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Dynamic Libraries

Kinetic Control of Complexity in Multiple Dynamic Libraries

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Dedicated to Prof. Víctor S. Martín

Abstract: Multiple dynamic libraries of compounds are generated when more than one reversible reaction comes into play. Commonly, two or more orthogonal reversible reactions are used, leading to non-communicating dynamic libraries which share no building blocks. Only a few examples of communicating libraries have been reported, and in all those cases, building blocks are reversibly exchanged from one library to the other, constituting an antiparallel dynamic covalent system. Herein we report that communication between two different dynamic libraries through an irreversible process is also possible. Indeed, alkyl amines cancel the dynamic regime on the nucleophilic substitution of tetrazines, generating kinetically inert compounds. Interestingly, such amine can be part of another dynamic library, an imine-amine exchange. Thus, both libraries are interconnected with each other by an irreversible process which leads to kinetically inert structures that contain parts from both libraries, causing a collapse of the complexity. Additionally, a latent irreversible intercommunication could be developed. In such a way, a stable molecular system with specific host–guest and fluorescence properties, could be irreversibly transformed when the right stimulus was applied, triggering the cancellation of the original supramolecular and luminescent properties and the emergence of new ones.

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Introduction

Complexity is intrinsic to living systems.[1] Intricate and functional biological architectures are constructed selecting the right elements from a myriad of molecular components through interconnected processes. Correct management of complexity by living organisms is behind many emerging properties, and intercommunication between dynamic chemical networks plays a major role in such task.[2,3,4]

Artificial chemical systems might also be inherently complex,[5] and yet traditional synthetic organic chemistry has avoided equilibrating mixtures. During the last decades, though, such scenario has gradually changed.[6,7] In this regard, dynamic combinatorial chemistry (DCC) has become a powerful method to generate complex molecular systems.[8–13] Under this approach, a small number of building blocks reacting with each other, yield a dynamic library composed by a larger number of compounds. DCC is based on reversible covalent chemistry,[14,15] and therefore, the components of a library can interconvert by exchanging building blocks within such library, constituting a dynamic molecular network, in which the composition is governed by thermodynamics.[16] Commonly, previous DCC works have been based on just one type of reversible covalent bond. However, incorporation of two or more dynamic reactions allows to increase complexity, because more than one dynamic library is generated. Most of the reported examples of multi-reaction dynamic systems consist of orthogonal reversible reactions,[17–42] in which the same functional group does not participate in two different reversible chemistries. Then, dynamic libraries obtained are not interconnected, or in other words, a building block from one library cannot participate in the other.

Communicating dynamic libraries are considerably less common. In this case, the same functional group reacts in two different reversible processes, and then, certain building blocks can participate in both libraries, which can then be mutually affected by the other (Figure 1).[43–54] All the communications between dynamic libraries reported so far are reversible in nature (Figure 1a): The shared building block can switch from one library to the other in a reversible way. Complexity can then be controlled because, by definition, when one of the libraries increases in size, the other has to decrease, which explains why reversible communication has also been called antiparallel dynamic covalent chemistry.[45]

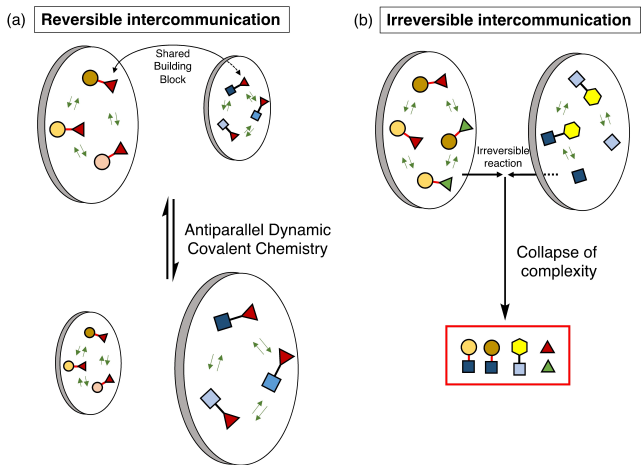


Figure 1. Schematic representations of intercommunication between two dynamic libraries: (a) reversible and (b) irreversible.

Although it might seem counterintuitive, dynamic libraries could also be intercommunicated irreversibly (Figure 1b). In such case, specific building blocks from one library would participate in the other and vice versa, but undergoing an irreversible reaction.[55] As a consequence, all the components of the two dynamic libraries would be eventually funneled towards kinetically inert structures that contain parts from both libraries, causing a collapse of the complexity.

