Chemistry Europe
European Chemical Societies Publishing

Special Collection

Strategies for Exploring Functions from Dynamic Combinatorial Libraries

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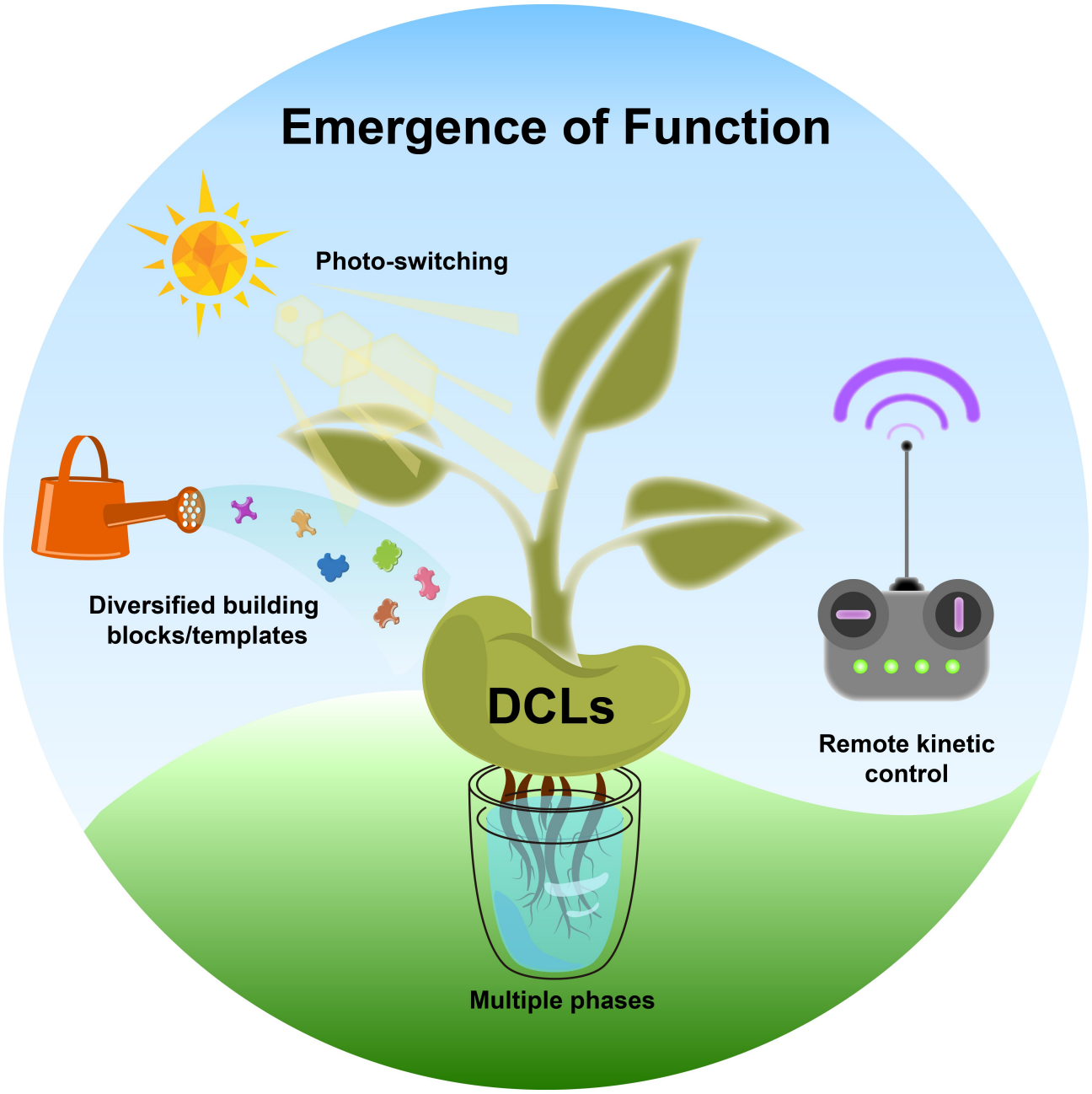

Dynamic combinatorial chemistry (DCC) is a powerful approach for creating complex chemical systems, giving access to the studies of complexity and exploration of functionality in synthetic systems. However, compared with more advanced living systems, the man-made chemical systems are still less functional, due to their limited complexity and insufficient kinetic control. Here we start by introducing strategies to enrich the complexity of dynamic combinatorial libraries (DCLs) for exploiting unexpected functions by increasing the species of building blocks and/or templates used. Then, we discuss how dynamic isomerization of photo-switchable molecules help DCLs increase and alter the systemic complexity *in-situ*. Multi-phase DCLs will also be reviewed to thrive complexity and functionality across the interfaces. Finally, there will be a summary and outlook about remote kinetic control in DCLs that are realized by applying exogenous physical transduction signals of stress, light, heat and ultrasound.

1. Introduction

During the past two decades, dynamic combinatorial chemistry (DCC)[1] has grown into a typical tool for fabricating complex chemical systems and provided outstanding synthetic platforms to study molecular complexity and explore the emergence of function.[2]

In dynamic combinatorial libraries (DCLs), building blocks are linked together through dynamic covalent chemical reactions to produce library members. Since the reactions are reversible, the library members are interconvertible by exchanging building blocks and thereby form dynamic molecular networks, in which their concentration distribution is governed by thermodynamics in most cases. Introduction of external stimuli can shift the equilibrium and shuffle the distribution. In typical cases, an external template molecule can lower the Gibbs energy level of a library member by complexing with it preferentially. Thus other ineffective members are consumed to feed this favorable one. Based on such a principle, many receptors/ligands[3] for biomacromolecules, catalysts[4] and interlocked structures[5] have been discovered.

