Kinetic and Thermodynamic Control in Dynamic Covalent Synthesis

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Abstract In recent years, dynamic covalent chemistry (DCC) has seen the synthesis of increasingly complex cyclooligomers, polymers, and diverse compound libraries. The reversible formation of covalent bonds characteristic of DCC reactions favors thermodynamic product distributions for simple unitopic reactions; however, kinetic effects are increasingly influential in reactions of multitopic precursors. In this review, we explore the interplay between thermodynamic and kinetic considerations when planning a DCC synthesis. Computational models, typically based on reaction thermodynamics, have aided in predicting DCC reaction outcomes with moderate success. A clear direction for the field is to develop more robust computational tools informed by thermodynamic and kinetic driving forces that can predict product distributions in DCC reactions.

Dynamic covalent chemistry (DCC) is an efficient synthetic strategy that utilizes **multitopic** precursors designed to form **reversible** covalent bonds, combining advantages of **error correction** during synthesis with the stability of a covalent compound as the final product. It has enabled the synthesis of a variety of molecular architectures, often isolated as a single, discrete species, including macrocycles [1], cages [2], and covalent organic frameworks [3,4]. A literature survey on 1,100 papers acquired through a search of the term “dynamic covalent” indicates that polymers are the most common target, followed by cages, macrocycles, and COFs [5]. Reversible bonds commonly in use include imine, boronic ester, hydrazine, disulfide, alkyne, oxime and alkene exchange, listed in order of their frequency. These structures have found applications in

host-guest chemistry [6], organic electronic materials [7], information storage and retrieval [8], catalysis [9], biological applications [10], chemical sensing [11], and as building blocks for other materials, such as nanofibers [12].

Most targets of DCC are constructed from a small number of different types of repeating units. Thus, DCC is commonly a **cyclooligomerization** process. The combination of a bimolecular oligomerization and intramolecular cyclization in the same reaction represents one challenge of dynamic covalent synthesis. Another challenge stems from the multitopic nature of DCC precursors. While the individual bond forming events are reversible, incorrectly joined structures may require multiple bond breakages to release an incorrectly placed precursor. Some erroneous structures fall out of **dynamic equilibrium** with the rest of the **reaction network**. This situation conjures up the notion of covalent bond **avidity**. Nonetheless, overcoming these challenges unleashes DCC's tremendous gain in synthetic efficiency reflected by the number of bonds made per operational step. Moreover, DCC product yields may approach quantitative, whereas cyclooligomerizations relying on strong irreversible bond formations tend to give low yields of final product, presumably because error correction is key to synthetic success [13].

Due to the reversibility of each bond forming event, DCC is generally thought to operate under **thermodynamic control**. The same literature survey mentioned above found that thermodynamic products and pathways are mentioned twice as much as kinetic products and pathways. However, as DCC advances to increasingly complex targets, there is good reason to suggest that kinetic factors may become more important. In this regard, there is an analogy between dynamic covalent synthesis and Levinthal's paradox for protein folding [14]. Levinthal's paradox states that because of the very large number of degrees of freedom in an unfolded polypeptide chain, the possible conformations are too vast to explore them all on the way to its native folded state. In a similar vein, the concatenation of multitopic precursors gives rise to a large number of structures on the way to the target product. These structures include polyhedra, polymers, and networks, and they may have very similar energies. This suggests a flat landscape, but complexes exhibiting covalent bond avidity are stabilized, which produces a vast landscape with somewhat regular variation. Given the complexity of DCC reaction networks and associated energy landscapes, synthetic intuition is unsuited to predict the outcome. Failures in experimental DCC often come at a high cost because multitopic, complex precursors require considerable structural

optimization and synthetic overhead [9]. Predicting outcomes is therefore essential and may require computational modeling to ensure a full understanding of the underlying factors that shape the energy landscape.

