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Antiparallel Dynamic Covalent Chemistries

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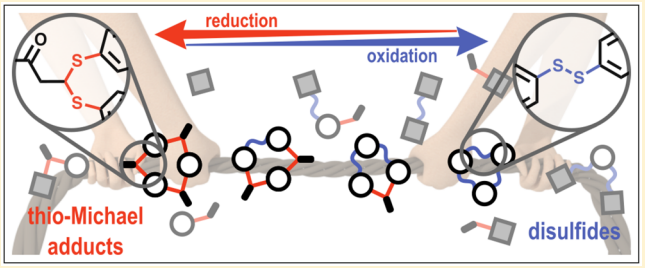
Supporting Information

ABSTRACT: The ability to design reaction networks with high, but addressable complexity is a necessary prerequisite to make advanced functional chemical systems. Dynamic combinatorial chemistry has proven to be a useful tool in achieving complexity, however with some limitations in controlling it. Herein we introduce the concept of antiparallel chemistries, in which the same functional group can be channeled into one of two reversible chemistries depending on a controllable parameter. Such systems allow both for achieving complexity, by combinatorial chemistry, and addressing it, by switching from one chemistry to another by controlling an external parameter. In our design the two antiparallel chemistries are thiol−disulfide exchange and thio-Michael addition, sharing the thiol as the common building block. By means of oxidation and reduction the system can be reversibly switched from predominantly thio-Michael chemistry to predominantly disulfide chemistry, as well as to any intermediate state. Both chemistries operate in water, at room temperature, and at mildly basic pH, which makes them a suitable platform for further development of systems chemistry.



INTRODUCTION

Complexity in chemistry; reaction networks, coupled equilibria, spatiotemporal compartmentalization, or feedback loops often result in emergent behavior characterized by responsiveness, adaptivity and nonlinearity; life being the prime example.[1−9] Even though our creations cannot yet rival those of Nature, the rise of interest in systems chemistry gives hope that the gap will decrease as we gather understanding and devise new mechanisms to create and control complexity.[10]

One of the more successful methods to generate complex (supra)molecular systems is dynamic combinatorial chemistry (DCC).[11−23] In this approach, a few small building blocks react reversibly with each other, giving rise to mixtures of much more complex library members, together constituting a dynamic combinatorial library (DCL). In its relatively short history, it has led to practical outcomes, such as discoveries of biologically active compounds[24−31] or responsive materials,[32−41] as well as to discoveries of fundamental value, such as emergence of self-replicating molecules[42−47] or complex reaction networks and cascades.[48−57]

DCC usually utilizes one type of dynamic covalent bond[58−61] to generate molecular diversity. Addition of a second type of reversible chemistry not only adds another layer of complexity, but also provides an additional handle to control it. However, only a small fraction of reported work takes advantage of this strategy,[62−76] and only a handful describe three or more dynamic covalent chemistries in a single system.[77−82] This situation stands in a stark contrast[83] with supramolecular systems, where several different interaction motifs are often used simultaneously.[84−87]

Combined combinatorial chemistries can be orthogonal (Scheme 1a), when one functional group can only be involved in formation of one covalent bond type, or promiscuous (Scheme 1b), which means that some of the functionalities can form more than one type of dynamic covalent bonds. For example, thiol−disulfide and hydrazone exchange are a pair of orthogonal chemistries, as in aqueous solution thiols do not form stable adducts either with aldehydes, or with hydrazides.[73,74] In such cases the two chemistries operate completely independently, unless they are coupled by an independent interaction, e.g., noncovalent bonds. On the other hand, libraries based on thiol−disulfide exchange can easily communicate with thioester-based libraries, as both reactions involve promiscuous thiol building blocks.[75] Depending on exact chemistries used, reaction conditions may be tuned in such a way that exclusively one type of exchange is active, or that two or more chemistries operate simultaneously (Scheme 1a). This is however more often defined by the nature of the exchange chemistries, than by the intentions of the experimenters. In the case of disulfides and thioesters, for example, the two chemistries tend to only work simultaneously at mildly basic pH. In contrast, hydrazone exchange, which normally operates at moderately to strongly acidic pH, was only