Furthermore, in this thermodynamics-dominated realm of DCLs, kinetic control can act as a powerful supplementary factor to selectively manipulate the landscape of activation energy profiles, introducing irreversible processes by generating "kinetic traps" or "energy rachets" to amplify and capture desirable products/structures (even the thermodynamically non-favorable ones). Or it can be a switch to turn on/off specific reversible reactions in a DCL to get more control on the exchange behavior. Applications like dynamic chiral resolution, self-replication and material fabrication have emerged from these energetically two-dimensional controlled DCLs,[6] which further resembles their primitive model of dissipating biological systems that mostly operate their reversible reactions out-of-equilibrium.

However, compared with biological systems, the DCC based synthetic systems are still in a primitive evolutionary stage and much less functional. This situation may be ascribed to two reasons: i) the limited complexities in the current DCLs have much less possibilities of producing functional molecules than nature; ii) insufficient kinetic control for amplifying and maintaining the desired function. Facing such complexed challenges arising from the exploration of functional DCLs, we should deliberate our strategies before getting dazzled in the arsenal of DCC. Thus, in this minireview, we will focus on the strategies that could be used to explore advanced functions from DCLs. Firstly, we will review strategies to enrich the complexity of DCLs for exploiting unexpected properties by diversifying building blocks and/or templates. Multiple types of building blocks will result in multiple dynamic molecular networks issued by different reversible reactions. Those networks could be orthogonal/communicating or simultaneous/asynchronous, leading to molecular motors or biomimetic chemical systems. Also two distinct pioneering work utilizing multiple templates in a DCL will be reviewed. They have shown that multiple templates could cooperatively result in divergent/convergent templating effects in a DCL, both of which are unprecedented behavior emerged in DCLs. Clarifying those principles of systemically flourishing covalent/non-covalent interactions to increase complexity will help us to design more sophisticated DCLs. However, besides diversifying the molecular species by adding new chemicals, *in-situ* dynamic isomerization of molecules mediated by photo-irradiation could also reversibly trigger new covalent/non-covalent interactions and then downstream cascades in a DCL, making contributions to complexity as well. Furthermore, DCLs in multi-phase environments offer an opportunity to emerge complexity and functions at interfaces. Finally, a flexible yet non-invasive remote kinetic control strategy realized by applying exogenous physical transduction signals to manipulate DCC will be discussed among its nascent emerging cases, which could avoid feeding additional

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chemicals into DCLs to grow extra challenges of analysis and purification of an already highly complex system.

By summarizing these strategies we hope this minireview could serve as a modest spur to trigger the enthusiasm of researchers to strengthen the power of DCC as that of living systems and develop the emerging field of systems chemistry.

2. Diversifying Building Blocks and Templates in DCLs

As mentioned above, the species of the building blocks will dictate what types of dynamic covalent reactions are constructing a thermodynamics-governed equilibrating DCL. The Gibbs energy levels of the library members can be regulated by their non-covalent interactions with the templates to reshuffle the chemical constitution at a systems level, which then automatically expresses systemic stimuli-responsiveness for the selection of the most favourite binders to the template molecules. Thanks to the complexity generated from building blocks and templates, a DCL can commend its own constitution to discover different applications. Hence, comparing DCLs with living organisms presenting infinite complexity from countless covalent/non-covalent networks, one can assume that diversified building blocks and templates should increase the possibility of producing more advanced cooperative interactions to boost the functions within a DCL. However, usually only a single type of dynamic covalent reaction is utilized in a DCC research.[7] And surprisingly, to our best knowledge, only two work introduced more than one template in a DCL.

Nevertheless, in the last decade, researchers have gradually discovered that diversifying building blocks to engineer multiple reactions in a single library will not only dramatically increase the complexity of the library, but also provide additional control knobs to the system, promoting the emergence of functions from DCLs at a system level. These reactions could be orthogonal or communicating and they could take place simultaneously or asynchronously. In this section, we choose the disulfide bond formation, a benchmark reversible reaction in DCC, as an original point to review its cooperation with other dynamic covalent reactions in multitudinous behaviours. Then, through the two distinct pioneer works using multiple templates in a single DCL, we see how multiple templates can work cooperatively in divergent/convergent manner to elevate the systematic complexity and finally emerge one allosteric or multiple selective receptors. Thereout we try to give an evolutionary perspective on the emergence of functions.

A typical example of orthogonal and asynchronous system was reported by Prof. Leigh and co-workers (Figure 1A).[8] They enabled the disulfide exchange under weak basic condition while the hydrazone exchange did not occur. When the condition was switched to acidic, the disulfide exchange was quenched but the hydrazone exchange was turned on. By alternatively controlling the pH, the Leigh's group could make a molecular walker along a linear track molecule. Furthermore, they utilized this orthogonal pair of reactions as a gating system on the circular track molecule of a catenane molecular motor

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Yucang Zhang received his PhD degree at the University of Tokyo and completed his postdoctoral research at the Tokyo University of Agriculture. Now he is a Professor and also the dean at the School of Material and Chemical Engineering, Hainan University. His research interest has been in the development of green materials and green energy from bio/waste resources.

Kari Rissanen received his PhD degree at the University of Jyväskylä, Finland and since 1995 has been professor and Head of Organic Chemistry at the same university. His research interests focus on understanding supramolecular interactions occurring in recognition and self-assembly events, studied in the solid state by single crystal X-ray diffraction and in solution by NMR spectroscopy, in solution by NMR and in gas phase by mass spectrometry.

Jianwei Li obtained his PhD degree in 2014 with Prof. Sijbren Otto at the University of Groningen, the Netherlands and was a postdoctoral researcher with Prof. Hagan Bayley at Oxford University, UK. From September 2016, he started his independent group as a senior researcher at the MediCity Research Laboratory, University of Turku, Finland. He was awarded as a Special-term Professor in 2018 at Hainan University, China. His research interests focus on the exploration of functional materials from dynamic combinatorial libraries.

