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Dissipative Dynamic Libraries (DDLs) and Dissipative Dynamic Combinatorial Chemistry (DDCC)

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This Concept is focused on the key features of dissipative dynamic combinatorial chemistry (DDCC). DDCC deals with transient libraries of compounds, maintained out-of-equilibrium by the consumption of a fuel, whose composition changes upon the selection pressure of kinetic and/or thermodynamic processes. Concepts and definitions of kinetic and thermodynamic dissipative dynamic libraries ("KDDL" and "TDDL"), are introduced and illustrated by a number of actual cases, thus showing the consistency of the present approach. Such concepts and definitions can help establish a common language for this emerging field, which, in our view, has the potential to become highly relevant to supramolecular chemistry.

1. Introduction

The study of the behavior of collections of compounds (Dynamic Libraries, DLs) capable of interconverting each other under equilibrium conditions is identified with either Dynamic Covalent Chemistry (DCvC) or Dynamic Combinatorial Chemistry (DCC).[1] After the seminal papers by Lehn[2] and Sanders & Otto,[3] a growing number of researchers has given relevant contributions to the field, disclosing the high application potential of DCC to discover receptors for target molecules[4] and new catalysts,[5] to synthesize mechanically interlocked molecules (MIMs),[6] to enable the operation of molecular walkers[7] and molecular motors,[8] to develop self-healing polymers,[9] and so on.

The members of a DL interconvert with each other by the reversible formation and cleavage of covalent bonds between terminal groups present in their building blocks.[10] Thus, in most cases, the DL consists of linear and cyclic molecules, with a composition strongly dependent on the operative concentration conditions.[11] Under the influence of an external stimulus (addition of molecular templates, pH changes, etc) the library adapts leading to the amplification of one or few specific members. Quantitative studies on the effects of the addition of template agents have been carried out over the years, which have clarified the roles and importance of the binding energy between templates and bound species[12] and the concentrations of building blocks and templates.[13] Examples of reversible reactions used in DCC are: transesterification,[14] transacetalation,[11b,15] olefin metathesis,[16] transimination,[17] hydrazone[4c,18] and disulfide[19] exchange, etc.

In the last half-decade, the investigation of abiotic dissipative systems[20] has been one of the hottest topics in chemistry research due to the aspiration to reproduce in the laboratory one of the characteristic features of living networks, i.e. the consumption of a fuel[20,21] (a chemical species or radiative energy) to maintain an out-of-equilibrium state, often associated to a particular function, over the time. When the fuel is exhausted, the dissipative system cannot maintain the out-of-equilibrium state anymore and reverts back to its equilibrium, resting state.

Very recently, we and others *(vide infra)* have explored the possibility of obtaining dissipative dynamic libraries (DDLs), which can be defined as transient libraries of compounds, maintained out-of-equilibrium by the consumption of a fuel, whose composition changes upon the selection pressure of kinetic and/or thermodynamic processes. This Concept is focused on the definition of the key features of DDLs with the aim of attempting a simple description of the factors at play in Dissipative Dynamic Combinatorial Chemistry (DDCC).

1.1. General mechanisms for DDLs

A dissipative system is constituted by a catalyst for the conversion of a fuel (F)[22] into waste (W), i.e., a species able to divert the free energy associated to the consumption of a fuel toward more valuable processes. Such a catalyst, playing the role of the deactivated or *resting state* (S_R), should be capable of reacting with the fuel to give an activated or *transient state* (S_T) that persists until a backward reaction, most often promoted by a deactivating reactant, takes the system back to the resting state. For the transient state to be present in significant amounts, the activating reaction must be initially much faster

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than the deactivating one until, under continuous fuel addition, the two rates become equal and a steady-state is reached. Taking inspiration from Hartley and co-wokers,[21b] a catalytic cycle for the fuel reaction can be depicted as shown in Figure 1.

Needless to say, for the efficient exploitation of the free energy of the fuel reaction, the catalytic cycle must be significantly faster than the corresponding background process in which the fuel is converted to waste without the intervention of the catalyst.

Depending on the nature of the resting and transient states, various behaviors can be conceived for such dissipative systems, e.g. molecular motors, dissipative self-assemblies, and DDLs. Here we focus on the possible mechanisms underlying DDLs. In this respect, two main types of DDLs can be envisaged: *kinetic dissipative dynamic libraries* (KDDLs) and *thermodynamic dissipative dynamic libraries* (TDDLs). The two types refer to DDLs under kinetic and thermodynamic control, respectively. Although a huge number of different species usually constitute a DL, to illustrate the two kinds of DDLs, we will consider DLs formed by just three members.

In the case of a KDDL, the resting state S_R, formed by a pool of reactants, reacts with the fuel to produce three transient species, S_T1-S_T3, that constitute the dissipative dynamic library under kinetic control. The three species are then deactivated to regenerate the resting state. In an ideal case, shown in Figure 2, the three kinetic cycles are independent, apart from the fact that they compete for the same pool of reactants and fuel. In fact, the three transient states might physically interact, without reacting with each other, as will be shown below. In any case,

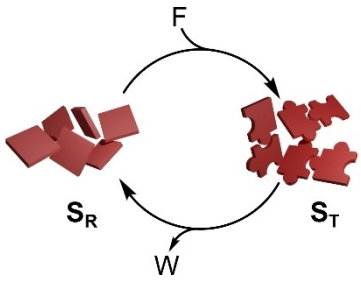
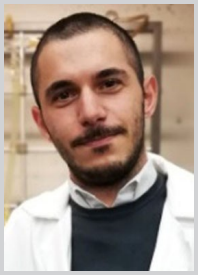


Figure 1. Catalytic cycle for the fuel reaction illustrating a typical dissipative system.

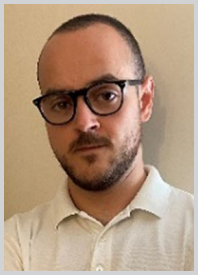
initially the composition of the dissipative library only depends on the relative rates of activation of the competing cycles. However, the composition of the library is dynamic because it can change upon the selection pressure exerted by the deactivating reactant and, possibly, the combined action of other processes acting on the library itself, e.g., phase separation, aggregation, presence of templates, etc.

In the case of a TDDL, the reaction of the resting state with the activating fuel produces a mixture of transient species, S_T1-S_T3, in equilibrium with each other, constituting the dissipative dynamic library (Figure 3). Similarly to the behavior of traditional DLs, the composition of a TDDL could be altered by a suitable template.