Examples of Thermodynamically Controlled DCC

The ability of dynamic systems to undergo reversible component exchange is key to the utility of DCC. Under thermodynamic control, even off-pathway intermediates typically error correct toward favorable product distributions on the timescale of the reaction (Figure 1) [15]. Work from the Swager group recently demonstrated the reversibility of S_NAr in the synthesis of macrocycles and covalent organic frameworks from both free starting material and off-pathway kinetic intermediates [16]. Accessing the product distribution regardless of entry point into the reaction landscape is a necessary condition to classify the product distribution as a thermodynamic equilibrium. In a second example, arylene ethynylene macrocycles are formed both by alkyne metathesis cyclooligomerization and by depolymerization-macrocyclization of linear poly(arylene ethynylene) species [17].

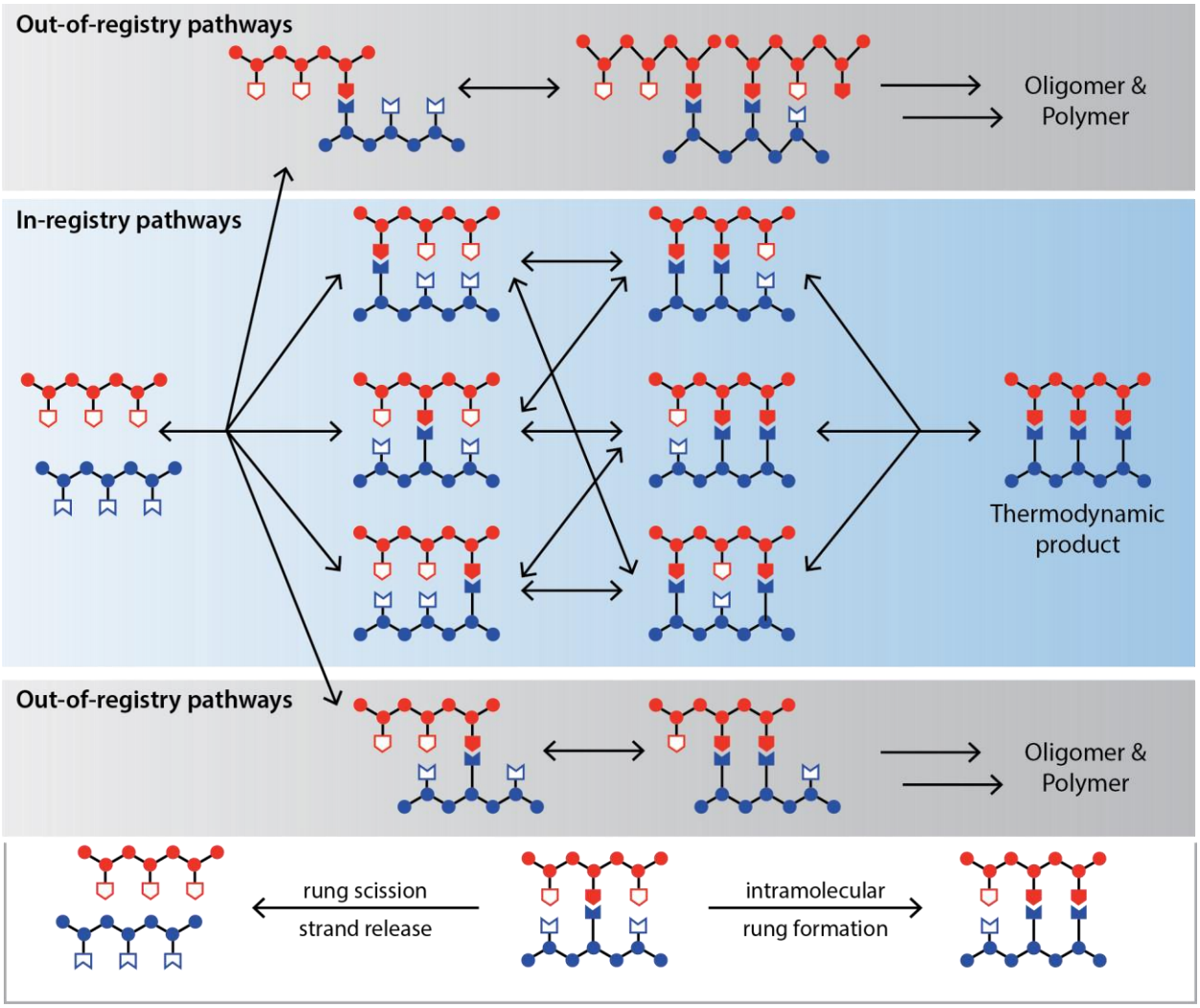

Figure 1. Reaction network of ladder formation under DCC. In-registry intermediates and products have correctly matched rungs where outer rungs bond to other outer rungs, and center rungs bond to other center rungs between two strands. Out-of-registry products have mismatched rung formation. Mismatched intermediates revert to free strands if rung scission is faster than intramolecular rung formation.