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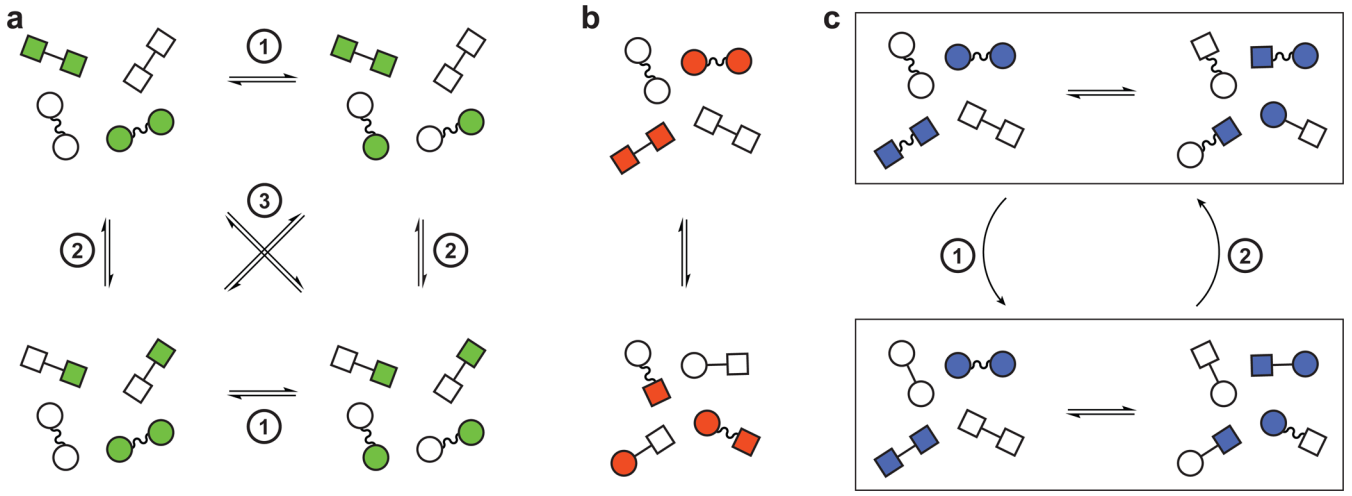
Scheme 1. Possible Relations between Binary Dynamic Covalent Chemistries[a]



[a]Different exchange types are represented by bond and building block (BB) shapes, whereas colors denote BB identity. For clarity, we omitted the issue of bond directionality/symmetry. (a) Orthogonal chemistries: under conditions (1) only one type of exchange is active, under conditions (2) only the other, whereas under conditions (3) both exchanges operate simultaneously. Under all conditions BBs exchange only within the same type of chemistry. (b) Promiscuous chemistries: BBs are shared by different chemistries. However, the number of components involved in each exchange pool remains constant. (c) Antiparallel chemistries (this work): BBs participate in both chemistries, but the ratio of the two chemistries can be tuned by altering the system conditions.

active simultaneously with disulfide exchange at the cost of both reactions being slow.[73]

Combining exchange chemistries that can communicate leads to another interesting possibility: if the two exchange pools share a building block, increase of its amount in one pool necessarily depletes it in the other one. In other words, the distribution of covalent bond types is reflected by the composition of the DCL, leading to the concept of antiparallel chemistries (Scheme 1c). The term "antiparallel" reflects that both reactions can take place at the same time (thus *parallel*) but occur at each other's expense (hence *anti*). In a system that comprises two parts which share a constituent that can be shifted from one to another by an external parameter, a new level of control emerges. Together with the thermodynamic control inherent to the DCL itself, its composition now also depends on the external parameter, which is in the hands of the experimenter. Thus, in antiparallel chemistries the two reactions can occur simultaneously and communicate through a common reactant, which is distinct from the situation in orthogonal chemistries in which all reactions operate independently of each other.