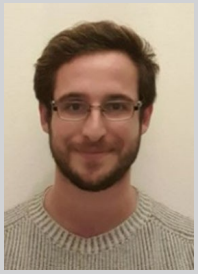
The distinctive trait of a TDDL is that the dissipative library composition depends exclusively on the relative thermodynam-



Daniele Del Giudice earned his master's degree in chemistry at the University of Rome La Sapienza in 2019, receiving the "Excellent Graduate" acknowledgment. Then, he enrolled in a PhD program under the supervision of Prof. Stefano Di Stefano, carrying out research activity on dissipative supramolecular systems such as molecular machines, host-guest interactions, dynamic combinatorial chemistry, and smart materials.



Emanuele Spatola was born in 1997. He studied Chemistry at Sapienza University of Rome and received his MSc degree in 2020. He began his Ph.D. studies in the same year under the supervision of Prof. Stefano Di Stefano working on dissipative supramolecular systems and supramolecular catalysis.



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Stefano Di Stefano received his PhD in Chemical Sciences in 2000 at the University of Rome La Sapienza. After a period in Merck Sharp & Dohme working in the field of clinical research, he came back to La Sapienza, where he is currently Full Professor of Organic Chemistry. His research interests focus on supramolecular chemistry and catalysis, dynamic covalent chemistry, chemically driven molecular machines and dissipative systems. He has been involved in many national and international scientific collaborations with esteemed researchers.

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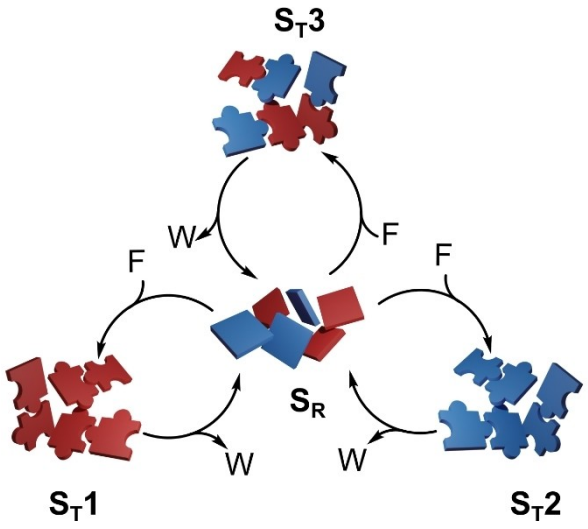

Figure 2. Kinetic scheme for a simple Kinetic Dissipative Dynamic Library (KDDL).

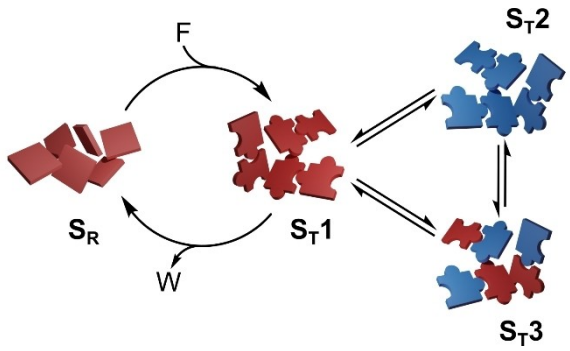

Figure 3. Kinetic scheme for a simple *Thermodynamic Dissipative Dynamic Library* (TDDL).

ic stability of its transient members at the given overall (and instantaneous) concentration of the constituent building blocks. If two or more DDLs follow each other along the same catalytic cycle, there is the possibility of having intermediate cases between K and TDDLs, as each DDL can be under kinetic or thermodynamic control.

As we will show below, the distinction between these two general mechanisms allows us to understand the behavior of the few examples of DDLs available in the literature, but, admittedly, in some cases, the behavior of DDLs is very complex and the distinction can be blurred.

We have selected for our highlighting only those cases promoted by chemical fuels in which it is possible to discern, at least in principle, a clear catalytic cycle for the fuel reaction.

2. Kinetic Dissipative Dynamic Library (KDDL)

Interesting examples of KDDLs were reported by Boekhoven and coworkers.[23,24] They exploited the free energy of the reaction of the fuel 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide (EDC), with water to yield 1-ethyl-3-(3-dimethylaminopropyl)urea (EDU) as the waste. The reaction, occurring in buffered water at pH 6, is catalyzed by carboxylic acids (the resting state) that react with EDC to yield carboxylic anhydrides (the transient state) and EDU. Hydrolysis then dissipates carboxylic anhydrides to regenerate the carboxylic acids (Figure 4a).

In an exciting experiment, propionic acid ($\mathbf{C_3}$) 300 mM, and valeric acid ($\mathbf{C_5}$) 300 mM are left to compete for batches of EDC.[23] The outcome of the experiment depends on the concentration of the EDC batches. At low inflow rates (5 mM h^{-1}), a library of $\mathbf{C_3C_3}$, $\mathbf{C_3C_5}$, and $\mathbf{C_5C_5}$ anhydrides is formed. Under this condition, all the anhydrides are soluble and dissipate at a similar rate within an hour (Figure 4b, left). At higher rates (35 mM h^{-1}), however, the total concentration of the $\mathbf{C_5C_5}$ anhydride exceeds its solubility and phase separates into droplets. The formation of droplets slows down the hydrolysis of the anhydride because it takes place only on the fraction that remains in the solution. Thus, in contrast with the lighter anhydrides, the total concentration of $\mathbf{C_5C_5}$ significantly persists after 1 h, when a new batch of fuel is added. The addition further increases the advantage of $\mathbf{C_5C_5}$ whose concentration keeps on increasing with each subsequent refueling (Figure 4b,

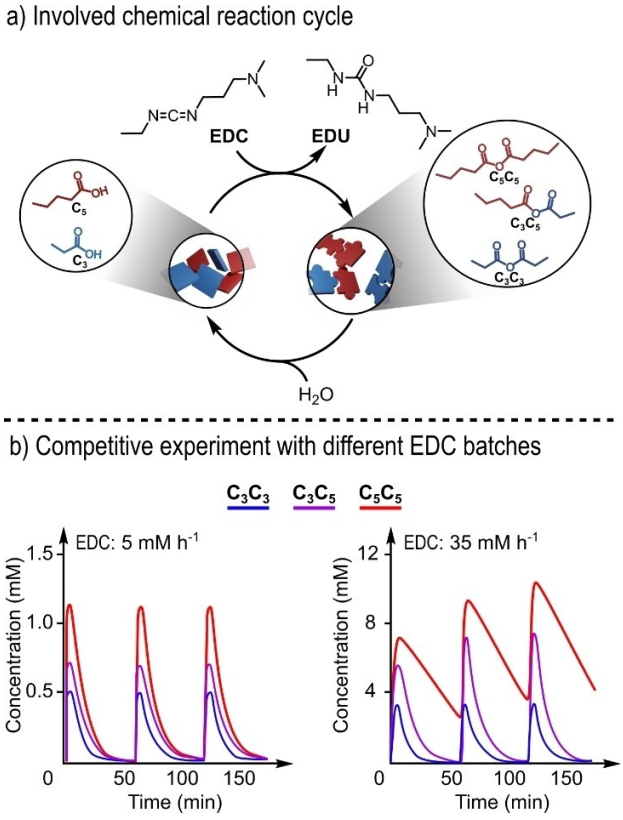

Figure 4. a) The catalytic cycle in which two equivalents of carboxylic acid are converted by EDC into one equivalent of anhydride that is then hydrolyzed to regenerate the starting carboxylic acid. b) The concentrations of the anhydrides over time when 300 mM $\mathbf{C_3}$ and 300 mM $\mathbf{C_5}$ are fueled with 5 (left) or 35 (right) mM EDC each hour.