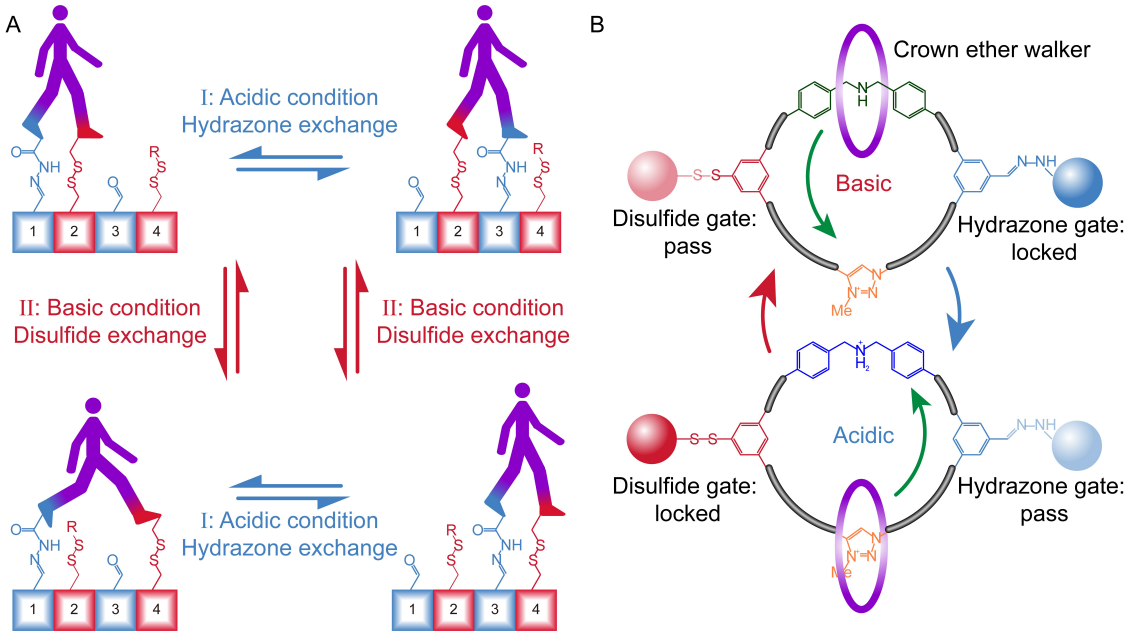

Figure 1. A) Molecular walker along a short linear track operated by disulfide exchange and hydrazone exchange at different pH values.[8] B) A directional circular catenane molecular motor enabled by asynchronous hydrazone/disulfide gates under acid-base oscillation.[9]

(Figure 1B).[9] In one rotational direction, alternant dibenzylammonium/triazolium binding sites were equipped on the track. Then there were alternant hydrazone-locked/disulfide-locked gates in between those binding sites. Dibenzylammonium was protonated under acidic condition thus the molecular walker of crown ether was thermodynamically favourable to travel toward this site. Acidic condition also unlocked the hydrazone-locked gate by activating hydrazone bond exchange while the disulfide-locked gate was closed for being inert. In basic condition, the contrary was the case. So that the walker molecule could only walk through the unlocked gate in a single direction. Applying acid-base oscillation on this catenane molecular motor managed to realize directionally circular movement of the molecular motor.

In a communicating system, different types of dynamic covalent chemical reactions could occur simultaneously and communicate with each other, generating a vast complexity and many library species even if only a small number of building blocks is used. The Pittelkow's group first investigated diselenide exchange in water at various pH, finding out that the reaction stayed efficient down to pH 5 (Figure 2).[10] Thus, at a physiological pH of 7.8, the diselenide exchange and disulfide exchange could react at the same time. By mixing a bis-diselenide macrocycle $(1)_2$ and a bis-disulfide macrocycle $(2)_2$ and a thiol initiator, the dominant species in the library were two homotetramers $(1)_4$ and $(2)_4$, and a mixed selenenyl based tetramer $(1)_2(2)_2$. Interestingly, the authors observed that diselenides could catalyse the oxidation of thiols. Given the fact that exchange of S–S, Se–Se and S–Se bonds are pivotal steps in some enzymatic catalytic cycles in human body,[11] this work of communicating dynamic covalent reactions has paved the

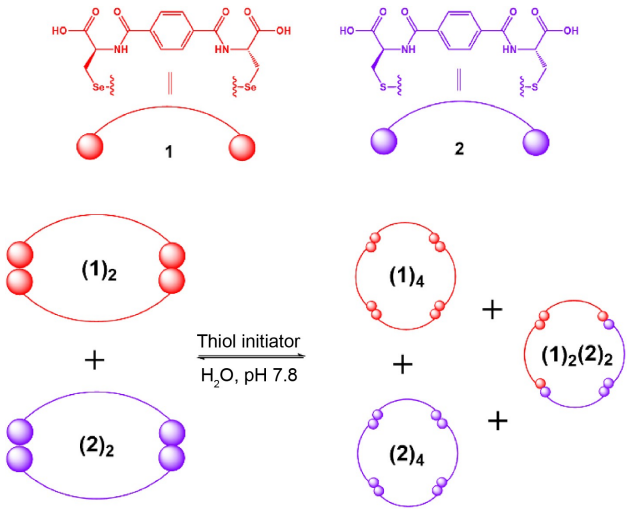

Figure 2. DCLs based on diselenide exchange and disulphide exchange simultaneously triggered by a thiol initiator at pH 7.8.[10]

way of investigating and establishing biomimetic homeostasis and enzymatic systems.