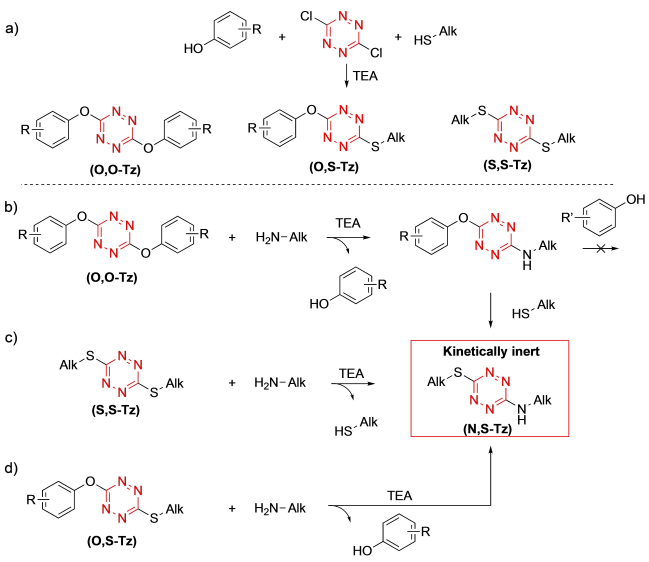
In this sense, it reminds to kinetic self-sorting examples described for single dynamic libraries by Miljanić and others,[56–68] in which a particular set of components of the mixture react considerably much faster than the others in an irreversible reaction, yet still slower than the dynamic process, allowing the mixture to re-equilibrate and to gradually select such components out of the system.

Herein, we report an irreversible intercommunication between two different dynamic libraries. Indeed, we have found that alkyl amines react irreversibly with a dynamic library of thiol/phenol tetrazine derivatives generated by nucleophilic aromatic substitution; interestingly, such amine can be part of another dynamic library, generated by imine-amine exchange. In such a way, the initial complexity is managed by an irreversible reaction between both libraries. Additionally, a latent irreversible communication was developed in order to control the whole process by an external agent. Taking advantage of this approach, a molecular system was able to be transformed into a completely different one upon application of a stimulus, concomitantly causing the cancelation of the original physical-chemical properties and the emergence of new ones.

Results and Discussion

Studies of Reactivity in the Nucleophilic Aromatic Substitution of Tetrazines (S_NTz)

The properties of a dynamic system utilizing multiple reversible reactions depend significantly on the relative reactivity of the functional groups participating in each reaction. Thus, we firstly studied the hierarchy of reactivity in our system. In previous works by our group,[69–71] the dynamic nature of the nucleophilic aromatic substitution of tetrazines (S_NTz) with phenols and alkyl thiols was described (Scheme 1a).[72,73] We reasoned that, analogously to what has been reported for other nucleophilic aromatic substitutions, alkyl amines could notably decrease the reactivity of the aromatic ring,[74–78] leading to the cancellation of the dynamic regime. In other words, alkyl amines might well lead to irreversible nucleophilic substitutions with tetrazines. In order to test our hypothesis, we carried out several experiments. First of all, an excess of alkylamines was able to react with phenol (O,O–Tz) or thiol (S,S–Tz) tetrazine homodimers, to yield the corresponding heterodimers, concomitantly releasing one equivalent of phenol or thiol respectively (Scheme 1b,c, Figures S2,3,5,6,7,8).[79] Double substitution by an alkyl amine was extremely difficult or not possible, even by using an excess of it. It is also worth mentioning that anilines were poor nucleophiles for this reaction (Figures S1,4).[79] Interestingly, phenol-amine (N,O–Tz) heterodimers did not react any further with other phenols, which confirms the deactivation of the aromatic ring by the amine (Figure S10,11). However, (N,O–Tz)



Scheme 1. a) Schematic example of nucleophilic aromatic substitution of tetrazines (S_NTz) with phenols and thiols; b) Phenol homodimers (O,O–Tz) react with alkyl amines to yield phenol-amine (N,O–Tz), but they cannot react any further with other phenols although thiols react efficiently to give the thiol-amine (N,S–Tz) heterodimer; c) Thiol homodimers (S,S–Tz) react with alkyl amines to yield (N,S–Tz) heterodimer, which is kinetically locked; d) Phenol-thiol dimers (O,S–Tz) also give the (N,S–Tz) heterodimer with an alkyl amine.

heterodimers did react with thiols (better nucleophiles), giving the corresponding thiol-amine (N,S–Tz) heterodimer and releasing phenol. As expected, the phenol-thiol (O,S–Tz) heterodimer with amine, led again to the thiol-amine (N,S–Tz) heterodimer (Scheme 1d, Figure S9). At this point, it could be concluded that all the components of a hypothetical dynamic library generated by S_NTz, would react with alkyl amine to generate only one compound containing tetrazine: The amine-thiol tetrazine heterodimer (N,S–Tz).

Interestingly, the dynamic nature of the reaction is frozen once a N,S–Tz heterodimer is formed: No further exchange with other amines or thiols was observed under the conditions employed in these reactions (Figures S11,15).[80] Therefore, it is clear that the selection of the N,S–Tz heterodimers is kinetically driven: They are the only kind of compound that cannot react any further under these reaction conditions, so once formed they cannot go back, and consequently they funnel the rest of components of the dynamic library. Even when N,S–Tz heterodimers might well be the most stable compounds, the fate of the initial mixture is exclusively based on the irreversibility of the process, regardless of the stability of the obtained compounds, analogously to previously reported kinetic self-sorting phenomena.[56–68]