Systems under thermodynamic control favor distributions that maximize entropy by generating structures with the fewest possible number of building blocks while minimizing angle strain of the resultant structures. These principles have enabled the intuitive design of a wide variety of cyclic molecular architectures on the basis of precursor topicity and geometry [18]. Furthermore, in systems with very flat energy landscapes, slight differences in thermodynamic stability lead to self-sorting and large amplifications of product concentrations, which can be

further improved by increased catalyst loading and thermal cycling [17,19-22]. The Cooper and Moore groups demonstrated that small energetic differences arising from chiral recognition are sufficient to direct the homochiral self-sorting of **dynamic covalent libraries (DCLs)** composed of racemic building blocks [19,23]. Zhang and coworkers recently demonstrated the synthesis of a cyclic porphyrin macrocycle via dynamic alkyne metathesis, which yielded the desired trimer in 82% compared to a mixture of trimer (18%) and dimer (20%) via a kinetically controlled cross-coupling cyclooligomerization [24].

While design principles are generally reliable predictors of product topology and stability, occasionally this thinking belies the nuances of DCC energy landscapes. Cooper and coworkers recently designed a computational screening procedure to predict the outcomes of imine condensation reactions based on product stability [25]. While most combinations of aldehyde and amine precursors produced the predicted imine cages, several pairings of precursors led to structures with unexpected topologies. In these cases, the less thermodynamically favored product was observed, and the energetic preference for the predicted structures was determined to be small (around 5 kJ mol^{-1}) compared to the observed products. The Zhang group reported similar phenomena in the synthesis of arylene ethynylene cages [26]. Slight variations in monomer size yielded structures with drastically different topologies, despite a consistent face-to-edge angle between substrates. Taken together, these results suggest that intuitive design rules are unreliable predictors of complex reaction outcomes, and that pathway-dependence may contribute to DCC syntheses in largely unexplored ways. Advancing DCC as a robust and reliable synthetic approach will likely benefit from extending the existing computational tools (*vide infra*).

Examples of Kinetically Controlled DCC

The reversible bonds used in DCC enable systems to undergo error correction. The faster the rate of exchange, the less prone the resulting system is to kinetic traps (Figure 2). A ladder with hydrogen bonded rungs demonstrates much higher fidelity (98% vs. 62%) than an imine-linked ladder with an identical backbone, due in part to the high exchange rate of hydrogen bonding [27,28]. However, while rapid exchange speed rescues a system from a putative kinetic trap, all covalent bonds are susceptible to trapping under some circumstances. Rigid complex architectures, such as COFs and cages, typically synthesized via DCC tend to be predisposed towards **kinetic control** due to precursor multitopicity. Macrocycles with ditopic precursors require two bond

breakage events before a precursor is released. After the first bond breakage, the two resulting reactive moieties are in close proximity and so have a faster rate of recombination than two unlinked precursors, an effect which is exacerbated by the rigidity of the structures. If the rate of bond reformation is faster than the breakage of the second bond, the macrocycle may behave as a kinetic trap. Kinetic trap behavior is even more likely for structures which require three or four bond breakages, where precursors are tritopic or tetratopic and the partially broken structures have higher rigidity [2,29]. This covalent bond avidity is apparent in the synthesis of ladder compounds, which generally have n-topic precursors, where n is the number of rungs. These studies show that beyond a certain number of rungs the structures can no longer undergo error correction and tend to form myriad mismatched products instead [8,30,31].