In another paper,[12] Pittelkow and his coworkers investigated a library prepared from aryl thiols, phenylboronic acids and catechols in the presence of 1,8-diazabicycloundec-7-ene. The disulfide exchange and boronic transesterification proceeded simultaneously but orthogonally in a single DCL. More excitingly, Anslyn's group developed a DCL having the most orthogonal-simultaneous dynamic covalent reactions so far, where boronic ester exchange, thiol-Michael addition, hydrazone exchange and terpyridine-zinc complexation took place both orthogonally and simultaneously in a methanol-water

solution at physiological pH,[13] which is of great potential for building much more sophisticated biomimetic chemical systems. Here we recommend their excellent review giving comprehensive insights into orthogonality in chemical systems constituted of dynamic covalent reactions and their applications in generating complex molecular assembly and dynamic materials.[14]

Otto *et al.* have recently reported that disulfide exchange can be coupled with thiol-Michael addition in an anti-parallel way.[15] Thiol building blocks could be assigned preferentially into one of the two reactions depending on the oxidation level of the system. Thiols could be oxidized to form disulfides, while the thiol-Michael addition does not require its oxidation states to generate the adducts. Thus, when all the thiols were in the reductive state, the products were only thiol-Michael adducts. As the oxidation reaction proceeded, the sulfur atoms in the adducts transferred to disulfide bonds. All the products were switched to disulfides in the fully oxidized library. The adaption of the library to the oxidation level of the environment is somehow similar to the switch between aerobic and anaerobic metabolisms.

The introduction of multiple template molecules can also enrich complexity of a library, as more possible non-covalent interactions will be available. To our best knowledge, now there are only two distinct papers that utilize multiple templates. The templates may work cooperatively to amplify one convergent library species, or assign the selective divergent binders for themselves. For the convergent situation, Li *et al.* reported a dynamic combinatorial strategy for a system giving rise to allosteric synthetic receptors based on the use of two different templates at the same time (Figure 3).[16] Without the introduction of any template into a DCL prepared from a naphthalene derived unsymmetrical dithiol building block **3**, the dominant species in the library were [2]catenane isomers interlocked by tetrameric isomers. The γ-cyclodextrin (γ-CD) template could amplify two tetrameric isomers, **ISO1** and **ISO2**. A benzene-derived ammonium salt was also chosen as a template molecule to the library, which resulted in the amplification of another tetrameric isomer **ISO4**. When the benzene-derived ammonium salt and γ-CD were added simultaneously as templates, the tetrameric isomer **ISO3** was synthesized in an almost quantitative yield. Interestingly, individually neither the ammonium salt template nor γ-CD was able to facilitate the synthesis of the **ISO3**. The binding constants of each binding step in the formation of the ternary complex consisting of the two templates and the **ISO3** suggested that such unusual amplification was due to a positively cooperative self-assembly of the three components together, implying that a receptor could be covalently synthesized with the assistance of non-covalent interactions among several target molecules.

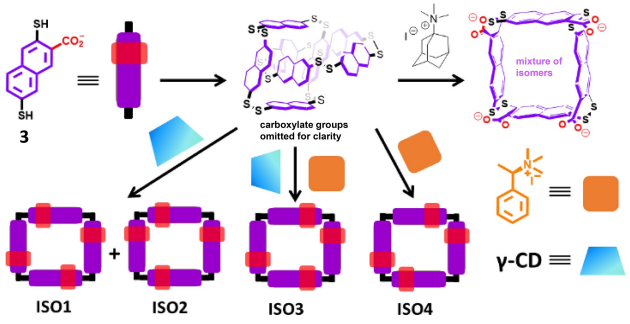

Figure 3. Selective amplification of isomers from DCLs by a specific template or combination of templates.[16]

For the divergent situation, Woon *et al.* used two or more ALKBH3 sub-family proteins to template a DCL manipulated by acylhydrazone exchange in order to screen out multiple subfamily-selective inhibitors in one pot.[17] Interestingly, they modified the protein templates by tagging them with non-denaturing zwitterionic peptides to fine-tune their melting temperatures. As a result, the gap between the melting profiles of the protein templates was widen and so did the shifted profiles of their complex with the selective inhibitors. Thus the proteins and the inhibited complexes could be well discriminated by differential scanning fluorimetry (DSF). The association of the modified DSF method with HPLC method explored by this work also set an example of addressing the analytical challenge of assigning multiple protein-inhibitor (template-library member) complex in one DCL. This work has also shed a light on using DCC to achieve batch screening of highly selective ligands/receptors for homologous biomolecules facilely.

3. Photoswitchable DCLs

Configuration and conformation of a compound decide its covalent/non-covalent interactions with other library members, altering the systemic properties of a DCL. Dynamic isomerization provides DCLs with versatile status of complexity in spare of replacing chemicals in the systems, helping it emerge switchable functions. Photo-switchable molecules can reversibly undergo *in-situ* isomerization upon photo-irradiation.[18] Then the thermodynamic metastable isomers of library members are able to trigger new downstream covalent/non-covalent responding cascades in a DCL, thereby transiently emerging another status of complexity and new possible functions.

Azobenzene is a well-known photo-switchable unit. At thermal equilibrium, its *trans* structure is dominant while the *trans* isomer is converted to the *cis* isomer under UV-irradiation. Waters et.al. reported the first photo-switchable DCL of coupling the azobenzene unit with hydrazone exchange (Figure 4A).[19] The dominant species of the library were *trans* isomers of the azobenzene macrocycles at thermal equilibrium. Shining UV-light (360 nm) to the DCL would lead to conformational change of the library members from *trans* to their corresponding *cis* structures. A pentaproline template was able to stabilize and amplify a *cis* species. The complexation of the template with the *cis* species slowed down the thermal relaxation to the *trans* form.