Simplification of S_NTz Libraries by Alkyl Amines

From that point on, we could generate increasingly complex dynamic libraries by S_NTz, which were efficiently managed by the addition of an amine to the equilibrating mixture.[81] For the initial experiment, we mixed equimolar amounts of p-methoxyphenol (**1**), benzylmercaptan (**2**) and 3,6-dichlorotetrazine (**$TzCl_2$**) in $CDCl_3$, together with triethylamine (TEA) as a base. A dynamic library of three compounds was obtained (Figure 2a). One equivalent of butylamine was added afterwards. Aliquots of the reaction were taken at different times, and the progression of the reaction was stopped by the addition of acid to each aliquot. They were analyzed by ^{1}H NMR and HPLC-MS (Figure S19). As it can be seen in Figure 2, all the compounds of the initial dynamic library, progressively react, yielding **2-Tz-NHBu** as the major compound together with released **1**. Even when other species, such as **1-Tz-NHBu**, were transitorily generated during the reaction, they continued reacting towards the final compound, as it was expected from the control studies shown in Scheme 1.

Such a successful kinetic control of complexity could be applied to more elaborated scenarios. Combining three phenols and three thiols under the S_NTz reaction, yielded a dynamic library with 21 potential compounds (Figure 3a), which were detected by ^{1}H NMR as mixtures of dimers (green points at time zero in Figure 3b). After a few hours, kinetically inert products were clearly obtained (red curves in Figure 3c), along with some remaining homodimers of phenols **1** and **2** (green curves in Figure 3b) and some transient N,O-heterodimers (blue curve in Figure 3b). 24 hours were enough for a successful simplification (Figure S32), reaching molar fractions of 0.29, 0.33 and 0.28 for

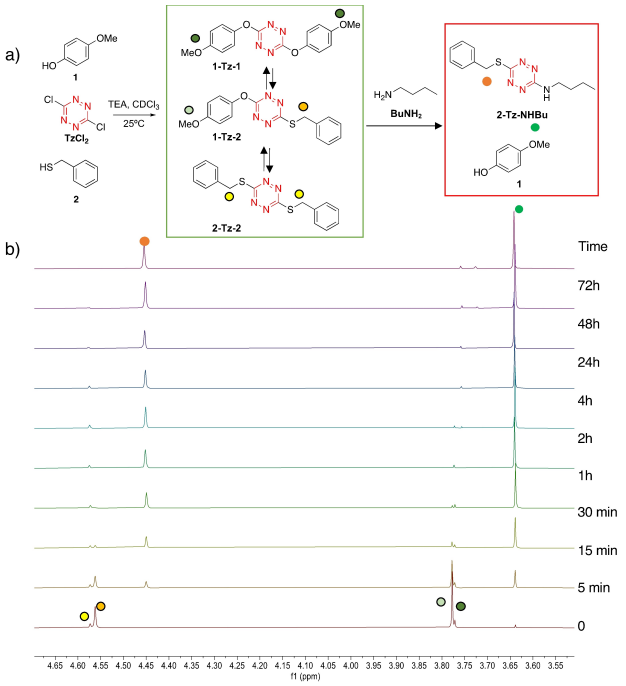


Figure 2. (a) Kinetic control of a dynamic library of three components. (b) Reaction was followed by ^{1}H NMR . To the aliquots in $CDCl_3$, trifluoroacetic acid was added, solvent was removed, and they were re-dissolved in DMSO-d_6, only to achieve sharper and less overlapped peaks. Dimethylsulfone was employed as internal standard.

products **2-Tz-NHBu**, **4-Tz-NHBu** and **6-Tz-NHBu** respectively, which sum a total of 90 % of the total tetrazine containing species. Thiol **4** led to the fastest reactivity, and in fact, its selection out of the initial mixture within 72 h is theoretically complete, with a molar fraction 0.33.

After all the mentioned results, it can be concluded that upon addition of an alkyl amine, the dynamic library of tetrazine derivatives evolves by an irreversible aromatic substitution, leading to a selected kind of structures: The equilibrating mixture is funneled towards those compounds that are kinetically inert under these conditions, specifically the amino-thiol tetrazine heterodimers (N,S–Tz).

Irreversible Intercommunication between two Dynamic Libraries

Interestingly, the amine nucleophile could be part of another dynamic library. In such a way, that second library would also be concomitantly simplified as the kinetically inert compounds contain building blocks shared by both dynamic processes: Complexity in two different dynamic libraries would be controlled by an irreversible intercommunication between them. We thought that an optimal choice for the second dynamic library would be an amine-imine exchange library, not only because it contains a reactive amine as one of its components, but also because the dynamic nature of such exchange has been very well studied.[82,83]

