully used in this exchange include water, alcohols, phosphonic acids and nitrogen-containing aromatic heterocycles, all of which exchange readily at room temperature.\textsuperscript{[107–109]}

To ensure that boronate ester formation is the favored pathway, one can increase the pH of the mixture to higher levels than the $pK_a$ of the present boronic esters.\textsuperscript{[108]}

### 1.3.1.7 N–X Bonds

Even though a wide range of dynamic polar reactions are available today, there is still much ongoing research towards development of new exchange processes. Some interesting types include Se–N bonds and P–N bonds. Se–N bonds can be formed between selenylhalides and pyridine substituents in the presence of heat or DMAP as a catalyst, and P–N bonds can be formed between azides and phosphines in a reaction that is readily reversible at ambient temperature without addition of a catalyst.\textsuperscript{[110,111]}

### 1.3.2 Other Dynamic Reaction Types

#### 1.3.2.1 Dynamic Covalent Pericyclic Reactions

Reversible pericyclic reactions have also been pursued, and some examples are summarized in Figure 1.23. The advantage of this class of transformation resides in the self-contained nature of the reaction, meaning all atoms present in the reactants are also incorporated into the products. This property is of high interest for dynamic polymers, as it entails potential self-healing properties to the resulting material without the need for any additives. Furthermore, pericyclic reactions are orthogonal with most other dynamic covalent bonds.

The Diels–Alder reaction is the prototypical pericyclic reaction (Figure 1.23a). Formally classified as a $[4 + 2]$ cycloaddition, the reversibility of this highly useful reaction has been well known for many years.\textsuperscript{[112]} However, since the Diels–Alder reaction can be defined as a net formation of two C–C $\sigma$ bonds at the expense of two weaker C–C $\pi$ bonds, it is inherently exothermic and the retro reaction can thus be kinetically disfavored. Usually, either high temperatures or highly tailored dienes and dienophiles are required for swift reversibility. An example of such a system is when electron-poor dienes and electron-rich dienophiles are employed. Then, the HOMO–LUMO energy gap is relatively small, resulting in facile dynamic $[4 + 2]$ exchange even under mild conditions.

Room-temperature dynamic covalent Diels–Alder reactions have been demonstrated.\textsuperscript{[113]} In one example, the dynamic exchange reaction between adducts formed from fulvenes and cyanoethylenes proceeded with very quick equilibration time (<1 minute) at room temperature in CDCl$_3$. Both the exchange specificity and the system stability were very high. In another example, dimethyl-substituted anthracenes were applied as efficient dienes for dynamic covalent $[4 + 2]$ reactions (Scheme 1.6).\textsuperscript{[114]} The exchange rates were slower as compared to the fulvenes, with room temperature equilibration in the order of days to weeks.

Due to higher accessibility and synthetic utility, efforts to understand and utilize the reversibility in the more conventional Diels–Alder reaction between maleimides and
furans have also been made. The practical utility of these systems is diminished by the kinetic barrier for the retro-reaction. Heating for prolonged times at 70–100 °C is normally required for full equilibration. A combined experimental and computational study with the aim of uncovering more facile maleimide-furan cycloadditions was recently reported.\footnote{115} It was discovered that the furan substitution dictated the reactivity and reversibility of the system, with changes on the maleimide moiety showing only minor influence in the system activity. With electron-poor furans such as furfural,
the Diels–Alder progressed at very low rates, and with electron-rich furans like 3-methoxyfuran the reaction was too exergonic and the reverse reaction thus hindered. An efficient dynamic covalent behavior reaction was only displayed for moderately electron-rich and neutral furans like 2-methylfuran (Figure 1.24).

Recently, the application of 1,2,4-triazoline-3,5-diones (TADs) as coupling partners in dynamic covalent ene reactions with indoles was reported (Figure 1.23b).\textsuperscript{116} Establishment of this connection proceeded almost instantly under ambient conditions and the reaction was fully reversible at elevated temperatures (ca. 100 °C). Despite the high reactivity of both coupling partners, exchange selectivity was excellent, providing an example of highly specific exchange operating in the presence of other functionalities.