In our design of antiparallel chemistries we decided to combine thiol−disulfide[27,31,88−94] and thio-Michael exchange[95−99] (Figure 1). The choice stems from the fact that both chemistries involve thiols, but the library members themselves require sulfur atoms to be in different oxidation states. Disulfides form from thiols by oxidation, whereas formation of thio-Michael adducts does not result in oxidation of thiols. Therefore, the oxidation state of the library controls the disulfide/thio-Michael ratio. In a fully reduced library there can be only thio-Michael adducts, while oxidation increases the amount of disulfides at the expense of the thio-Michael adducts until the library is fully oxidized, and the thio-Michael adducts are replaced by disulfides. Such antiparallelism of these two chemistries is possible only because the thio-Michael reaction has different number of thiols on both sides of the equilibrium, allowing for depletion of its reaction pool by thiol removal.

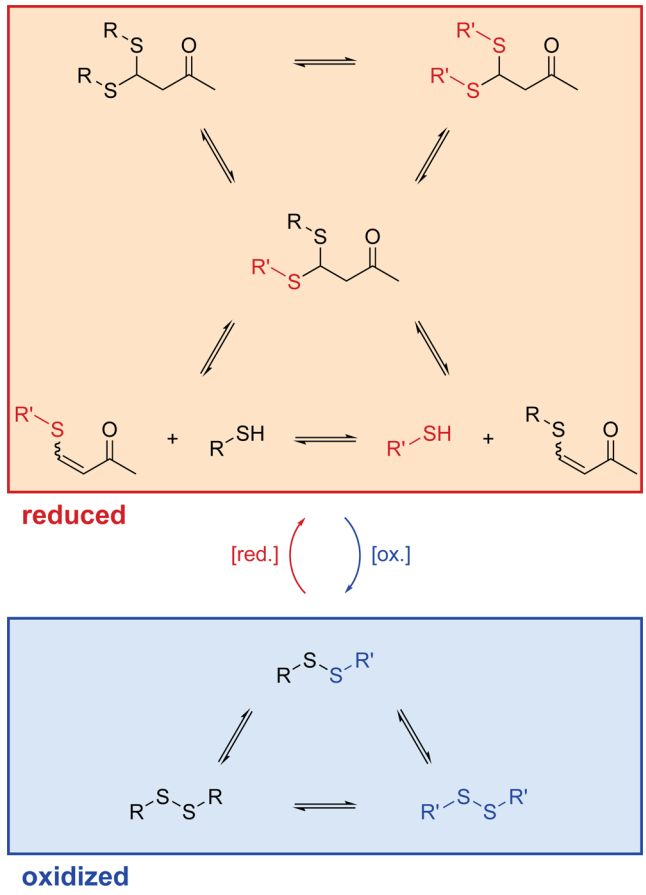


Figure 1. Antiparallel exchange chemistries used in our design: top - thio−Michael addition and exchange; bottom - disulfide exchange.

Such operation would not be possible with e.g., thioester exchange, where both sides of the equilibrium contain the same number of each species.