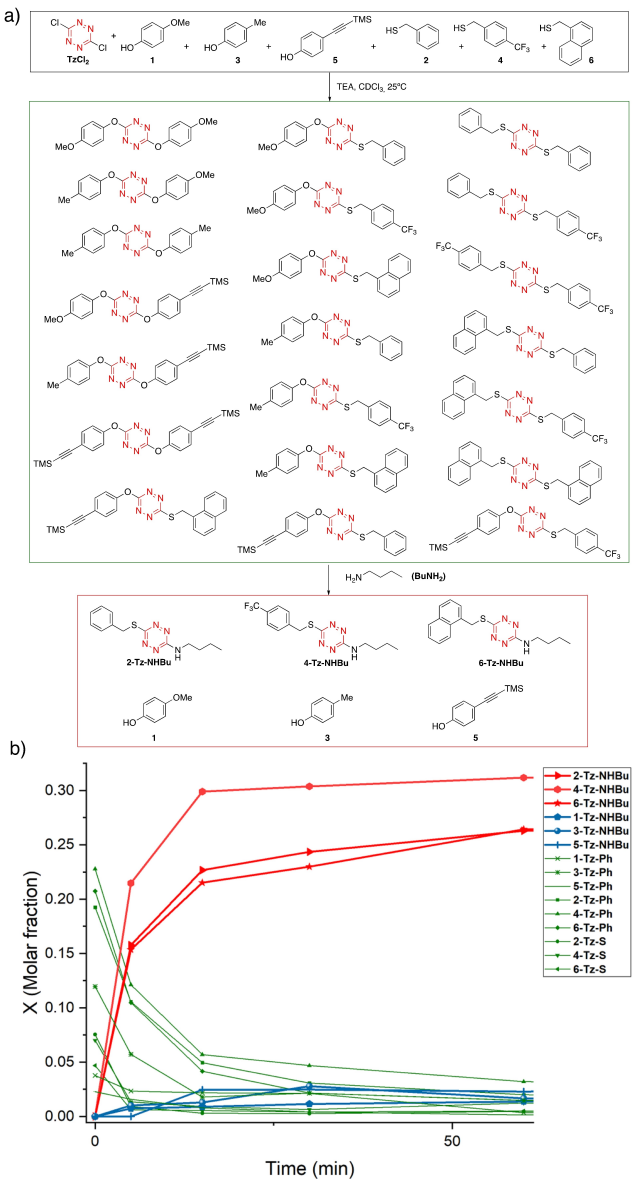


Figure 3. (a) Kinetic control of a S_NTz dynamic library of 21 components. (b) Reaction was followed by ^{1}H NMR after stopping the reaction with trifluoroacetic acid, remove solvents and redissolve in DMSO-d_6 just to obtain better resolution in the NMR spectra. Dimethylsulfone was employed as internal standard. The nomenclature **X-Tz-OPh** and **X-Tz-S** refers to all the dimers containing any phenol or thiol respectively.

In Figure 4 it is shown the control of the complexity of two dynamic libraries by irreversible intercommunication between them. A S_NTz library, comprised by 21 potential compounds, was merged with the imine-amine dynamic library shown in Figure 4a. We chose a small imine library for visualization ease, to avoid an unnecessary complication of the experiments, because a larger library would have led to the same conclusions although in a more complicated way. Such library was initiated by an equimolar mixture of N-benzylidenebutylamine (**Im-Bu**) and p-chloroaniline (**AnNH$_2$**). Those two compounds remained as the major