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right). Thus, after several starvation-refueling cycles, the library self-selects the phase separating anhydride.

A remarkable case of competition in KDDLs has been observed when the precursor 2-buten-1-ylsuccinic acid **1** is put in competition with either competitor **2**, succinic acid, or competitor **3**, 2-hexen-1-ylsuccinic acid, for a batch of EDC (Figure 5a).[24] When 50 mM of the precursor **1** and variable amounts of competitor **2** are fueled with 100 mM EDC, the lifetime of the anhydride product of the precursor **1**, defined as the time period during which the average product concentration exceeds the threshold concentration of 2 mM, decreases on increasing the concentration of competitor **2** as shown in Figure 5b (left). This behavior is easily understood as the two reaction cycles compete with each other for fuel. Rather surprisingly, when the same experiment is carried out with competitor **3**, the lifetime of the anhydride product of the precursor increases (Figure 5b, right), instead of decreasing as in the previous case. This counterintuitive behavior is explained considering that the anhydride product of competitor **3**, in contrast with that of competitor **2** as well as that of the precursor, phase separates into micron-sized oil droplets, which are more resistant to hydrolysis. When the precursor reacts in the presence of competitor **3**, its product dissolves into the oil droplets of the product of competitor **3** and thus is protected from the hydrolysis occurring in the aqueous phase. This behavior is analogous to that of a parasite that benefits from the protection offered by the environment of its competitor and illustrates an intriguing case of direct interaction between transient states in KDDLs.

A very sophisticated DDL was ingeniously devised by Fletcher and coworkers.[25] However, before illustrating such DDL, it is helpful to understand how the single kinetic cycle works.[26] The fuel reaction, providing the driving force for the reaction cycle, consists of the hydrogen peroxide (the fuel) oxidation of the phase separated hydrophobic octanethiol **4a** (the deactivating reactant) to yield 1,2-dioctyldisulfane **5a** (the waste). The reaction cycle is illustrated in Figure 6. The resting state, 2-nitro-5- sulfidobenzoate dianion **6a**, is oxidized by the fuel to give the aqueous disulfide **7a** as a first transient state. The latter undergoes a thiol/disulfide exchange with the hydrophobic thiol **4a** forming 1 equiv. of **6a** and, as a second transient state, an amphiphilic molecule **8aa** that aggregates into micelles. The micelles increase the rate of formation of **8aa** by favoring phase mixing so that the reaction is autocatalytic and the micelles self-replicating. The surfactant **8aa** is destroyed by a second thiol/disulfide exchange with the deactivating reactant **4a** giving the waste **5a** and regenerating the resting state **6a**.

Among the many competitive experiments reported by Fletcher et al,[25] two types of DDLs are worth considering here. The first one is obtained by the competition between sterically differentiated hydrophobic thiols **4a**–**4c** toward the disulfide **7a** (Figure 7a), whereas the second one is obtained by the

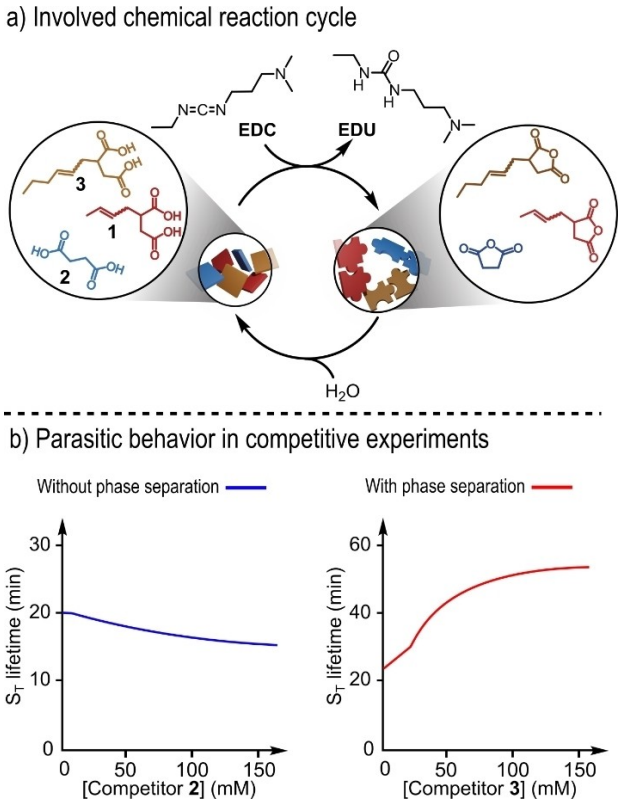

Figure 5. a) The chemically fueled reaction cycle of succinic acid derivatives. b, left) The lifetime of the product of the precursor **1** (transient state S_T) against the concentration of competitor **2** when 50 mM of the precursor and the given concentration of competitor **2** are fueled with 100 mM EDC. The lifetime decreases with increasing competition. b, right) The lifetime of the product of the precursor **1** (transient state S_T) against the concentration of competitor **3** when 50 mM of the precursor and the given concentration of competitor **3** are fueled with 100 mM EDC. The lifetime increases (red line) because of phase separation, instead of decreasing as shown on the left in the absence of phase separation.

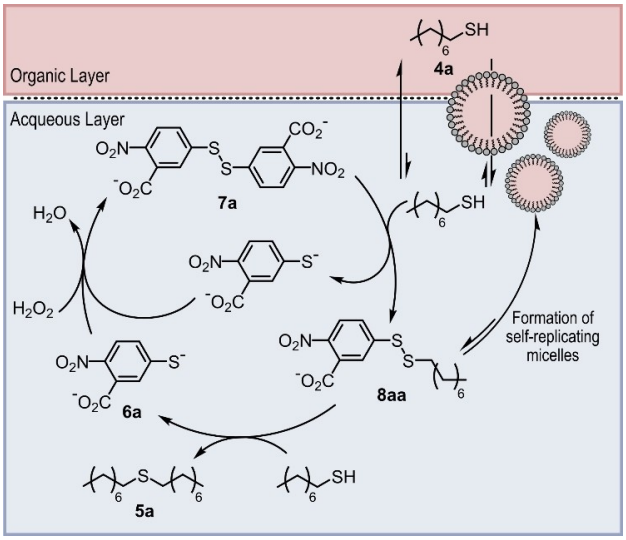

Figure 6. The reaction cycle in which 2 equivs of thiolate **6a**, the resting state, are oxidized by H_2O_2 to disulfide **7a**, the first transient state. The latter, reacting with hydrophobic thiol **4a**, yields 1 equiv. of thiolate **6a** and the amphiphilic disulfide **8aa**, the second transient state, that self-assembles into micellar aggregates. The aggregates catalyze their own formation by solubilizing the hydrophobic thiol **4a**. Finally, the surfactant is deactivated by **4a** to give the waste **5a** and the resting state **6a**.