Like the azo N=N group, the C=N group of hydrazone is also conformationally photo-switchable between *E* and *Z*.[20] Together with its constitutional dynamics, the Lehn's group

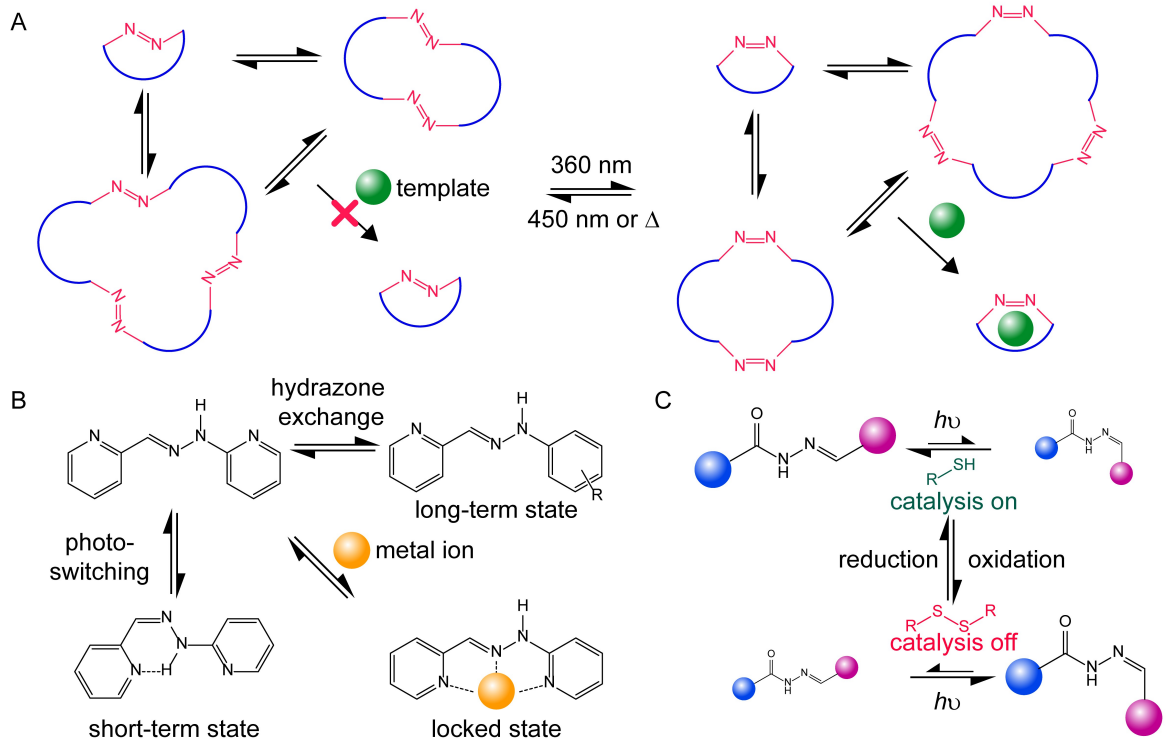

Figure 4. A) Templation of a photoswitchable DCL prepared from an azobenzene building block.[19] B) Configurational exchange, constitutional exchange and metal coordination of library members enable the DCL with short-term, long-term and immobile information storage state.[21] C) Nucleophile thiol catalyzes *Z*→*E* conversion. Catalysis could be deactivated by oxidizing thiol into disulfide.[22]

developed a system based on pyridyl and acylhydrazone where there were multiple dynamics at different time scales achieved by elegant molecular design (Figure 4B).[21] The configuration of *E* could be isomerized to that of *Z* shortly upon UV-irradiation for the relatively low activation energy barrier, so did its reverse process. As the constitutional dynamics is from dynamic covalent exchange that has a relatively high activation energy barrier, it needs a long-term time scale to fulfil the reaction for the new chemical entity. The system can also be locked or unlocked by controlling the coordination between the terpyridine-like acylhydrazone library members with metal ions, adding a relatively immobile time scale to the system. As configurational and constitutional dynamics can all be utilized in DCC to generate "hits" to molecular information input, this work provided us a prototype of multi-timescale molecular information storage system.

Recently the Otto's team discovered that aromatic thiols can work as efficient nucleophilic catalysts to speed up *Z*→*E* conversion (Figure 4C).[22] Given the catalyst thiol could be oxidized to dysfunctional disulfide, the authors further used the oxidation state of the catalyst and the UV irradiation to control the *E*/*Z* state of the whole system. Notably, this external control method does not depend on molecular design for the building blocks or templates in the DCL or have any effects on the final constitution of the DCL. Therefore, this concept can be applied as a broad-spectrum method for controlling the diversity of an acylhydrazone-based DCL. And the authors also gave a reasonable outlook that, in photo-pharmacology, the intracellular dynamic redox pair of glutathione and glutathione disulfide can be harnessed to regulate the pharmacokinetics of photo-inactivated drugs.

Very recently, the Hecht's group has designed a photoswitchable ketone which can perform dynamic covalent imine/hydrazone formation.[23] The condensation and the cleavage processes were precisely controlled by irradiation of lights at different wavelengths, resembling an intermolecular energy ratchet. Though this example is not based on DCC, it operated dynamic covalent chemical reactions by light, opening a door of controlling complexities of DCLs by using light via photoswitches.

Sulfoxide isomerization is another photo-switching tool. Stefano and Lanzalunga *et al.* equipped two sulfinyl groups in the same molecule thianthrene dioxide **4** (see Figure 5).[24] Upon UV irradiation at 280 nm of *trans*-**4** in C_6D_6 and other organic solvents, a partial *trans*-**4** was isomerized to the *cis*-**4** as analysed by ^{1}H NMR. The two interconverting isomers formed a simple DCL where the equilibrating species were brought about by electromagnetic irradiation rather than the thermal bond-forming and bond-breaking processes. As $SnCl_2$ bound with the *cis*-**4** far more effectively than the *trans*-**4**, it worked as a template molecule that could almost fully shift equilibrium to *cis*-**4**. These results suggest that the sulfoxide isomerization proves a useful photo-switchable reaction for DCC.