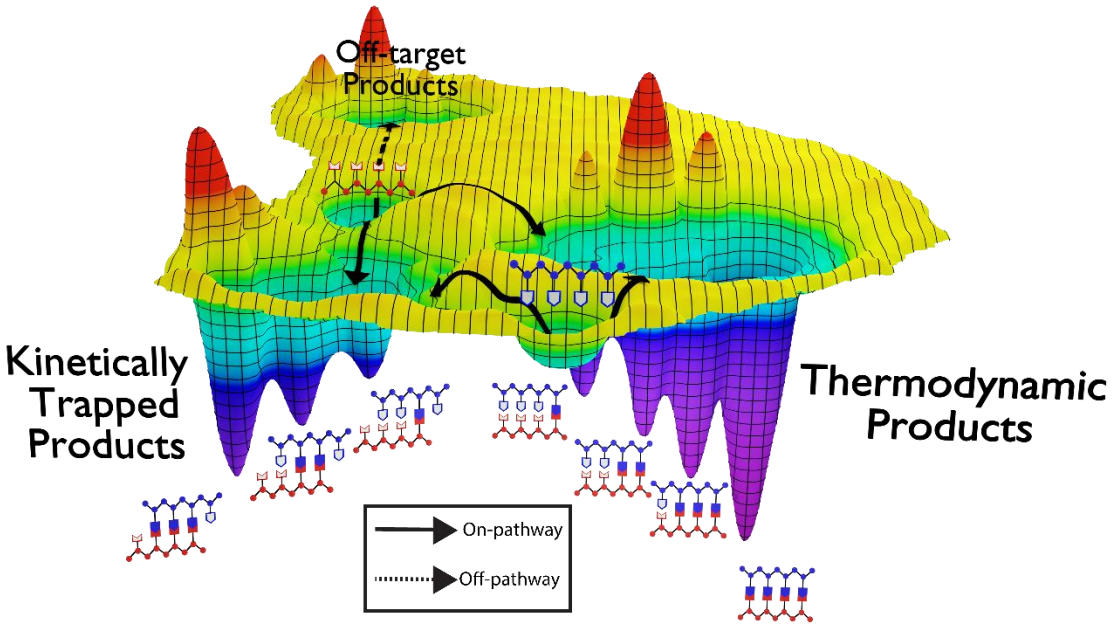

Figure 2. In reactions with complex energy landscapes, species can become kinetically trapped even if reversible chemistry is used. Kinetic traps can persist if small barriers funnel material back to the trapped structure rather than out of the kinetic trap and toward a thermodynamic minimum. In the case of molecular ladders, out-of-registry products may be kinetic traps if rung scission is immediately followed by reformation of the rung. Kinetic factors such as proximity-induced high effective concentration prevent error correction in a dynamic system where the thermodynamic product is desired.

Rigidity also influences reaction outcomes by rendering certain transition states geometrically inaccessible. This is particularly relevant for reactions with conformationally restrictive transition states, such as the transition state leading to the metallocyclobutadiene intermediate in alkyne metathesis. Work in the Moore group to synthesize a molecular Möbius strip has demonstrated total kinetic diastereoselectivity because only one of the two possible diastereomeric intermediates could form the key metallocylobutadiene transition state (Figure 3) [32].

Solubility is an ever-present consideration in the synthesis of complex architectures. Large structures common in DCC have decreased kinetic solubility. Heavily conjugated structures are common because they are rigid enough to be shape-persistent, but large, planar π surfaces contribute to insolubility due to π-π stacking, removing the compound from dynamic equilibrium and promoting its formation. Dichtel and coworkers developed a system which produces macrocycle only when it is insoluble in the reaction solvent; dissolving the macrocycle and bringing it back into dynamic equilibrium leads to conversion into polymer, the putative thermodynamic product [1]. Many DCC syntheses are driven by precipitation [5,33-35]. Adding solubilizing groups or changing the size and planarity of the π surface allows modulation of solubility. Northrop and coworkers produce a planar and non-planar version of the same boronate ester cage by inserting ethynylene units into a biaryl backbone with a 90° twist [33]. They demonstrate that the more planar version is less soluble and more stable to protic solvents.