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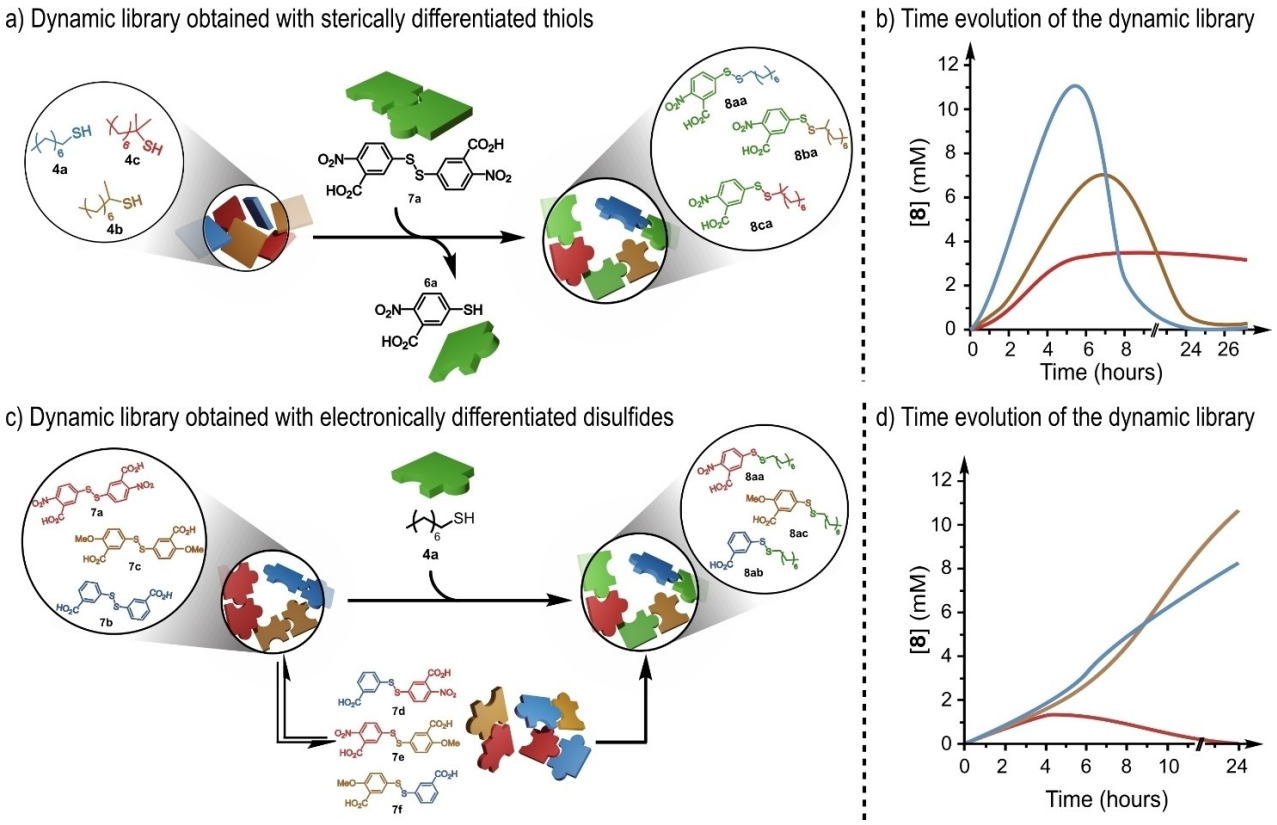

Figure 7. a) Thiol-disulfide exchange reaction employed in this study to obtain the dissipative dynamic library. Destruction step of the surfactant molecules leading to a mixture of dialkyl disulfides waste **5**, and **6a** is omitted for clarity. b) Concentration of the surfactant molecules **8aa**, **8ba**, and **8ca** as a function of time when a mixture of hydrophobic thiols **4a**–**4c** is reacted with aqueous disulfide **7a**. c) Thiol-disulfide exchange reaction employed in this study to obtain the dissipative dynamic library. Note that the mixture of homodisulfides **7a**–**7c** undergoes a fast equilibrium metathesis to give the heterodisulfides **7d**–**7f**. Destruction step of the surfactant molecules leading to dialkyl disulfide **5** and thiolates **6a**–**6c** is omitted for clarity. d) Concentration of the surfactant molecules **8aa**, **8ab**, and **8ac** as a function of time when a mixture of aqueous disulfides **7a**–**7c** is reacted with hydrophobic thiol **4a**.

competition of the hydrophobic thiol **4a** for the electronically differentiated disulfides **7a**–**7c** (Figure 7c). Both the DDLs were studied in the absence of hydrogen peroxide, thus not allowing the closure of the reaction cycle illustrated in Figure 6.

The first DDL appears to be a clean KDDL, in which there is the concomitant formation under dissipative conditions of the three self-reproducing surfactants **8aa**, **8ba**, and **8ca**, as illustrated in Figure 7a. Increasing the steric hindrance at the α position of the alkyl thiol decreases both the formation and destruction rates of the corresponding product surfactant. Thus, a clear succession pattern is observed (Figure 7b): **8aa** is the fastest to form and shortest-lived (pioneer species), followed by **8ba** (the follower species) and **8ca** (the mature species). However, the growth of **8ba** and **8ca** is not completely independent of the growth of **8aa**; they both benefit from a high **8aa** concentration since the corresponding micelles are not substrate specific catalysts.

In the second DDL, the three surfactants **8aa**, **8ab**, and **8ac** are formed under dissipative conditions, as illustrated in Figure 7c. This DDL shows an intermediate behavior between a K and a TDDL, since the three homodisulfides reactants **7a**–**7c** are in equilibrium through a metathesis reaction with the heterodisulfides **7d**–**7f**. The reactivity of the disulfides in the thiol/disulfide exchange reaction depends on the more electron-poor moiety acting as the leaving group, thus the disulfides **7a**, **7d**, and **7e**, all having a nitro group in at least one of the moieties, display a similar higher reactivity. Accordingly, the heterodisulfides **7d** and **7e** may be viewed as activated forms of the parent disulfides **7b** and **7c**, respectively. This emergent mechanism of *dynamic covalent activation* through metathesis would explain why the initial rates of **8aa**–**8ac** formation are so similar before the destruction step favors the most kinetically stable surfactant **8ac** (Figure 7d).