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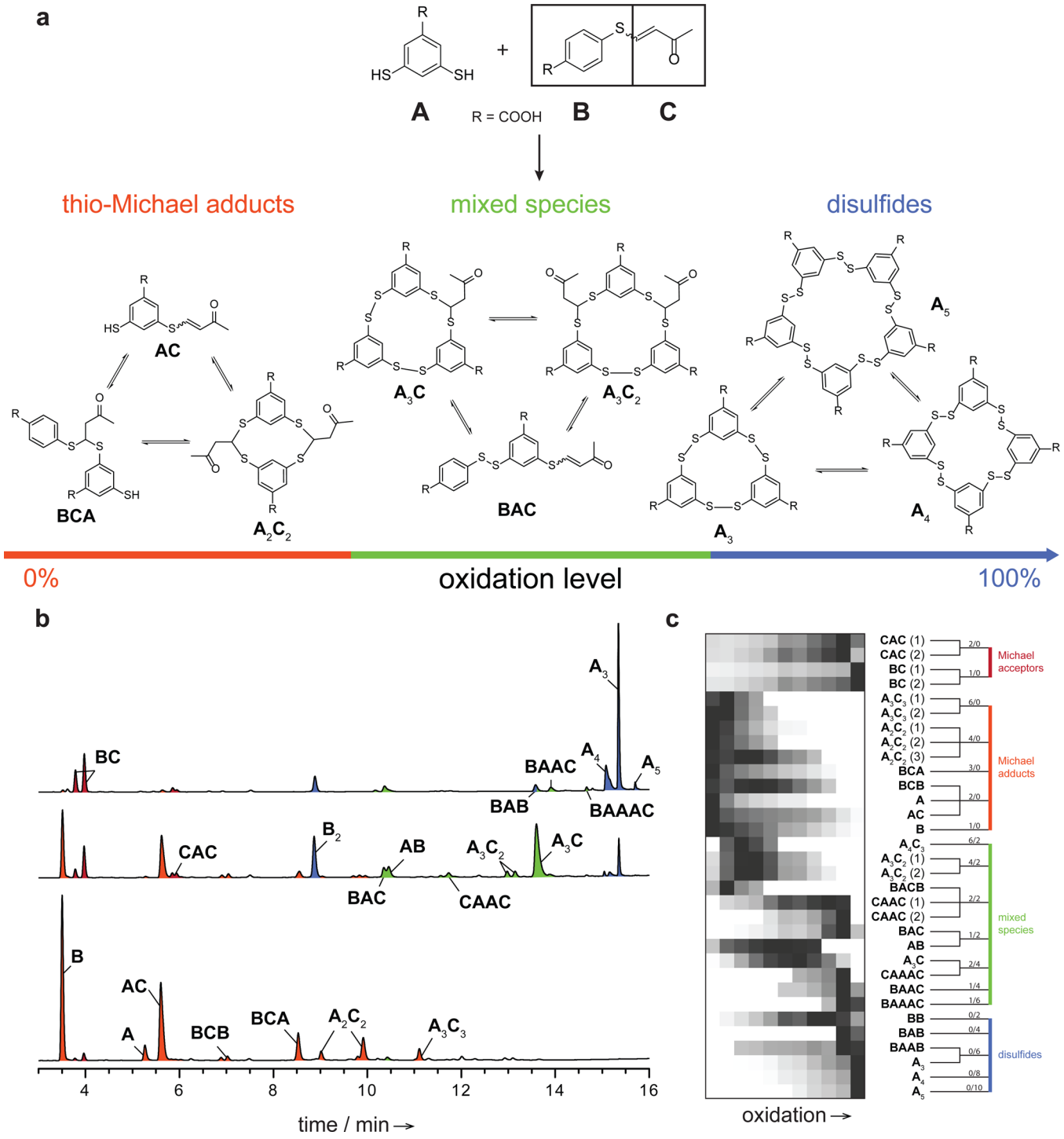

Figure 2. Model system for antiparallel dynamic chemistry. (a) Building blocks (above) and characteristic representatives of thio-Michael adducts (left), disulfides (right), and intermediate species (middle); (b) chromatograms of the antiparallel DCLs at different oxidation levels: fully reduced (bottom), 50% oxidized (middle), and fully oxidized (top); (c) heat map plot showing the abundances of the library constituents depending on the oxidation level (shade represents the peak area normalized to the maximum amount the particular species reach; the numbers next to the species show the red/ox ratio of the sulfur atoms in their structures).

RESULTS AND DISCUSSION

For the thiol building block we chose dithiol **A**, already known to form a series of macrocycles upon oxidation,[31] while instead of a classical Michael acceptor we decided to use **BC**, previously reported by Joshi and Anslyn (Figure 2a).[96] The latter, being a Michael acceptor with one thiol group already present (and unable to dissociate into thiol and alkyne), is in fact bivalent, which means that in combination with **A** it can give rise to a mixture of linear and macrocyclic compounds, thus being a promising starting material for making diverse DCLs. Upon mixing the starting materials in the absence of oxidants we expected a mixture of linear and macrocyclic thio-Michael mono- and bis-adducts would form. Mixing fully oxidized **A** with **BC**, on the other hand, should not lead to any changes, as