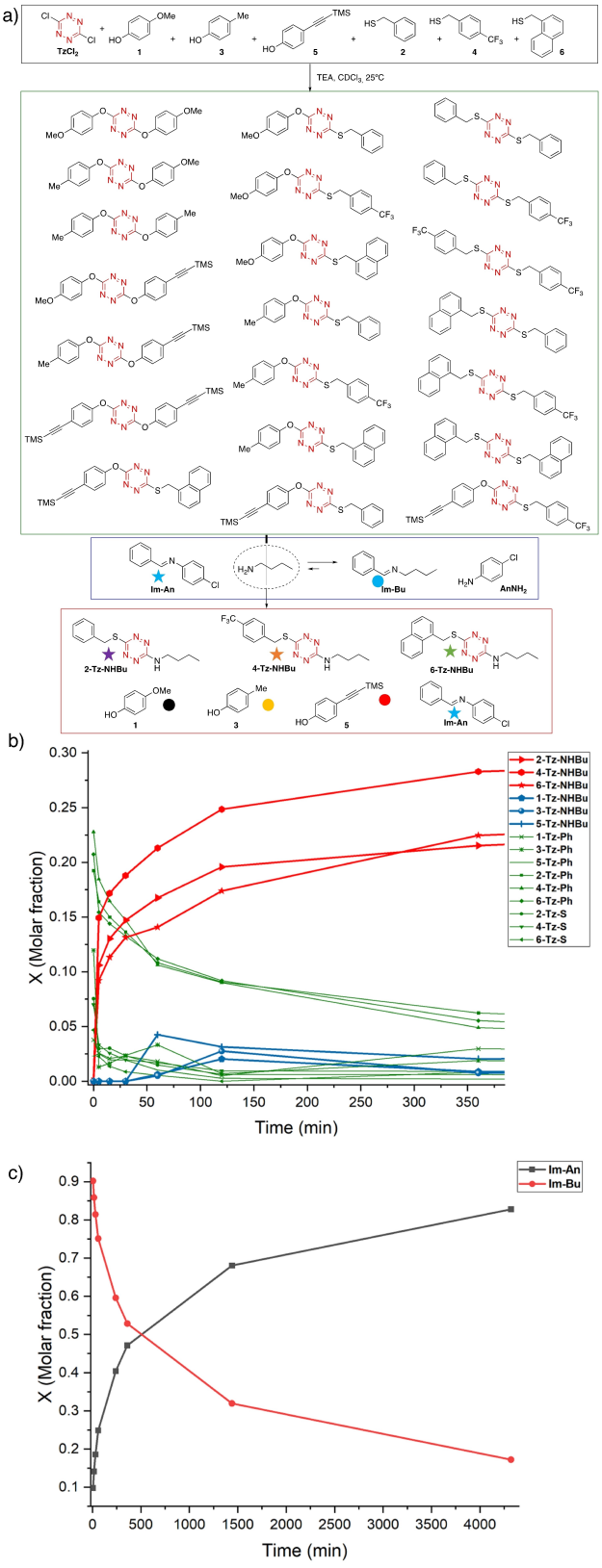


Figure 4. (a) Mutual kinetic control of a S_NTz dynamic library and an imine-amine exchange dynamic library. (b) Reaction was followed by ^{1}H NMR and it is clearly seen that **N,S-Tz** heterodimers (red curves) were sorted-out. The nomenclature **X-Tz-OPh** and **X-Tz-S** refers to all the dimers containing any phenol or thiol respectively. (c) The initial ratio of imines is completely inverted after the collapse of complexity.

components once thermodynamic equilibrium has been reached, while N-benzylidene-4-chloroaniline (**Im-An**) and butylamine (**$BuNH_2$**) were the minor components, in concordance to previously reported results.

As it was above mentioned, anilines are very poor nucleophiles in the S_NTz reaction and, consequently, only the small amounts of free butylamine present in the reaction mixture, reacted with the tetrazine library. In such a way, the imine-amine exchange progressively re-equilibrated, and N-benzylidene-4-chloroaniline (**Im-An**, the less stable imine) eventually became the major component of this library. It is clearly seen in Figure 4c that the initial ratio between imines is completely inverted in the end. In this sense, it reminds to previous works on dissipative dynamic covalent chemistry, in which a coupled reaction or a stimulus, allows the equilibrium to shift uphill,[84] although in this case, the compound is irreversibly sorted out.

The experiments were carried out in $CDCl_3$ and followed by ^{1}H NMR, by taking aliquots at specific times, and diluting them with DMSO-d_6 (1:10), only because better resolution of the spectra was achieved this way: Peaks were sharper and there was less overlapping.[85] Intercommunication of libraries is slightly slower compared to the previous examples, where the amine was added as an isolated reagent. Nevertheless, after 72 h, the set of 25 equilibrating compounds collapsed into only seven major components (Figure 4a): The products **2-Tz-NHBu**, **4-Tz-NHBu** and **6-Tz-NHBu** represented the 90 % of all the compounds containing tetrazine in the final mixture, together with released phenols and the N-benzylidene-4-chloroaniline (Figure S40 and 41). As expected, the rather complicated initial ^{1}H NMR spectrum (Figure 5), ended up as a quite simpler one.

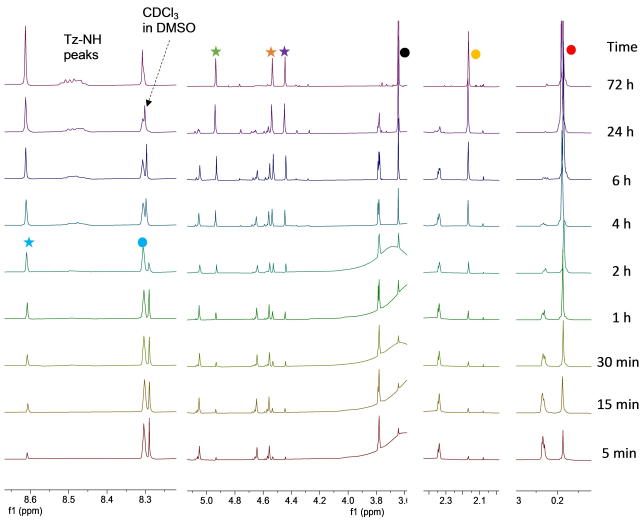


Figure 5. Stacked ^{1}H NMR spectra of the aliquots of the reaction. Reaction was carried out in $CDCl_3$, and the aliquots diluted with DMSO-d_6 (1:10), to obtain sharper and less overlapped peaks. Dimethylsulfone was employed as internal standard. See Figure 4a to correlate each marked NMR peak with the right hydrogens in the right compounds.

Manipulation of function by irreversible inter-communication

The kinetic control of the complexity could also be implemented to manipulate the properties of an adequately designed system.[86–88] Indeed, a latent irreversible intercommunication was developed by taking advantage of the hierarchical reactivity of the building blocks. In such a way it was possible to control the cascade of events that transform a system into another one,[89–91] displaying different emerging properties, in a way that is loosely reminiscent of a biological cascade of events. Particularly, we designed the System 1 shown in Figure 6a which is able to transform its luminescent and supramolecular properties while it is converted into System 2 (Figure 6b) by the action of an aniline.