Another case of intermediate behavior between a K and a TDDL is illustrated by the recent investigation of Otto and coworkers on the complexification of self-replicators by chemical fueling.[27] Upon oxidation (air O_2 or $NaBO_3$ used as oxidants), the common precursor **9** can generate an equilibrium mixture of $\mathbf{9}_3$ (a cyclic trimer) and $\mathbf{9}_6$ (a cyclic hexamer) due to fast disulfide exchange reactions allowed by the presence of thiolate functions (Figure 8). Both $\mathbf{9}_3$ and $\mathbf{9}_6$ are self-replicators because of their ability to aggregate and phase separate into fibers, $(\mathbf{9}_3)_{Assembly}$ and $(\mathbf{9}_6)_{Assembly}$, that catalyze the formation of their own building blocks at their templating ends. Aggregation of building blocks is promoted by stabilizing intermolecular β-sheet interactions among the peptide pending arms. However,

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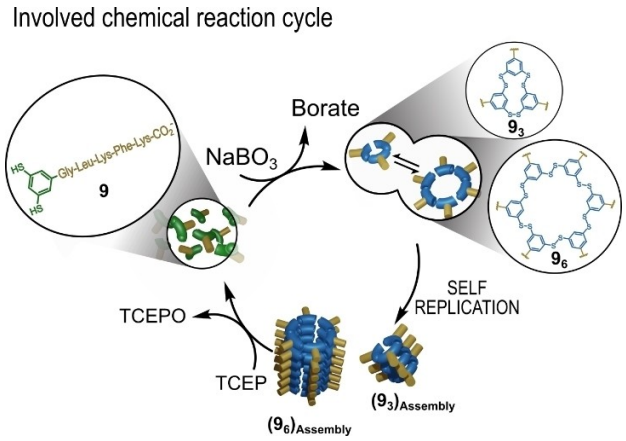

Figure 8. Cartoon representing precursor **9**, self-replicators $\mathbf{9}_3$ and $\mathbf{9}_6$, and fibers $(\mathbf{9}_3)_{Assembly}$ and $(\mathbf{9}_6)_{Assembly}$.

in the presence of the oxidant only, assembly $(\mathbf{9}_3)_{Assembly}$ is favored over assembly $(\mathbf{9}_6)_{Assembly}$ due to its faster formation. Fibers of $(\mathbf{9}_3)_{Assembly}$ are indeed more fragile and, consequently, shorter, thus exposing more fiber ends, which are responsible for self-replication. The process can be schematized as reported in Figure 9a. Conversely, when the system is contextually supplied with the oxidant ($NaBO_3$, the fuel) and a reductant (tricarboxyethylphosphine, TCEP, the deactivating reactant), the mixture of the two replicators behaves as a DDL, and its composition is shifted towards the $(\mathbf{9}_6)_{Assembly}$ (Figure 9b). This shift occurs because, under the new dissipative conditions, the destruction of $(\mathbf{9}_3)_{Assembly}$ is faster than the corresponding process involving $(\mathbf{9}_6)_{Assembly}$, since the reduction reaction occurs at the exposed fiber ends. Thus, while replicator $\mathbf{9}_3$ is

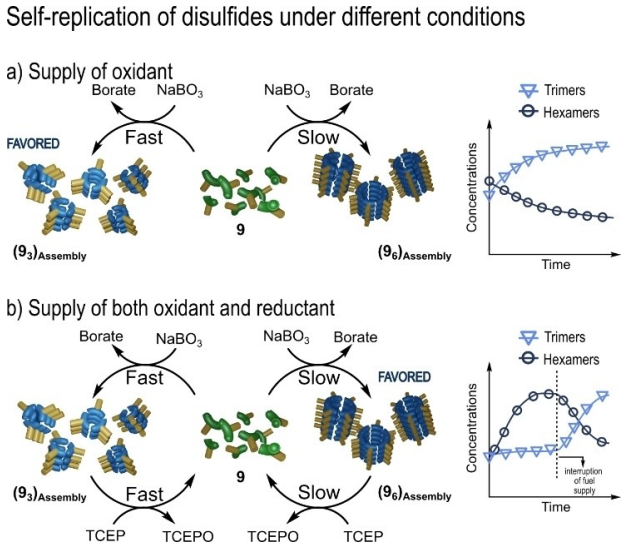

Figure 9. Schematic representation of the DL of fibers generated from precursor **9** under different conditions and the corresponding kinetic profiles: a) the system is supplied with the oxidant only, b) the system, now a DDL, is supplied by both the fuel ($NaBO_3$, the oxidant) and the deactivating reactant (TCEP, the reductant).

continuously formed and destructed to regenerate precursor **9**, once formed from the same precursor, self-replicator $\mathbf{9}_6$ remains trapped into the $(\mathbf{9}_6)_{Assembly}$, which is much more slowly disassembled. Interestingly, when the supply of both fuel and deactivating reactant is interrupted, the system reverts back towards the initial equilibrium conditions, with $(\mathbf{9}_3)_{Assembly}$ prevailing over $(\mathbf{9}_6)_{Assembly}$, confirming the dissipative character of the DDL in Figure 9b. Remarkably, it was demonstrated that in the absence of precursor **9** and its derivates, oxidant $NaBO_3$ and reductant TCEP do not react to any significant extent. Thus, the free energy of the redox fuel reaction is completely diverted through the catalytic dynamic library that persists in its dissipative state as long as the fuel and the deactivating reactant are both present.

3. Thermodynamic Dissipative Dynamic Library (TDDL)

A prototypical example of a TDDL compliant with Figure 3, has been reported by Otto and coworkers in 2014.[28] Here the fast thiol/disulfide exchange reaction is exploited to generate a DL of interconverting disulfides. More in detail, partial oxidation of dithiol **10** generates a DL of disulfides, mainly consisting of a series of isomeric 2-catenanes **11**, each one composed of two tetrameric cycles, and a series of isomeric, cyclic tetramers **12**. The presence of a controlled amount of dithiol allows to maintain dynamic the library (Figure 10a), whose equilibrium composition is shifted towards catenanes **11** in the absence of any added fuel (D_2O, borate buffer 50 mM, pD = 8, **10** 1 mM, 50 °C). Addition of guest **13** (0.25 mM) (the fuel) immediately shifts the DL towards cyclic tetramers **12**, which are better hosts for **13** than catenanes **11**. However, this DL has a temporary existence because the guest **13** is unstable. Indeed, it initially undergoes an aza-Cope rearrangement to give an iminium ion (Figure 10b). This reaction is catalyzed by the hosts **12** since they bind the transition state better than the reactant **13**. Then, the iminium ion rapidly reacts with water (the deactivating reactant) to give the product **14** and dimethyl amine **15** (the waste), which have no significant affinity for any of the members of the library (Figure 10c). Thus, when fuel **13** is exhausted, the library comes back to the initial conditions, with catenates **11** prevailing over cyclic tetramers **12**. Three subsequent shots of fuel allowed three successive $DL_0 \rightarrow DDL \rightarrow DL_0$ cycles, without the necessity of adding any other additive (Figure 10d). When working at lower (room) temperature, the operation of the system is somewhat damaged by the formation of fibrous aggregates of cyclic tetramers **12**, that, after fuel exhaustion, retard the restoring of the DL_0.