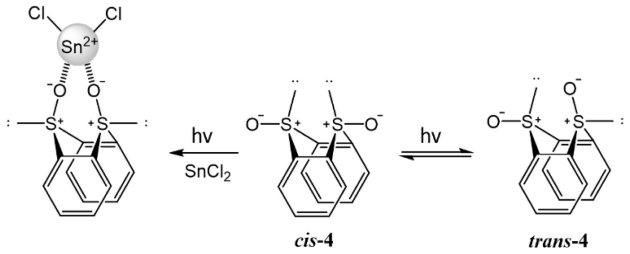

Figure 5. Photochemical interconversion and templated-amplification of two diastereoisomers *cis*- and *trans*-thianthrene dioxide **4**.[24]

4. DCLs in Multiple Phases

Interfaces between multiple phases are everywhere in biological systems and govern the exchange of substances and energy. Exchanging behaviour within DCLs could also be governed by their inhabiting multi-phase environments. The discrimination of affinity between building blocks/templates and multiple phases would generate a driving force to re-assign the DCL within multiple phases, providing us an opportunity to amplify the desirable components, modify surface patterns and address the inherent analysis and purification challenges in DCLs.

Besenius *et al.* functionalized a resin with template molecules and developed a strategy of solid phase synthesis of a DCL to identify receptors for fixed templates.[25] Such resin-directed synthesis suggested a convenient approach to screen and purify the target receptor molecule.

Apart from the resin based solid-liquid diphase systems, DCLs containing nanoparticles also have been well studied. Kay and his co-workers first functionalized gold nanoparticles with a linker terminated by a hydrazine group.[26] The surface of the gold nanoparticles can perform hydrazone exchange with various functional aldehydes, providing a simple approach for reversibly switching the properties *i.e.* solvophilicity of the nanoparticles. The surface of gold nanoparticles could also be equipped with aldehyde groups to have reversible reactions with a range of hydrazines. Under the direction of a biomolecular template DNA, the surface of the nanoparticles was localized by hydrazines with positive charges, transferring the molecular information of DNA into the positive pattern on the surface of the nanoparticles.[27] This work revealed an unprecedented spatial control method of the functional groups on a nanoparticle.

It is well accepted that changes of the environment are able to direct the evolution of DCLs. Reversely, the component change of the library may alter the environment. The Lehn's team reported the first example that the adaption of a DCL could lead to liquid/liquid phase separation (see Figure 6).[28] By temperature change or on the addition of a salt, a hydrophilic carbohydrate or a hydrophobic solvent, the acetonitrile and water phase separation was observed. The component analysis revealed that the hydrophobic species were dominant in the organic phase and the hydrophilic ones were mainly in water. These results suggested that the library could amplify the fittest components for each phase and accordingly induce the

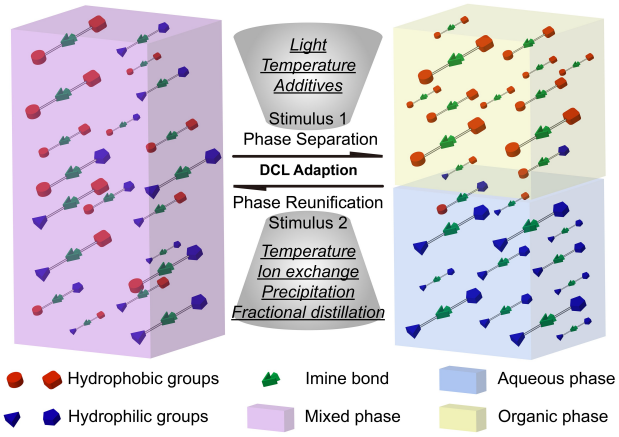

Figure 6. Liquid/liquid phase separation induced by DCL adaption under the stimuli of temperature, ion exchange, precipitation and fractional distillation.[28]

separation of the organic and water phase. The two separated phases can be reunited by gentle heating, ion exchange, precipitation, or fractional distillation. The library component returned to the original distribution as that in the homogeneous solution.

Sub-molecular resolved scanning tunnelling microscopy (STM) has been applied to investigate the constitutional dynamics of a DCL directed by olefin metathesis at the interfaces.[29] By the collaboration by Prof. Zhang and Prof. Hu's group, the authors not only visualized the formation of species, but also found that the confinement on the highly oriented pyrolytic graphite (HOPG) surface played significant roles in the dynamic system and discovered linear polymers and some specific oligomers at the interfaces that were not obtained in bulk solutions.

DCLs in multiple phases presented by above mentioned works may pose a potential pharmaceutical application. The properties of the solid-liquid surface on drug delivery nanoparticles have a critical impact on their storage stability, pharmacokinetics/biological interaction, adsorptive property and targetability/penetrativity toward specific tissue or cell.[30] However, precise and reproducible control or characterization of chemical constitution on those nanoscale surfaces still remain a great challenge, limiting the development of advanced function for these nanoparticles. As a bottom-up constitutional strategy that could explore selective binder for biomolecules or answer to molecular/environmental information, DCLs in multiple phases reveal a novel path to address this challenge, especially if it can make to cooperate with the microfluidic technology, where the high-throughput liquid-liquid multiphase interplay precisely tune the overall geometry, chemical composition and drug loading content of the drug delivery nanoparticles.