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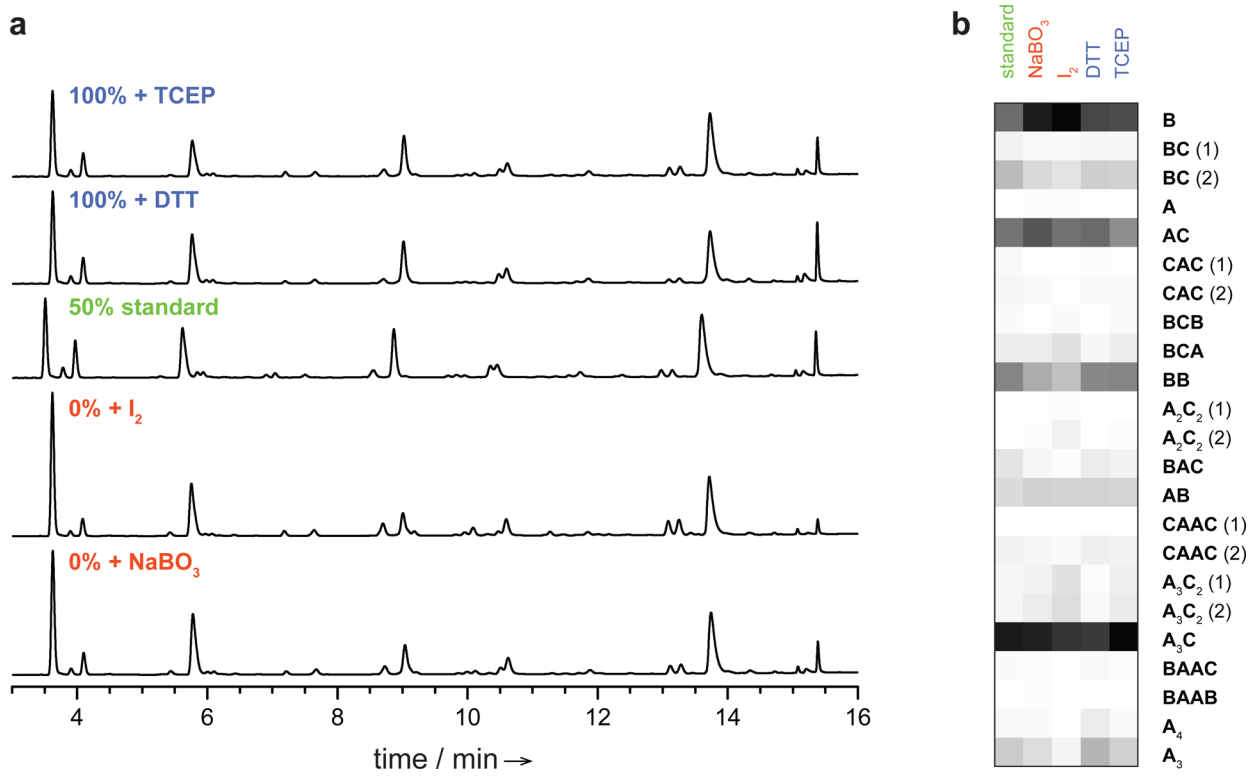

Figure 3. Redox reversibility of the thio-Michael–disulfide system. (a) Comparison of 50% oxidized libraries obtained in five different ways (from top to bottom): addition of reducing agents (TCEP or DTT) to 100% oxidized DCL; mixing half-oxidized **A** with **BC**; addition of oxidizing agents (I_3^- or $NaBO_3$) to a 0% oxidized DCL. (b) Heat map showing the distribution of the library constituents in the 50% oxidized libraries.

disulfides do not form adducts with Michael acceptors, while at intermediate oxidation levels the system should contain the thio-Michael adducts, disulfides and possibly a number of species containing both types of bonds. (Note that in fully oxidized libraries, building block **C** has to be present as a single Michael adduct as it cannot undergo a β-elimination. Thus, such DCLs will contain 2/3 of their **A**,**B** content in the form of disulfides and 1/3 as single Michael adducts. Fully reduced DCLs will comprise exclusively Michael adducts and thiols. Note that for Michael acceptors that can undergo complete β-elimination, fully oxidized DCLs will not contain any Michael adducts or free thiols.)