Another example of TDDL that can be described with the scheme depicted in Figure 3 was reported by Di Stefano and coworkers.[29]

In this case, reversibility of the imine chemistry is initially exploited to generate a minimal DL consisting of alkylimine **16** and arylimine **17** and the corresponding amines (Figure 11a). In the absence of any added fuel the composition of the DL (DL_0)

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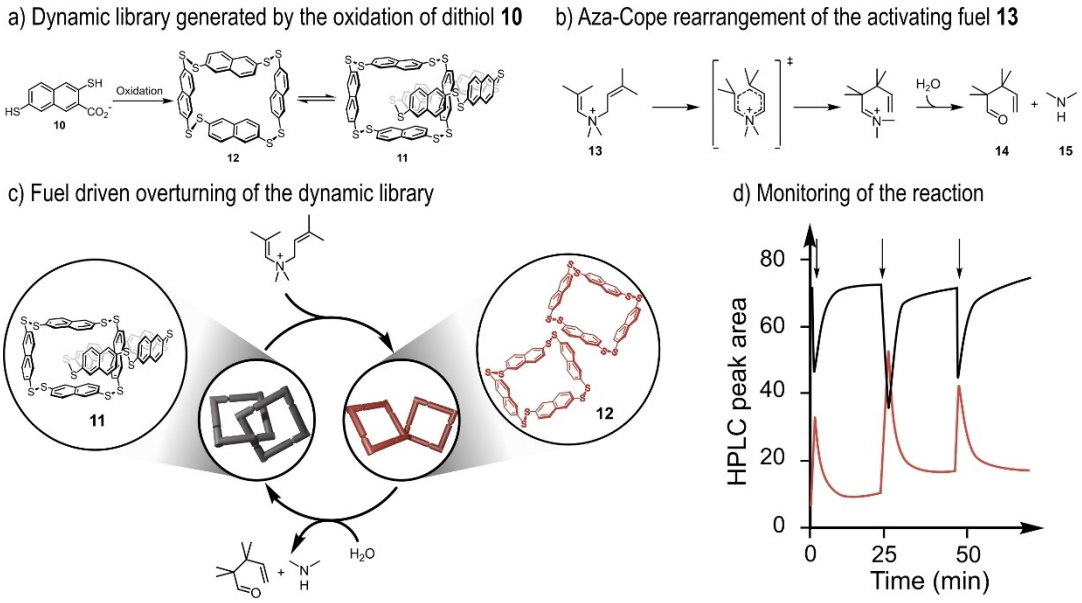

Figure 10. a) The DL mainly consisting of 2-catenanes **11** and cyclic tetramers **12**. b) The fuel reaction consisting of the intramolecular aza-Cope rearrangement of the fuel **13** followed by hydrolysis of the resulting iminium ion (water is the deactivating reactant). c) Transient change of the library composition due to the addition of the fuel. d) HPLC peak area related to 2-catenanes **11** (red trace) and cyclic tetramers **12** (black trace) as a function of time (D_2O, borate buffer 50 mM, pD = 8, **10** 1.0 mM, 50 °C). The arrows indicate addition of 0.25 mM fuel **13**.