5. Remote Kinetic Control

Besides the conventional approach of adding chemical reagents into DCLs, applying exogenous physical transduction signals (shear stress, light, heat, ultrasound) have recently emerging as a remote strategy to realize kinetic control. Compared with chemical modulations, this flexible yet non-invasive procedure not only provides diversified parameters to establish multi-layer controllability and complexity, but also avoids engaging additional challenges of analysis and purification to DCLs. Actually, this remote kinetic control strategy has been extensively studied among many applied researches like polymerization[31] and drug delivery,[32] which could be suggestive references to its inchoate implementation in DCLs for exploring functions. In this section there will be cases that apply physical transduction signals on DCLs to directly manipulate their covalent/non-covalent processes, in light of which we discuss their potential as prototypes for developing smart materials.

Otto's group have conducted a series of work based on a mechano-sensitive self-replication system constituted by a dithiol building block tailed with a GLKLK peptide that could self-assemble into β-sheets (Figure 7A).[33] These systems realized remote kinetic control by shear stress. Without any mechano-interference, the DCL was dominated by trimer and tetramer of the building blocks. However, upon applying shear stress to the system, fibers stacked from β-sheets-linked hexamers/heptamers (one kind at a fiber) were formed exponentially from a nucleation-elongation self-replication process. Hexamers/heptamers acted as the nuclei, at the ends of which elongation of fibers took place. When there was no shear stress, the quantity of the nuclei was under the threshold value to initiate self-replication while trimer and tetramer dominated in the system. Once sufficient shear was applied, the quantity of the nuclei would dramatically increase above the threshold value for elongation by stress-induced nuclei fragmentation. Then this cyclic process finally turned into exponential self-replication induced by mechanical agitation. While depending on it was rotational or oscillatory shearing, fiber could be more favorably formed by heptamers or hexamers. Thus it revealed that shear modes also had a major impact. By characterizing the fiber length formed upon different constant shear rates, they also found that fiber length had a negative correlation with the shear rate.[34] More excitingly, when the shear rate was above 16850 s^{-1}, fiber length exhibited a very narrow polydispersity index (PDI) between 1.04 ~ 1.06, presenting a fascinating approach for controlled living supramolecular polymerization.

Furthermore, they added another remote kinetic control factor, photo-irradiation, into the mechano-sensitive system.[35] Without photo-irradiation, adjacent hexamers within the fiber stayed inert with each other so the fiber remained as fragile supramolecular polymers. However, with the irradiation of 365 nm UV-light, disulfide bonds from adjacent hexamers were activated and started to form disulfide-linked polymers within the fibers. As a result, the fibers were covalently captured and attained more stability than the non-irradiated ones. The more inspiring thing was that the photo-irradiation finally helped the systems step over the stress-induced quantitative changes and completed a photo-induced qualitative change to transform

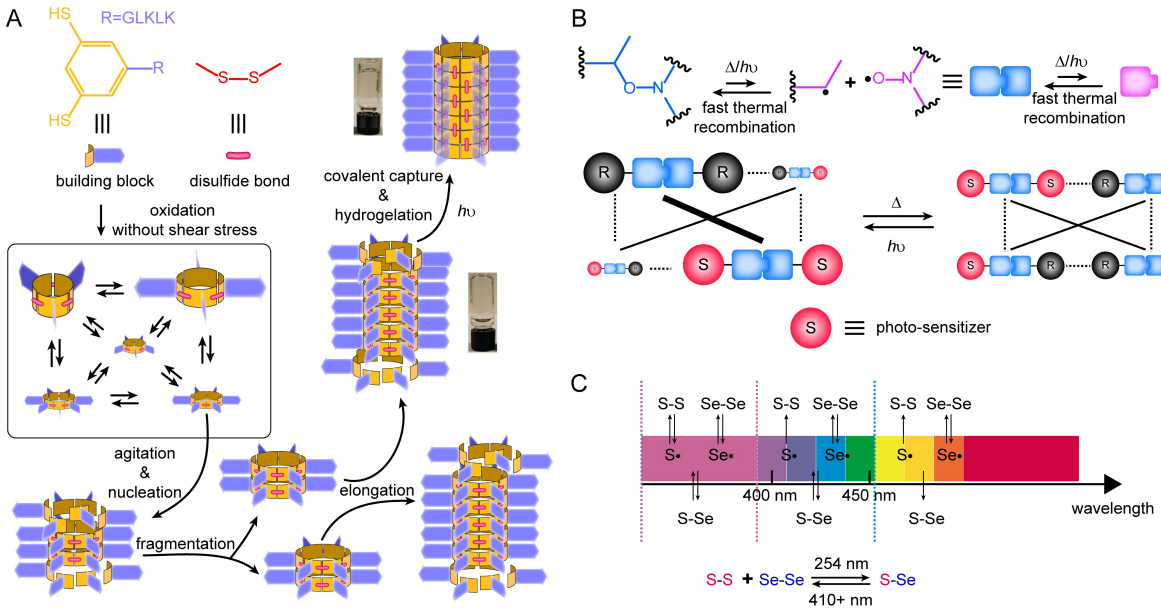

Figure 7. A) Dithiol building block tailed with a GLKLK peptide that could self-assemble into β-sheets constituted a trimer&tetramer-dominated DCL when there was no shear stress. Fibers stacked from β-sheets-linked hexamers self-replicated by a nucleation–fragmentation–elongation mechanism upon agitation induced shear stress. Photo irradiation covalently captured the fibers and transformed the DCL into a hydrogel.[35] B) Molecular information within the DCL could be repeatedly amplified/neutralized by selectively photo-activating the photo-sensitized alkoxyamines and evenly thermo-activating all alkoxyamines.[37] C) Decrease/increase the wavelength of input light signal to sequentially turn on/off the metathesis among S–S, S–Se and Se–Se bonds to manipulate the constitution of DCL.[38]

into a supramolecular hydrogel, realizing a two-stage kinetic control.