To test our hypotheses, we performed two series of experiments, the first to see the outcome of mixing of **BC** with **A** at various levels of oxidation, and the second to see whether the system can be reversibly reduced and oxidized. In the first series we investigated libraries initially containing equimolar amounts of **A** and **BC** (both 2.5 mM), at oxidation levels ranging from fully reduced to fully oxidized, in 10% increments. We prepared these libraries by mixing 5.0 mM solutions of **A** and fully oxidized **A** ($\mathbf{A}_n$) to obtain the desired redox level, followed by the addition of an equal amount of 5.0 mM **BC** (all components were dissolved in an aqueous borate buffer, pH = 8.2). After mixing, the solutions were kept stirred in an oxygen-free atmosphere at r.t. until equilibrated (kinetic experiments showed no changes after 24 h, except for the fully oxidized library), and subsequently analyzed by UPLC, while the library members were identified by UPLC-MS. Control experiments revealed that the UV response is a linear function of the concentrations of the various library members (see Supporting Information (SI) section 3).

The results show that upon mixing **A** and **BC** a diverse library is formed rapidly, containing 20 different detectable species. The expected linear or macrocyclic thio-Michael adducts accounted for a large part of the library (the dominant species are **B** and **AC**, as visible in Figure 2b, bottom). In the fully oxidized library (Figure 2b, top), also expectedly, the disulfides stemming from **A** and the initial Michael acceptor **BC** dominate, while the presence of exchange products ($\mathbf{B}_2$, **CAC**, and **BAB**) can be explained by traces of thiols remaining after oxidation of **A**. Due to low exchange rates, the data for the fully oxidized library may differ from what would be present at equilibrium, but, as later analysis will show, the difference is small in the worst case and the general trends hold at all oxidation levels. Solutions at the intermediate oxidation levels (e.g., 50%, as shown in Figure 2b, middle), together with the thio-Michael adducts and the disulfides, also contain a number of species which contain both kinds of covalent bonds, altogether forming libraries of over 30 different compounds.

Plotting the normalized peak areas of the library constituents against the oxidation level (Figure 2c) shows that the library composition can indeed be tuned by the oxidation level. The thiols and the Michael adducts generally reach their maximum concentrations when the system is fully reduced, and gradually diminish as the oxidation level increases. Disulfides and Michael acceptors (**CAC** and **BC**) follow exactly the opposite pattern, and reach their maximum concentrations at high oxidation levels. The intermediate species, which contain both thio-Michael and disulfide linkage, are nearly absent at the two extremes. Altogether, these observations confirm the initial hypothesis that, in a system comprising thiols and Michael acceptors, the distribution of the bond types and therefore the composition of the library depends on the oxidation level.

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In the second series of experiments we tested the redox reversibility of the system; i.e., whether the library composition can be controlled by an external input, in this case reducing or oxidizing agents. For that purpose we prepared fully oxidized and fully reduced libraries of **A** and **BC**, in a similar way as described for the first series. After 48 h equilibration, which led to the same compositions as described previously, samples of the fully reduced library were oxidized by $NaBO_3$ or I_2, and samples of the fully oxidized library were reduced by TCEP or DTT. For each reagent, 0.3, 0.5, 0.7, or 1.0 equiv were added to the corresponding libraries. The libraries were again left to equilibrate for 48 h and then analyzed by UPLC. The results (Figure 3) show that the system is indeed redox reversible and also that the reactions proceed without any side products, as no new peaks appeared in the chromatograms. Therefore, the library can be switched to any intermediate oxidation level and the corresponding composition by simply adding redox agents, allowing for easy external control. Only the fully oxidized library does not equilibrate readily because the disulfide exchange is catalyzed by thiolate anions, which are absent under these conditions.

Our attempts to rationalize the behavior of the system revealed an interesting phenomenon: as shown above, $\mathbf{A}_n$ macrocycles and **BC** dominate at 100% oxidation, whereas **B** and **AC** adducts are main species at low oxidation levels (Figure 4). However, we can imagine the opposite scenario, where $\mathbf{B}_2$

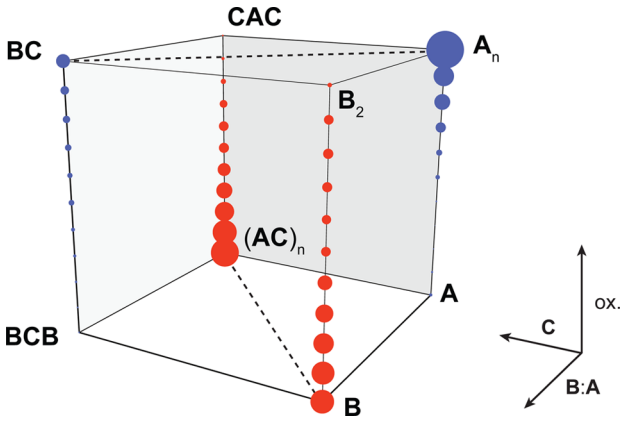

Figure 4. Three-dimensional plot showing abundances of representative DCL member families coupled by antagonistic relations, as a function of the oxidation level of the library. The diameter of the circles represents the summed peak area of library members connected by a vertical edge.