System 1 is composed by **Im-OMe-Tren**, cyclobis(paraquat-*p*-phenylene) (**$CBPQT^{4+}$**), tetrabutylammonium chloride, and **2-Tz-Umb**, a tetrazine compound containing benzyl mercaptan (**2**) and umbelliferone (**Umb**), all solved in CD_3CN. **2-Tz-Umb** displays a weak orange fluorescence with a maximum of intensity at 575 nm in acetonitrile (Figure 6g and 6 h). **Im-OMe-Tren** is a triple imine synthesized from tris(2-aminoethyl)amine (tren) and three equivalents of a moderately electron-rich aromatic aldehyde. Each of the resulting imines individually are expected to be poor guests for **$CBPQT^{4+}$** in acetonitrile. Indeed, it is known that similar compounds, like 1,2-dimethoxybenzene, show very low affinity for **$CBPQT^{4+}$** in acetonitrile ($<10\ M^{-1}$).[92] However, **Im-OMe-Tren** displays three of those donor moieties distributed close enough to reinforce binding by a multisite interaction, similarly to reported zipper-featured molecular duplexes,[93] or to [2]pseudorotaxanes comprised of **$CBPQT^{4+}$** and a thread incorporating three naphthalene residues.[94] Actually, the association constant of **Im-OMe-Tren** and **$CBPQT^{4+}$** measured by UV/Vis titration in acetonitrile, indicated a respectable affinity ($271 \pm 4\ M^{-1}$) (Figure 6c).[95,96] Finally, tetrabutylammonium chloride did not interact with any other element of System 1 and thus, it was a mere spectator that would play a role after intercommunication is triggered. Even when anion metathesis between chloride and one of the hexafluorophosphate from **$CBPQT^{4+}$** could be possible, it did not affect solubility of System 1, nor the envisioned purpose for chloride anion.

System 1 was stable for hours, showing no change in the NMR spectrum. However, as soon as p-chloroaniline was added to this system, the imine-amine exchange began (Figure 7a).[97] Such exchange is markedly shifted towards the formation of **Im-OMe-Tren** (Figure S46). Nevertheless, any minute amount of free alkyl amine generated, is able to react irreversibly with **2-Tz-Umb**, releasing the coumarin. A series of reversible equilibria coupled to irreversible processes, progressively funneled the mixture towards kinetically inert structures (Figure 7a). Temporary species such as the Tren-di-imine or the Tren-mono-imine, and even 2-hydroxy-3-methoxybenzaldehyde (Figure S49) were generated during the process. After 5 days (Figure 7b), System 1 had mostly evolved into System 2: A mixture of **Tren-(Tz-2)$_3$**, **Im-OMe-**