Speaking of photo-irradiation, it has been a major kind of exogenous physical transduction signal, exhibiting a high spatio-temporal resolution and infinite controllability on its spectral parameters to regulate chemical systems mainly by photo-switchable isomerization[18] and photo-cleavable deprotection.[36] However, rare examples have used photo-irradiation to directly manipulate the kinetic factors of metathesis in DCLs to access molecular information. Lehn *et al* modified alkoxyamines (AOAs) into room-temperature photochemically yet thermo-chemically dynamic compounds (SSs) by grafting them with photo-sensitizing groups on distal ends, while the non-sensitized analogues (RRs) could only be effectively activated through heating (Figure 7B).[37] Uniform distribution among library members of RR, SS, SR and RS were reached via thermally activating the DCLs started with RRs and SSs, for all local maxima energy states were accessible to every library member. In turn RRs and SSs were amplified after photo-activation. Because RRs kept draining into kinetic trap upon formation without thermo-activation, leaving stoichiometrically accumulated SSs. Thus with alternatively applied irradiation and heat, reversible process of amplification and neutralization of molecular information was achieved.

In a parallel situation, Xu's group developed DCLs that utilizing different wavelengths to sequentially turn on/off the metathesis among S–S, S–Se and Se–Se bonds (Figure 7C).[38] All the bonds were alive and commutative with each other under 280 ~ 390 nm UV-irradiation, which could also execute a program reset in the DCL at any time. Only Se–Se and S–Se bonds were effectively communicating under 410 ~ 500 nm irradiation, consuming S–Se bonds to amplify the kinetically trapped S–S bonds and the stoichiometrically accumulated Se–Se bonds. Wavelength above 500 nm would leave Se radicals to talk with themselves. No more S radicals would be released for S–S formation. Thereafter this phenomenon was translated into on-demand photo-switching self-healing polymer materials and dynamic polymer vesicles,[39] exhibiting potential application in controllable degradation material and drug release for tissue engineering materials. As you would perceive now, the works from Xu's group are also good cases supplementing the situation of communicating-asynchronous reversible reactions in section 2. However, it was the remote kinetic control strategy that be on top of all the tricks. Thus we decided to illustrate them here.

Besides the above mentioned series of cases, Fritze and Delius conducted a work that novelly utilized only ultrasound to remotely turn on disulfide metathesis, in spite of any oxidation reagents or thiolate groups, just disulfides and solvent within the system.[40] Upon sonication, the yield of the metathesis product exhibited an exponential growth. Once the sonication stopped in the middle, the growth then became linear. Halting sonication and add a radical scavenger (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) at the same time, the growth would then pause. However, same disulfides in solvents other than chloroform or bromoform could not undergo the metathesis upon sonication.

6. Conclusions and Outlook

Systems chemistry has become an emerging field dealing with complex chemical systems to uncover their underlying fundamental principles and explore emergent functions. Thanks to reversible chemical reactions used for fabricating dynamic molecular networks, DCC has become a powerful tool of providing ideal platforms for studying the subject of systems chemistry. Compared with the sophisticated function achieved from living organization, the exploration of function from man-made molecular network is lagging. Thus, in this minireview we have summarized strategies for exploring functions from DCLs.

The original concept of DCC was conceived to find out suitable receptors to the target molecules. We have noticed that the increase of complexity in DCLs could provide more possibilities of obtaining better receptors. The complexity could be enriched directly by introducing more types of reversible chemical reactions. It also could be enriched by more complexed environments. Given the adaptive nature of DCLs, dynamic isomerization of the components within mediated by photo-irradiation drives the whole system into different status to explore functions. Also multi-phase DCLs can interplay along the interfaces to re-assign their own distribution to help emerge functions. Thermodynamic control dominates the synthetic processes in the above strategies. Introduction of kinetic control to DCLs can add kinetic elements into the downhill systems, resulting in the emergence of unexpected functions. Accordingly, the concept of remote kinetic control has been noticed and its combination with DCC has also been summarized.

As we have reviewed, so far, the most functions from DCLs have been in the direction of synthetic receptors for the target molecules. Although self-assembly in the complex chemical systems is able to drive the equilibrium to selectively synthesize the very molecule that can self-assemble and further give rise to self-synthesizing nanostructures, their functions in more advanced applications such as in drug delivery, tissue engineering and energy have not been reported yet. We envision this situation will be changed if related functional groups are equipped in the relating building blocks and templates.

Apart from the suggestion on molecular design, it will be also significant to extend the application of other technologies i.e. microfluidics into the area of DCC. We have discussed that the physical condition like multiple phases can have an impact on the component selection in DCLs. Reversely, the adaption of the library also could give adjustment to its environment and result in phase separation. Indeed, microfluidics is capable of offering unique physical conditions that would direct the self-assembly[34] of species in DCLs, which will allow us to isolate intermediate states and unprecedented non-equilibrium structures and to achieve novel functions. It is challenging to develop complex systems with functions as powerful as life. Nevertheless, as the working principle at systems level underneath the synthetic molecular networks is alike that of biological systems, we are confident that DCC has a very bright future to mimic nature and achieve functions in catalysis, information translation and production of energy.

Acknowledgements

We greatly acknowledge the financial support from the National Natural Science Foundation of China (21801052, 21562018), Hainan University start-up fund (KYQD(ZR)1852), the construction program of research platform in Hainan University (ZY2019HN09), the University of Jyväskylä, the start-up fund of the Turku Collegium for Science and Medicine (TCSM), the University of Turku, the Finnish Culture Foundation, the Sigrid Jusélius Foundation and the Academy of Finland (Decision No. 318524).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: chemical complexity · dynamic combinatorial chemistry · kinetic control · noncovalent interactions · supramolecular chemistry

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Manuscript received: March 25, 2020
Version of record online: April 22, 2020