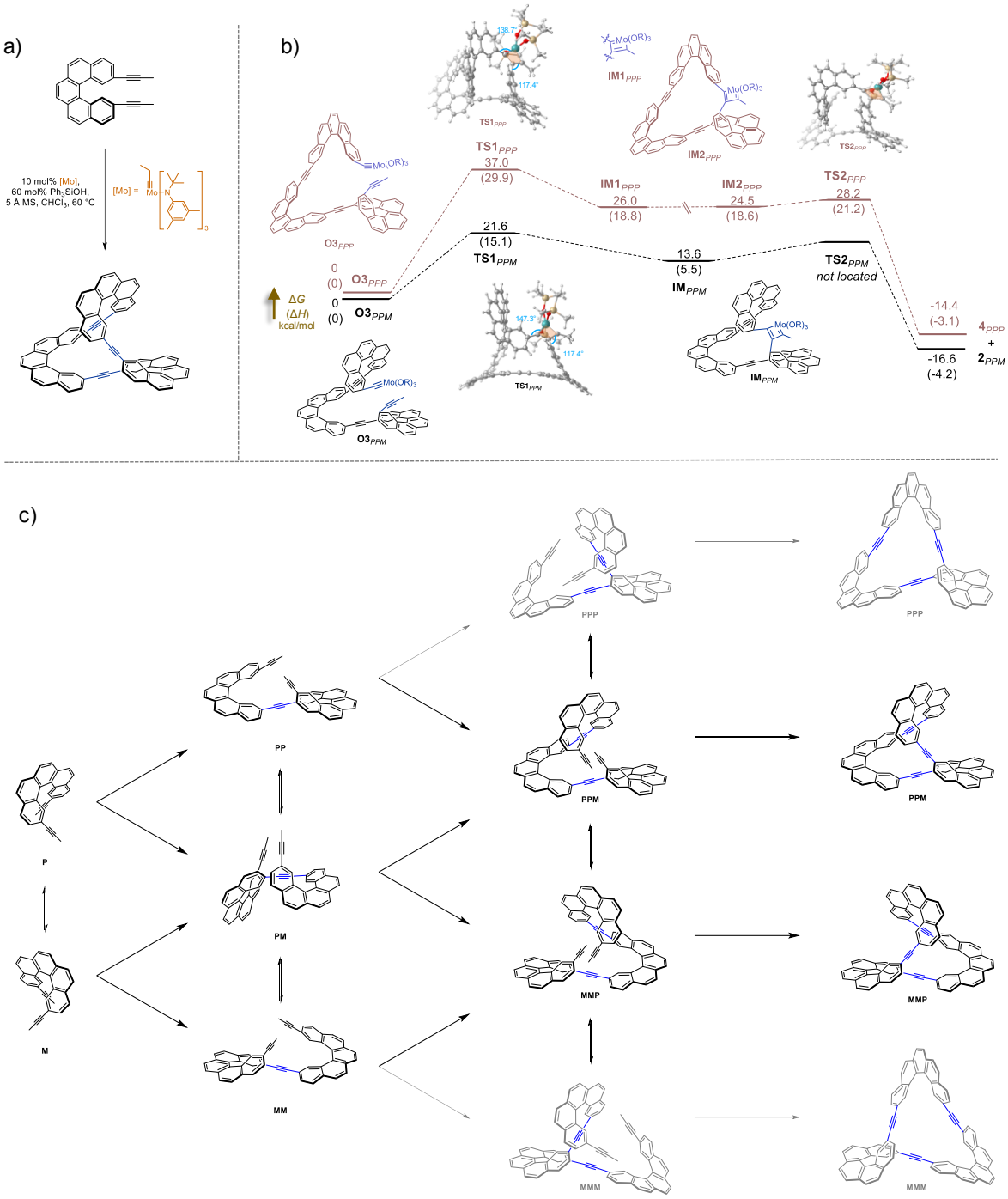

Figure 3. a) Alkyne metathesis of 2,13-bispropynyl helicene to form a C_2 symmetric molecular Möbius strip b) Energy profile demonstrating kinetic diastereoselectivity in macrocyclization c) reaction network showing intermediates leading to all possible stereoisomers. Structures in gray were not observed as products of the reaction.