and **CAC** would be the main species in a fully oxidized DCL, with **A** and **BCB** dominating the unoxidized library. Such behavior is most likely caused by entropic contributions. Their effect becomes clear as we analyze the equilibria for oxidized (eq 1) and reduced (eq 2) DCLs, connecting the two alternative scenarios:

$$n\mathbf{CAC} + n\mathbf{B}_2 \rightleftarrows \mathbf{A}_n + 2n\mathbf{BC} \quad (1)$$

$$n\mathbf{A} + n\mathbf{BCB} \rightleftarrows (\mathbf{AC})_n + 2n\mathbf{B} \quad (2)$$

As we can see, the left sides of both equilibra have $2n$ molecules, whereas there are $2n + 1$ molecules on the right sides. Thus, it is entropically preferred to shift the equilibrium to the right side, i.e., in favor of, respectively, $\mathbf{A}_n$ and **BC**, and **B** and $(\mathbf{AC})_n$.

Interestingly, the composition of the system does not follow monotonically from one oxidation extreme to the other. For example, $\mathbf{B}_2$ and **CAC** reach their maximum concentrations at partial reduction while they are both fully oxidized species (Figure 2c). To better understand this counterintuitive behavior, we found it informative to plot different library member families onto a single three-dimensional graph, represented as a cube (Figure 4). One axis of the plot corresponds to **A**:**B** ratio within a library member, another to the **C** content. The third axis corresponds to the oxidation level: as it increases, the thiol:disulfide ratio decreases and double thio-Michael adducts become single adducts. Species sharing an edge of the cube are antagonists,[48,49,51,60,100−102] as they compete for the same building blocks *or* oxidation state. The latter results from the wiring of the network, which makes the antagonistic effects distinct from previous reports based solely on the competition between library members for common building blocks involving only one type of chemistry.

Library members can be mapped onto the cube as a function of their composition and oxidation state of their sulfur atoms. Plotting the sum of all library members corresponding to different oxidation levels for the four composition extremes as a function of library oxidation reveals that the equilibria 1 and 2 dominate only at the extreme oxidation levels. In fact, the diagonals connecting the agonistic species at the favored sides of these equilibria are perpendicular to each other. Therefore, compounds like $\mathbf{B}_2$ that, at full oxidation, suffer from antagonism by entropically favored compounds (equilibrium 1) start to benefit from agonism by compounds that become entropically favored at lower oxidation levels. Hence, despite being fully oxidized themselves they benefit from partial reduction of the mixture. Thus, the concentration of library members is a complex function of the structure of the building blocks, the wiring of the molecular network, and the experimental conditions.

While the design of the thio-Michael system shown in Figure 2 is somewhat unconventional, we also performed similar experiments on a classical Michael acceptor **D** ((*E*)-4-phenylbut-3-en-2-one), while retaining the dithiol **A**. The results (SI, pages S39−S50) show that the concept also applies to more traditional thio-Michael additions, in which only a single thiol adds to the Michael acceptor.

CONCLUSIONS

To conclude, we have designed a system in which two chemistries, namely thiol−disulfide exchange and thio-Michael exchange, operate simultaneously, giving rise to diverse DCLs. As both chemistries use the same building blocks, as one exchange pool grows, the other has to shrink, making these two exchange chemistries antiparallel. Furthermore, as the two pools require sulfur atoms at different oxidation level, external control of their ratio is possible using reducing and oxidizing agents. We envisage that dynamic covalent antiparallelism should be applicable to other pairs of dynamic covalent chemistries, e.g., disulfide/thiazolidine,[103] or the recently developed dithioacetal/disulfide system.[63,104] Especially exciting should be a combination of antiparallel, orthogonal, and communicating chemistries, allowing for complex and addressable feedback between different subsystems. The particular system studied has also shown how the antiparallelism of the two chemistries, combined with opposing entropic effects, gives rise to a complex network of interactions, resulting in nonlinear changes in the library composition in response to the external

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stimulus. Externally addressable complexity achieved in such way should prove useful in functional screening of DCLs, where the library can be biased toward a desired connectivity type, rather than just building block composition.