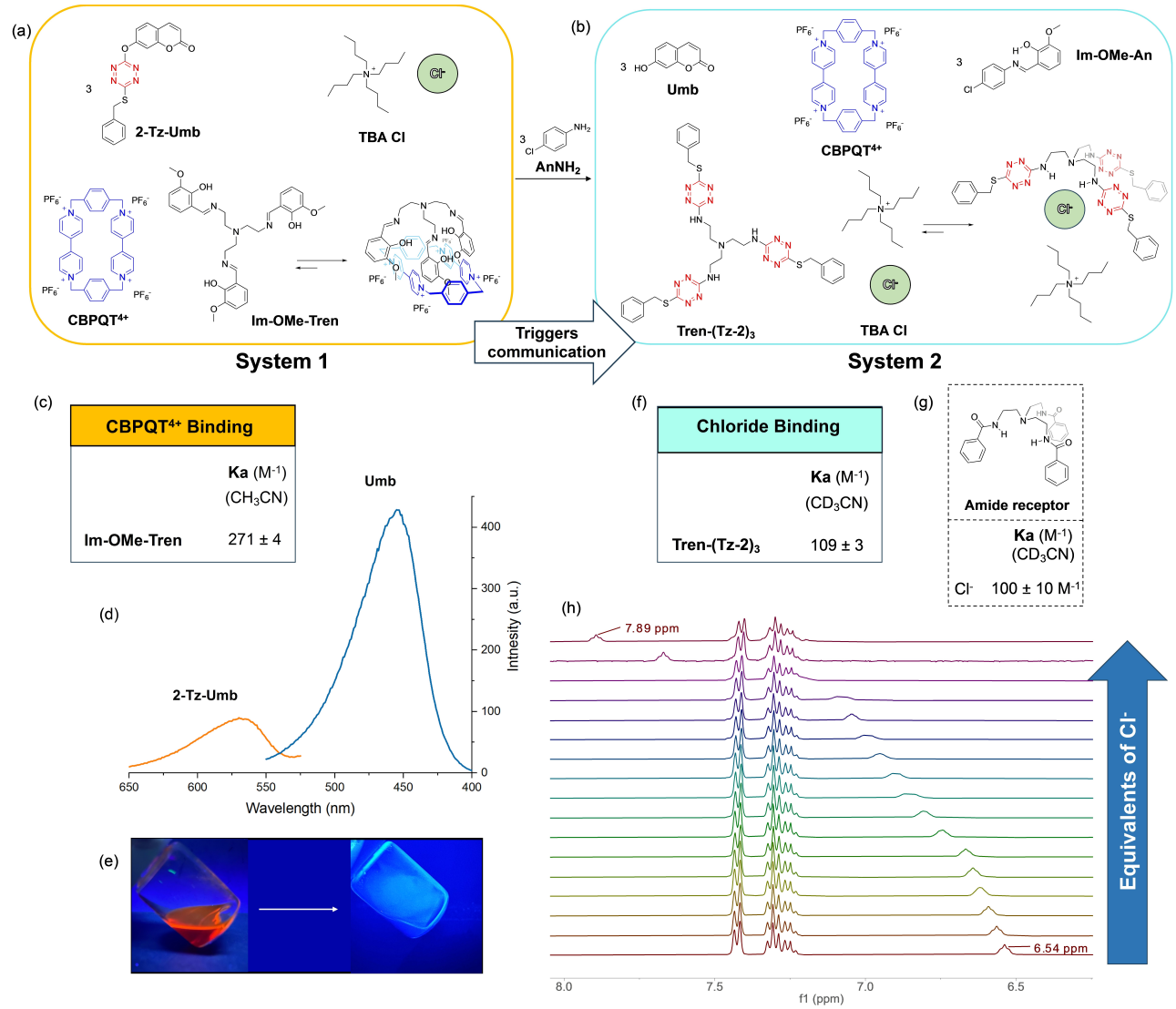


Figure 6. Latent irreversible intercommunication can be triggered by a stimulus. (a) System 1 shows orange fluorescence and a supramolecular interaction with **CBPQT^{4+}**. (b) Addition of 4-chloroaniline triggers the intercommunication, which yields System 2, displaying blue fluorescence and chloride affinity. (c) Association constant of **Im-OMe-Tren** with **CBPQT^{4+}** was measured by UV/Vis titration. (d) Overlapped fluorescence emission spectra in acetonitrile of **2-Tz-Umb** and umbelliferone. (e) Visual change of the fluorescence by transformation of System 1 into System 2. (f) Association constant of **Tren-(Tz-2)$_3$** with tetrabutylammonium chloride was measured by ^{1}H NMR titration in CD_3CN. (g) Previously reported amide receptor. (h) The peak corresponding to NH–Tz in **Tren-(Tz-2)$_3$** shifted downfield upon addition of tetrabutylammonium chloride in CD_3CN.

An and umbelliferone, besides **CBPQT^{4+}** and **TBACl** (Figure 6b).[79]

Regarding the latter two, their role is to provide with supramolecular properties to both molecular systems, and therefore, irreversible intercommunication is equally successful with or without them (See Figure S51. In Figure 7, they are not incorporated for visualization ease). Importantly, when they are present in the reaction mixture, the expected supramolecular interactions occur, even in such complex matrix (Figure S52).

The emerged System 2 showed blue fluorescence caused by the release of umbelliferone, with a maximum of intensity at 460 nm in acetonitrile (Figure 6d and 6e). **CBPQT^{4+}** showed no relevant interactions with any of the components of System 2: **Im-OMe-Tren** disappeared, generating three equivalents of an aromatic imine (**Im-OMe-An**). In other words, reinforced multisite binding is no longer possible, and as it was abovementioned, guests such as **Im-OMe-An** acting individually, display very low affinity for **CBPQT^{4+}** ($4.99 \pm 0.04\ M^{-1}$).[79] Umbelliferone and tetrazine-based compounds showed no association constant with **CBPQT^{4+}** either. Additionally, from the tris(2-aminoethyl)amine (Tren) originally constituting **Im-OMe-Tren**, emerged **Tren-(Tz-2)$_3$**, a novel tripodal chloride receptor. Anion receptors containing tetrazine rings have been previously described, although always relying on an anion-π interaction with the electron poor tetrazine ring.[98,99] However, in this case, we hypothesized that NH groups attached to a tetrazine should behave as good hydrogen bond donors, due to the electron withdrawing effect of the aromatic ring.