Supramolecular interactions in solution also affect the product distribution in some systems. The enthalpic benefit of the interactions themselves drive the equilibrium toward compounds that promote more stabilizing supramolecular interactions.[1] In addition, supramolecular structures that form between cages and other complex products affect exchange rates. Dichtel and coworkers report an imine macrocycle that assembles into nanotubes which prevent further imine exchange, and Otto and coworkers report a similar effect [12,37]. In the synthesis of knots and catenanes from a DCL, multiple products are kinetically trapped as a result of intramolecular π-π stacking in ambiphilic molecules, analogous to the hydrophobic effect in protein folding [38].

While kinetic traps may introduce synthetic obstacles, they sometimes provide products in higher yields than the same system under thermodynamic control (Box 1). In some cases, the kinetic trap is also the thermodynamic product [2,45]. In other cases, the pathway-dependence of kinetically controlled systems can be leveraged. Multiple products may be accessible from the same precursors under different conditions, especially useful given the high synthetic overhead of DCC precursors [12]. Otto and coworkers have provided evidence that mechanical agitation has a strong influence on product distribution [11,36]. Slow addition of monomer has been demonstrated to produce COFs with larger crystal domains than a single-addition protocol [46].

Kinetic control also allows improved information storage. Scott and coworkers show that a high-fidelity synthesis of an information-bearing five rung imine ladder is only achieved by increasing and then decreasing the concentration of scandium (III) triflate, commonly used to promote imine exchange [31]. This sort of chemical annealing is reminiscent of thermal annealing of DNA [31]. Keeping the concentration at the same low levels throughout the reaction leads to mismatched byproducts instead; this dependence on pathway suggests that the information-bearing ladders are kinetic products. Lehn and coworkers have developed libraries of acyl hydrazones and imines generated from simple aldehyde, acyl hydrazine, and aniline building blocks [8]. In the presence of metal cation with the appropriate coordination geometry, kinetically trapped species were favored. Upon precipitation of the directing metals, the libraries were expected to return to equilibrium, favoring formation of the more stable acyl hydrazone. However, because the exchange rate of imines and acyl hydrazones is on the order of weeks, the composition of the DCL remained unchanged on a relevant laboratory timescale, or until it was erased by thermal cycling.

Furthermore, the library could be trained to adopt an altered kinetic equilibrium through the addition of a different metal cation, demonstrating the versatility of a simple system for information storage. In this case, kinetic factors allow access not only to targeted materials, but also to emergent properties from simple chemical systems.

Computational Studies

Most efforts at rationally designing DCC systems have utilized thermodynamic modeling. Computational predictions of reaction outcomes based on thermodynamic driving forces have been used to design precursors and generally rely on the assumption that reactions will reach their thermodynamic end point (Box 2). The most common approach to thermodynamic modeling uses **DFT** to locate the energy of the various possible structures that could be formed in a given reaction network. The lowest energy structure is then assigned as the expected product. For DCLs, a common approach is to predict the equilibria in the library to understand the likely primary product and how that will change when reaction conditions are modified [47]. Thermodynamic modeling has also been widely used in designing molecular cages. The successful synthesis of a molecular cage by DCC requires precursors with the proper geometry. Cages designed by solely accounting for geometry have been moderately successful but some lack **permanent porosity** or fail to form [4,26]. The Cooper group has developed a **computational workflow** that accounts for both aspects [48]. Using this workflow combined with high throughput chemistry, they have synthesized a large number of unique cages [49]. However, their results still revealed unexpected cages as well as the failure of certain predicted cages to form at all[49,50]. While they attribute inconsistencies between theoretical and experimental results to entropy and solvent influences, it is likely that kinetic factors influenced the reaction outcome.