The dynamic covalent [2 + 1] cycloaddition between stabilized diamidocarbenes and olefins or aldehydes to yield reversible three-membered ring formation has also been demonstrated, as shown in Figure 1.23c.\textsuperscript{117} Interestingly, both electron-poor and electron-rich olefins could participate in the reaction. Dynamic exchange between cyclopropane and epoxide derivatives could also be performed with equilibration times around 16 h at 80 °C (Scheme 1.7). A further report has also uncovered the mechanism of the epoxide formation through use of magnetization transfer spectroscopy, revealing that this reaction (unlike the cyclopropanation) essentially proceeds stepwise via an anionic intermediate.\textsuperscript{118}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1_24.png}
\caption{The influence of furan substitution pattern on Diels–Alder reversibility.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme1_7.png}
\caption{Dynamic [2 + 1] cycloadditions between diamidocarbenes and olefins or aldehydes.}
\end{figure}
In addition to the thermal cycloadditions presented above, reversible photochemical \([4 + 4]\) cycloaddition of functionalized anthracenes to create dimers (Figure 1.23d) has also been reported.\(^{[119]}\) As can be seen from Scheme 1.8, irradiation at wavelengths above 350 nm led to complete dimerization within a few hours, while heating at 60 °C for 20 h or irradiating at shorter wavelengths regenerated the monomers.

While most dynamic covalent pericyclic reactions belong to the cycloaddition subclass, dynamic sigmatropic rearrangements using bullvalone derivatives have also been developed (Figure 1.23e), resulting in fluxional dynamics where the “shape-shifting” molecules can undergo continuous internal rearrangement and interconvert via hundreds of different isomers.\(^{[120,121]}\) Early efforts to turn on and off the fluxionality via photocontrol have also been reported.\(^{[122]}\)

Overall, dynamic covalent pericyclic reactions represent a growing class of reversible connections with importance for many areas of adaptive chemistry. However, several issues remain unaddressed with current systems, such as the inability to switch on or off exchange to freeze the equilibrium, or finding conditions tolerant of a wider variety of functional groups.

### 1.3.2.2 Dynamic Covalent Radical Reactions

The final class of dynamic covalent bonds highlighted in this chapter is that of dynamic radical reactions (Figure 1.25).

**Dynamic radical reactions**

(a) Alkoxyamine exchange

(b) Diarylbibenzofuranone exchange

(c) Trithiocarbonate exchange

**Figure 1.25** Dynamic covalent radical reactions.
A well-explored dynamic covalent radical system is based on the formation of persistent aminoxyl radicals (Figure 1.25a). Apart from its application in radical polymerization, the system has been used to achieve self-healing and reversible cross-linking for a range of different materials.[123] Recently, new types of dynamic radical exchange such as diaryl dibenzofuranone exchange (Figure 1.25b) have been demonstrated.[124,125] This functional group is derived from arylbenzofuranone and displays very high air and water tolerance as well as good functional group compatibility. The resulting dynamic polymers displayed autonomous self-healing properties at room temperature without any stimuli. The trithiocarbonate functional group also displays good reversibility at room temperature under UV irradiation (Figure 1.25c).[126] Dynamic covalent polymers based on this scaffold exhibited efficient photoinduced self-healing properties at room temperature in MeCN.

1.4 Conclusions

In a relatively short time, DCvC has evolved from a tool intended for macrocycle synthesis to a highly advanced framework with broad applicability within many areas in contemporary chemistry. Many types of dynamic covalent bonds have been developed, and their properties have been examined in various amounts of detail. Dynamic systems have been utilized in an exceptional range of problems within molecular recognition, lead compound discovery, catalyst design, nanotechnology, materials science, and many other areas. Furthermore, DCvC allows access to highly advanced molecular architectures where the form and shape is dictated by thermodynamics. Subsequent chapters will focus more specifically on the applications of DCvC within these different areas.

References

References

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