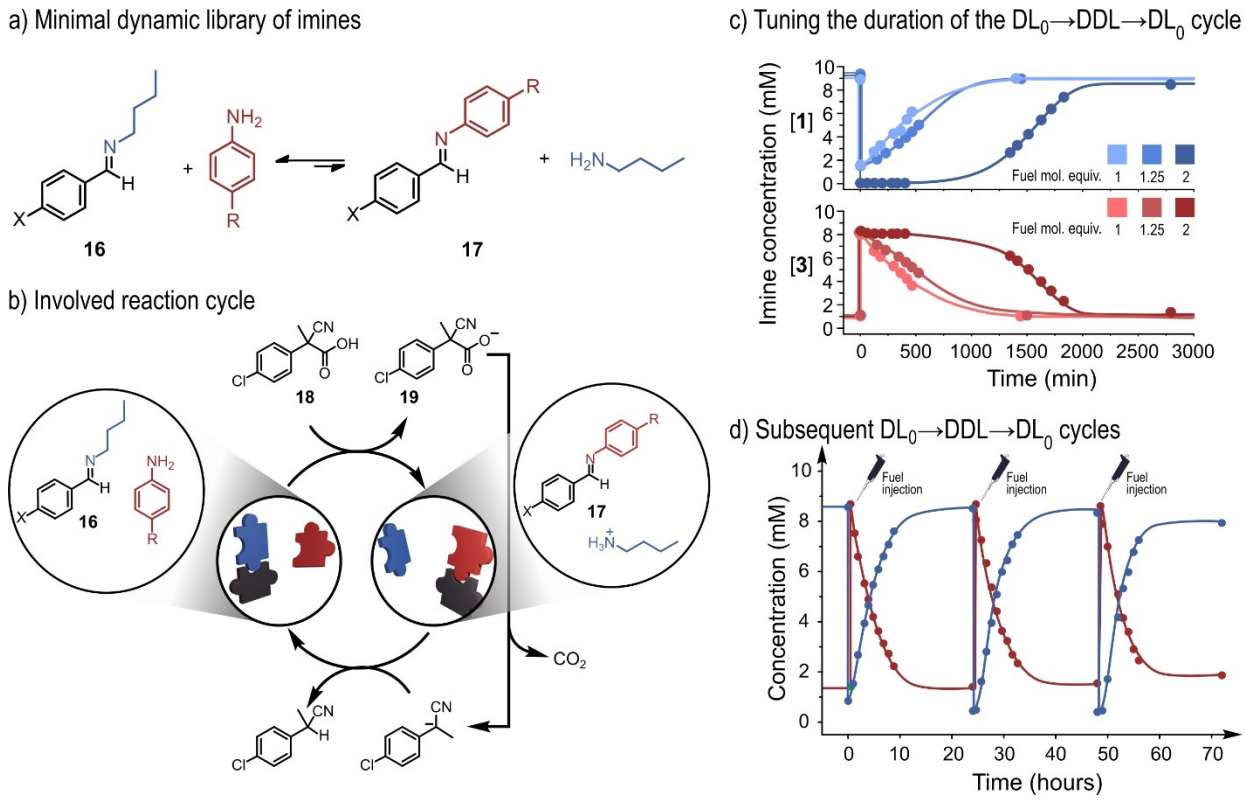

Figure 11. a) A minimal imine/amine DL obtained after 48 hours from addition of 10 mM alkylimine **16** and 10 mM *p*-toluidine. Under equilibrium conditions the DL is shifted to the side of alkylimine **16**. Addition of 10 mM fuel **18** shifts the equilibrium towards arylimine **17** due to protonation of butylamine, as long as the conjugated base **19** is present in solution. b) General scheme for $DL_0 \rightarrow DDL \rightarrow DL_0$ cycles involving alkyl/aryl imines and triggered by the addition of fuel **18**. c) Addition of excess of fuel extends the time spent by the system in the DDL state. d) Three subsequent $DL_0 \rightarrow DDL \rightarrow DL_0$ cycles obtained by three successive additions of fuel.

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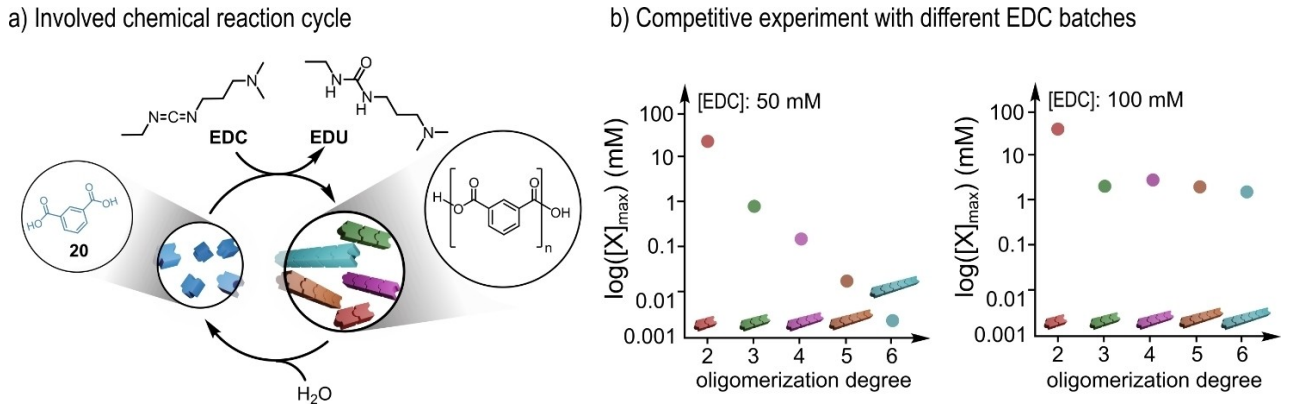

Figure 12. a) Dissipative step-growth oligomerization of isophthalic acid **20** fuelled by EDC, which leads to a TDDL equilibrated by the transacylation reaction. b) Maximum concentration of the library oligomers with $i = 2$-6, plotted on a logarithmic scale when fuelling with 50 mM EDC (left) and 100 mM EDC (right).

is strongly shifted to the side of alkylimine **16**. After addition of the fuel acid **18**, an immediate over-turning is observed with the generation of a TDDL whose composition is dominated by the alternative arylimine **17** (Figure 11b, R = Br, X = CH_3). The fuel acid has indeed protonated the alkylamine (activating process), which is the strongest base in solution, to the corresponding alkylammonium ion, shifting the equilibrium in Figure 11a towards the arylimine. However, the new state is an out-of-equilibrium state since the conjugate base of the fuel (carboxylate **19**) is not stable; it starts to slowly decarboxylate forming a strong carbanionic base, which immediately deprotonates the alkylammonium ion. As a consequence, due to fast back-transimination, the initial DL_0 is restored at the end of the decarboxylation process (Figure 11b). It has to be noted that fuel **18**, besides thermodynamically driving the equilibrium between the two imines, is also a catalyst of the transimination process responsible for the rapid reversibility of the DL. The system proved to be very robust with respect to the nature of the involved imines/amines, solvents and temperature. Variation of the added amounts of fuel **18** allowed to control the time spent by the system in the DDL state (Figure 11c). Furthermore, three subsequent shots of fuel drove three successive $DL_0 \rightarrow DDL \rightarrow DL_0$ cycles (Figure 11d). More complex TDDLs were obtained, where three or four imines and related amines were involved (Figure 11b with varying R and X). All of them show a reversible and predictable behavior. The arylimine/alkylimine dissipative exchange guided by CBr_3CO_2H, another carboxylic acid whose decarboxylation can be promoted by primary alkylamines, has been lately and magistrally exploited by Badjic et al to temporally control the formation of a nano-cage.[30]

The dissipative anhydride formation fueled by EDC described in the previous section has been also used to generate TDDLs. Indeed, Boekhoven and coworkers showed that when isophthalic acid **20** is fueled by EDC in buffered water at pH 6 in the presence of pyridine, a step-growth oligomerization of **20** takes place with the formation of a mixture of oligoanhydrides.[31] Although the growth of the average length of the chains depends on the fuel promoted irreversible

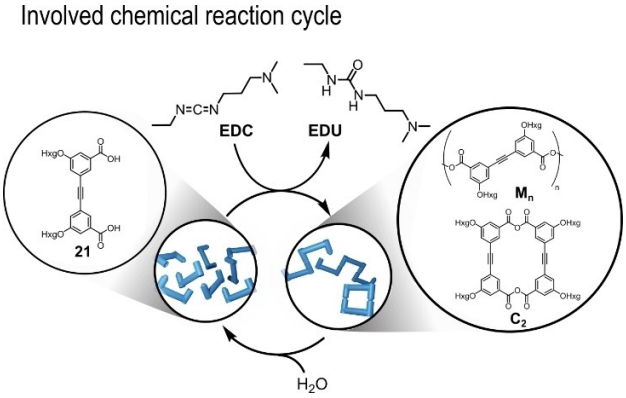

Figure 13. The TDDLs obtained after the addition of EDC to diacid **21** (Hxg = hexaethylene glycol).