Kinetic modeling accounts for complex reaction networks and utilizes the rate coefficients for each reaction to predict the concentrations of species in the reaction. One technique for kinetic modeling involves manually calculating the reaction network and developing a master equation for all species in solution [51]. Another approach is to use **rule-based modeling** to state the rules of the reaction (e.g. changes in bonding or state) and to computationally generate the reaction network [29]. A third approach ignores the reaction network, and uses **Monte Carlo algorithms** to simulate the reaction [46,52,53]. Each of these approaches aims to predict the concentrations of all species in solution thus indicating key intermediates and the rate determining step [51], as well

as the presence of any kinetic traps [29]. Kinetic simulations provide guidance on optimal reaction conditions to increase the yield of the desired product [52]. Dichtel and coworkers recently utilized kinetic Monte Carlo simulations to better inform the synthesis of boronic ester covalent organic frameworks (COFs) [46,52,53]. Slow addition of monomer and inclusion of a competitive binder slowed growth and delayed nucleation, promoting controlled growth rather than uncontrolled nucleation of polycrystalline frameworks. These approaches yielded COFs with larger crystalline domains than structures synthesized via typical procedures, as well as larger diameters, greater uniformity of size, and higher signal to noise ratios in transient absorption and wide-angle x-ray scattering spectra.

Conclusion

While dynamic covalent chemistry is a relatively young field, consensus has already emerged around the importance of predicting reaction outcomes. Reversible covalent bonds combine the stability of covalent products with rapid error correction. However, not all linkages necessarily reversibly equilibrate and multitopicity of the resulting structures leads to complex reaction networks and energy landscapes. Unfortunately, the high overhead required to conceive of and develop precursors raises the cost of unpredictable outcomes [8]. Many researchers tend to overemphasize thermodynamic factors when planning a synthesis based on reversible covalent linkages even though the desired geometric complexity, rigidity, and extended conjugation often subject the synthesis to kinetic control. In response, computation has enhanced human intuition. New approaches have begun to incorporate kinetic factors into computation shedding light on COF nucleation, ladder formation and trapping, and other processes with observable kinetic effects [29,53]. However, few studies to date have incorporated both kinetic and thermodynamic factors in computational prediction.

We envision a future where computational models will be vital to developing new precursor structures. However, a new vision for a computational workflow which incorporates thermodynamic and kinetic considerations, and is accessible to organic and materials chemists, is sorely needed (Box 2). Developing and utilizing this new workflow will hopefully yield insights about unobservable intermediates and rate constants, and aid in our understanding of the fundamentals of DCC (outstanding questions). We hope that this will enable the synthesis of new complex and responsive materials and libraries.

Box items

Box 1. Dynamic Systemic Resolution

Dynamic Resolution

In many biological and synthetic systems, molecular recognition events are triggered by a slow, irreversible step which occurs due to a perturbation of a system previously under thermodynamic control. This perturbation occurs either through internal or external selection, and the resulting irreversible step removes kinetically trapped species from the dynamic pool, shifting equilibrium to favor their formation. This phenomenon, referred to as dynamic systemic resolution (DSR), is one way to combine the adaptive nature of thermodynamic control with the selectivity of kinetic control [10]. As an extension of classical dynamic kinetic resolution, this technique has been used for chiral resolution of epimers [40], as well as in biomimetic applications to amplify strong binders in the presence of receptor molecules [41].

Unlike thermodynamic DCC syntheses, the selectivity of DSR arises from reaction kinetics rather than product stability. Thus, the external kinetic stimulus must be chosen judiciously: it must be selective enough to operate quickly on the fastest-responding component of the DCL without directly affecting the rest of the DCL or halting the ongoing thermodynamic equilibrium [15]. Osowa and Miljanić used irreversible oxidation to enable self-sorting of a DCL of imines [42]. Slow oxidation of the imine species ensured that only the fastest-reacting amine and aldehyde pairs were removed from the dynamic pool, enabling highly efficient resolution of three discrete products from a library capable of producing nine different imines. Similar processes have been reported by Rizzuto and Nitschke in the synthesis of imine-based coordination cages [43]. Antagonistic amplification of thermodynamically disfavored structures by kinetic requisition of more reactive imines resulted in the self-assembly of heteroleptic cages inaccessible by straightforward DCC synthesis. A major goal for DCC would be to use such DSR strategies to access and amplify kinetically trapped structures with low symmetry and unique functionality [44].