From the systems chemistry perspective, we are excited to see how antiparallelism creates molecular systems that can adapt to environmental changes by switching to the type of chemistry better fitted for the new conditions. This emergent behavior to some extent resembles homeostatic processes in living organisms, or switching between aerobic and anaerobic metabolisms.

EXPERIMENTAL SECTION

Methods and Materials. Water was doubly distilled prior to use. 4-Mercaptobenzoic acid (technical grade, 90%) and 3-butyn-2-one (96%) used for the synthesis of **BC** were purchased from Sigma-Aldrich and Acros Organics, respectively, and used without further purification. Boric acid and potassium hydroxide utilized for the preparation of buffers and pH adjustment were obtained from Acros Organics and Merck Chemicals, respectively. Sodium perborate, potassium iodide, dithiothreitol (DTT), and tris(2-carboxyethyl)-phosphine (TCEP) used for the reduction/oxidation of **A** and libraries were purchased from Sigma-Aldrich. Acetonitrile (ULC/MS grade) and water (ULC/MS grade) were obtained from Biosolve BV. Formic acid was purchased from Sigma-Aldrich.

Building block **A** was prepared via a previously reported procedure.[31] Building block **BC** was prepared according to the literature.[96]

Library Preparation and Sampling. The 50 mM borate buffer was prepared from boric acid dissolved in doubly distilled water, and adjusted with 1.0 M KOH to pH 8.2. Afterward, it was degassed by nitrogen purging under reduced pressure for 60 min. Libraries were prepared in clear HPLC glass vials (12 × 32 mm) closed with Teflon-lined snap caps purchased from Jaytee. Library solutions were stirred using Teflon-coated microstirrer bars on a magnetic stirrer at 1100 rpm. All experiments were carried out in a glovebox.

We prepared a 5.0 mM stock solution of **BC**, a 10 mM stock solution of **A**, and a 10 mM stock solution of $NaBO_3$. Equal volumes of **A** and $NaBO_3$ solutions were mixed to obtain 5.0 mM oxidized **A**, and left stirring for 3 h before further use. Simultaneously, **A** was diluted twice with buffer solution to obtain 5.0 mM unoxidized **A**.

Libraries were prepared by mixing adequate volumes of **BC**, reduced **A**, and oxidized **A** (as listed in Table S1). The volume of each library was 100 μL.

For UPLC and UPLC-MS analyses, 3 μL samples were drawn from solutions and diluted with 6 μL of DMSO prior to injection.

Redox Experiments. A 6.11 mM stock solution of **BC** was prepared; 5.0 mM stock solutions of reduced and oxidized **A** were used from previous experiments. Solutions were prepared by mixing 550 μL of either reduced or oxidized **A** and 450 μL of **BC** to give equimolar mixtures with a final concentration of 2.75 mM (of each building block). Samples were left for 48 h to equilibrate.

Solutions of redox agents, dithiothreitol (DTT), tris(2-carboxyethyl)phosphine (TCEP), sodium perborate ($NaBO_3$), and iodine in potassium iodide (KI + I_2) (25 mM each), were prepared right before use. They were mixed with the above solutions (reduced or oxidized) of **A** and **BC** in proper ratios (as listed in Tables S5 and S6) to obtain DCLs with oxidation level set as 0%, 30%, 50%, 70%, or 100%, and left for 2 days to equilibrate. Afterward, UPLC analysis was performed.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b02575.

UPLC and LC-MS analysis procedures; experimental procedures for preparation of DCLs for various experiments; kinetic measurements; MS spectra of all compounds; design, experimental procedures, UPLC and LC-MS analysis for the (*E*)-4-phenylbut-3-en-2-one based DCLs (PDF)

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Notes

The authors declare no competing financial interest.

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