condensation of the terminal carboxylic acid groups, equilibration between the oligomers is assured by the reversible transacylation reaction that is faster than hydrolysis in the presence of pyridine. The resulting library is shown schematically in Figure 12a. Note that in the transacylation, two oligomers, say i and j, react to give two other oligomers, $i-x$ and $j+x$, thus transacylation does not alter the average degree of oligomerization of the library. When 300 mM of isophthalic acid is fueled with 50 mM EDC, the solution remains clear and the maximum of the concentration of each oligomer plotted as a function of the oligomer length shows an exponential decay (Figure 12b left). In contrast, when the same amount of substrate is fueled with 75 and 100 mM EDC, the solutions become turbid because of the formation of micron-sized transient assemblies mainly formed by oligomers with $i = 4$-6. Moreover, the maximum concentration of the anhydrides does not decay exponentially with oligomer length as observed before, owing to the increased maximum concentrations of heavier oligomers (Figure 12b right). The likely explanation is that the self-assembling oligomers separate themselves from the aqueous phase, thus becoming less reactive. Interestingly, if the assemblies are removed from the solution and added to

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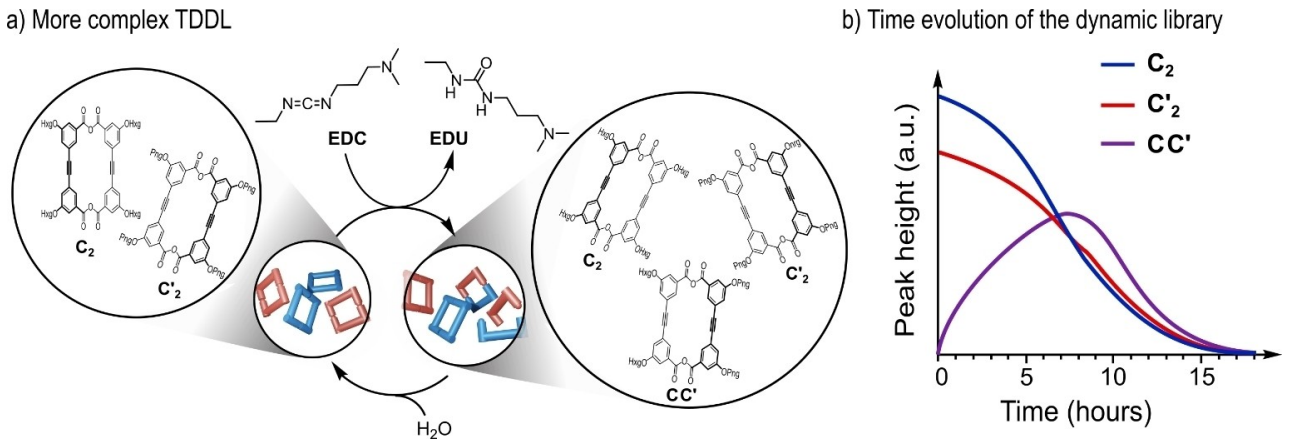

Figure 14. a) The transient TDDL of cyclic dianhydrides obtained by addition of EDC to an equimolar mixture $\mathbf{C_2}$ and $\mathbf{C'_2}$. b) Time evolution (HPLC) of the TDDL reported in Figure 14a (Png and Hxg, penta and hexa ethylene glycol residues, respectively)

300 mM of substrate fueled with 30 mM EDC, a seeding effect is observed consisting of the formation of a detectable amount of the pentamer, almost twice the amount added with the seed, whereas in the absence of seed, the pentamer is not observed. This remarkable result has been explained by a feedback mechanism exerted by the self-assembly.

Another example of TDDL based on the EDC fuel was reported by Hartley and coworkers in 2020.[32] They showed that dicarboxylic acid **21** (Figure 13) can be transiently assembled into a mixture of linear oligomers $\mathbf{M_n}$ and the cyclic dimer $\mathbf{C_2}$ by means of EDC used as a chemical fuel (deuterated water, pD 5.5, pyridine buffer, 1.0 M NaCl). After addition of the fuel, **21** is initially converted into a mixture largely consisting of oligomers $\mathbf{M_n}$ that, in the course of time, are extensively transformed into $\mathbf{C_2}$. The above mixture ($\mathbf{M_n}+\mathbf{C_2}$), whose members interconvert with each other by fast transacylation, can be described as a TDDL although the kinetics of the phase separation of a subset of the (transient) products can play a role. The out-of-equilibrium state, which favors the anhydride over the carboxylic acid functions, turns out to be more persistent the larger the amount of added fuel. When the fuel is exhausted, hydrolysis takes over and diacid **21** is restored at the expense of the transient library members. Hydrolysis of $\mathbf{C_2}$ is found to be retarded by self-aggregation that protects its anhydride functions. Such phase separation might make the transient state not exclusively governed by thermodynamic factors.

A more complex dissipative library was obtained by mixing the cyclic homodimers $\mathbf{C_2}$, $\mathbf{C'_2}$, and EDC (25, 25 and 50 mM, respectively) in water (Figure 14a). After about 11 h, although the anhydride functions underwent partial hydrolysis, a statistical distribution of the initial homodimers and the new cyclic heterodimer **CC'** was found ($\mathbf{C_2}$:**CC'**:$\mathbf{C'_2}$ = 1:2:1), proving that transacylation ensures fast equilibration (Figures 14a and 14b).

4. Conclusion

Dissipative dynamic combinatorial chemistry (DDCC) is an emerging field of supramolecular chemistry, which endows the classical dynamic combinatorial chemistry with the dimension of time. With DDCC the high potential of the dynamic combinatorial chemistry, which has been widely demonstrated in the fields of recognition, self-assembly, catalysis and, more in general, in systems chemistry is further expanded by temporal control and programmability. Variation of the nature or the amount of added fuel allows the regulation of the duration of the dissipative state of the library and make available a further control mode (time) of the library and related chemical-physical properties.

In the previous sections, we have illustrated the kinetic and thermodynamic key features of DDCC. The concepts of kinetic and thermodynamic dissipative dynamic libraries, KDDL and TDDL, have been effectively applied to a number of actual cases showing the consistency of our approach. Hopefully, this Concept article will stimulate the thoughtful investigation of other systems.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Systems chemistry · Dissipative systems · Dynamic covalent chemistry · Dynamic libraries · Chemical fuels

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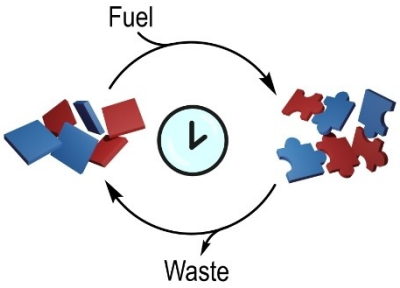
CONCEPT

Dissipative Dynamic Libraries: In this Concept, the fundamental features of Dissipative Dynamic Libraries (DDLs) maintained out-of-equilibrium by the consumption of a fuel are described with particular emphasis on the factors that govern the composition of the libraries over time.



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Dissipative Dynamic Libraries (DDLs) and Dissipative Dynamic Combinatorial Chemistry (DDCC)