Box 2. A computational workflow for synthetic design of DCC

Rational design of DCC requires both thermodynamic and kinetic modeling and consideration. Solely considering either thermodynamic or kinetic impacts on DCC will not allow fully rational design, as both aspects influence DCC reactions. DCC needs a unified design

workflow that combines thermodynamic modeling for precursor design and kinetic modeling for conditions optimization while confirming that the desired product can actually be reached given the topicity of the precursor and kinetics of the type of DCC being used. The workflow should include initial thermodynamic modeling used to find likely candidates for the desired product, kinetic modeling to understand the reaction network leading to the predicted product, and possible thermodynamic redesign of the precursor if kinetic modeling shows there are many traps between precursor and product. The findings of the modeling are then applied to synthesis. We believe that this unified workflow is the future of DCC.

Glossary Terms

Avidity: A measure of total binding strength between multitopic components.

Computational workflow: A defined sequence of computational tasks that produce a desired outcome.

Cyclooligomerization: A reaction that converts monomers to macrocycles with a finite number of components.

Density-functional theory (DFT): A computational method used to model the electron density clouds of atoms and molecules in order to investigate their electronic and nuclear structure and predict their energies.

Dynamic covalent chemistry (DCC): A synthetic strategy typically utilizing reversible covalent bonds and multitopic precursors in order to synthesize networks, cages, and other architectures which would be difficult or impossible to synthesize in a stepwise manner.

Dynamic covalent library: Precursors designed to form a variety of different species via reversible covalent bonds are mixed to study the resulting product distribution and its response to perturbation.

Dynamic equilibrium: The concentration of all species is constant because the forward and reverse reactions are proceeding at equal rates. The system is at a thermodynamic minimum.

Error correction: The breakage of a bond which is incompatible with the system's intended product. This process is vital for the synthesis of complex architectures by DCC.

Kinetic control: The outcome of the reaction is primarily determined by which product is formed at the fastest rate and has the lowest activation energy of its formation, generally observed when the reaction is irreversible.

Monte Carlo algorithms: A type of computational algorithm which uses repeated random sampling and subsequent statistical analysis to obtain results for values which would otherwise be difficult to predict.

Multitopic: A precursor with multiple reactive sites which forms multiple bonds in the course of the reaction or synthesis.

Permanent porosity: Cavities are present in a molecule or material that do not collapse when the original hosts of the cavity (generally solvent molecules) are removed.

Rational design: The use of computer modeling to design a structure with specific desired properties, rather than using chemical intuition.

Reaction network: The total set of reactants, products, and intermediates in a system, and all the reactions that transform one into another.

Reversible: A reaction is reversible if the products react to reform starting material on an reasonable laboratory timescale.

Rule-based modeling: A model is defined by a set of rules repeatedly applied to progressive reaction conditions, allowing a complex model to be generated without specifying the system in its entirety.

Supramolecular interactions: Non-covalent interactions between molecules.

Thermodynamic control: The outcome of the reaction is primarily determined by which product is lowest in energy, generally observed when the reaction is reversible. Despite the rapid formation of the kinetic product, the thermodynamic product accumulates over time in a reversible reaction because the reverse reaction is slower for a more stable product.

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Author Contributions

†These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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5. The literature survey was completed by downloading all the unique articles found on SciFinder with the search term “dynamic covalent”. Once the non-searchable documents were removed, 1102 papers remained. These papers were text searched for various phrases using the command line tool ‘grep’. If a paper mentioned a specific structure (e.g. cage or polymer) ten or more times, it was considered to be the target structure. The specific percentages of target structures were: 55.4% polymer, 7.5% cages, 7.3% macrocycle, 4% dynamic covalent library, 3.5% covalent or metal-organic framework, 1% ladder, 21.3% did not include any of these structures at least ten times. If a paper mentioned a specific chemistry ten or more times, it was considered to be the primary chemistry of the paper. The specific percentages of chemistries were: 22.5% imine, 14.0% boronic ester, 11.8% hydrazone exchange, 7.7% sulfide exchange, 4.3% metathesis (alkyne, olefin, or imine), 1.8% alkyne metathesis, 1.7% oxime exchange, and 1.2% olefin metathesis.
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