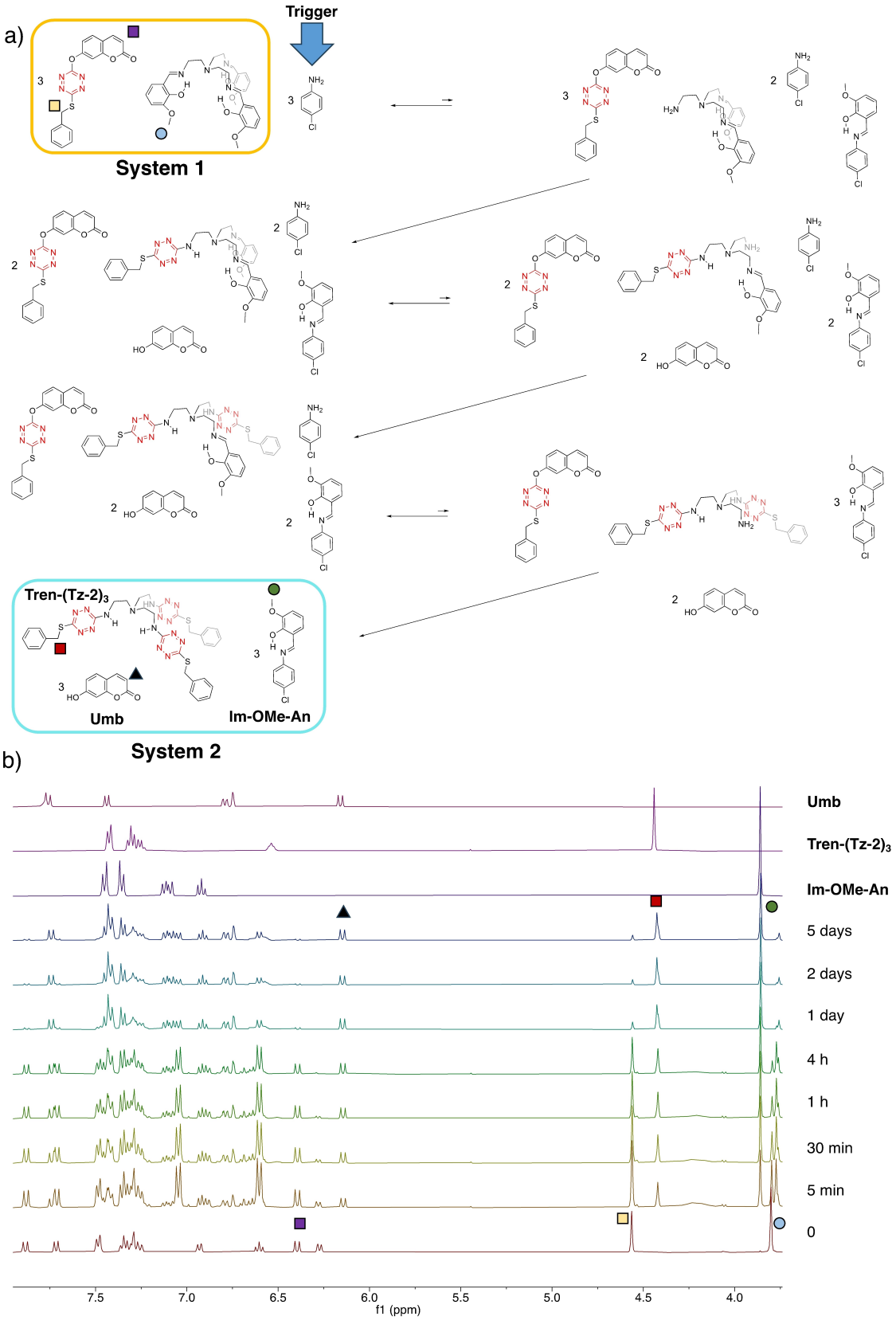


Figure 7. (a) A series of reversible equilibria are coupled to irreversible processes which funnel the mixture from System 1 to System 2. Supramolecular interactions, either with **CBPQT**$^{4+}$ or with **TBA Cl** are not displayed to ease the visualization of the intercommunication. (b) Zoom of the stacked ^{1}H NMR spectra in CD_3CN of the conversion of System 1 into System 2 at different times, compared to the pure final compounds.

Confirming such hypothesis, the NH peak of receptor **Tren-(Tz-2)$_3$** was shifted downfield almost 1.5 ppm during the ^{1}H NMR titration with tetrabutylammonium chloride in CD_3CN (Figure 6h), corroborating the key role of hydrogen bonding by the NH groups in the binding event. In fact, the association constant with chloride ion measured in CD_3CN ($109 \pm 3\ M^{-1}$) (Figure 6f), is similar to that obtained with an analogous amide receptor by Reindhout et al. in the same solvent ($100 \pm 10\ M^{-1}$) (Figure 6g),[100] and by Pluth et al. in CD_2Cl_2 ($160 \pm 20\ M^{-1}$).[101] Other anions, such as bromide and iodide, displayed considerably lower association constants,[79] and PF_6^- did not show affinity for **Tren-(Tz-2)$_3$**. According to these results, the NH–Tz group shows similar performance than amides for anion binding. Actually, such moiety could be quite helpful for building anion receptors,[102] not only because of the obvious synthetic advantages of the click-like amine-tetrazine substitution, but also because tetrazines could undergo Inverse Electron Demand Diels Alder reactions (IEDDA) or redox processes, that could help to modulate the anion affinity.

In the end, the initial orange fluorescent system with affinity for **CBPQT^{4+}**, was selectively transformed into a blue fluorescent system that binds chloride instead, just by adding an aniline, which triggered the irreversible intercommunication between dynamic processes.

Conclusion

In summary, simultaneous kinetic control over two different dynamic libraries has been exerted by means of an irreversible intercommunication between them. Such strategy takes advantage of an irreversible reaction of specific building blocks from both dynamic libraries. Indeed, the reaction of alkyl amines with a dynamic library generated by nucleophilic aromatic substitution of tetrazine with phenols and thiols, led to kinetically inert products, the N,S–Tz heterodimers. As a consequence, the initial mixture was eventually funneled towards those compounds. Importantly, the alkyl amine was part of another dynamic library based on imine-amine exchange, and therefore both libraries are intercommunicated by an irreversible process that competes for such amine, causing the re-equilibration of this library too, and accordingly, all the pools of compounds are simultaneously affected. In the end, the initial complexity is managed through kinetic control, resulting in a smaller set of kinetically inert compounds, composed by building blocks from both original libraries.

Interestingly, irreversible intercommunication can be designed to remain latent, until the whole process is triggered by the addition of an external agent. Indeed, we developed a molecular system which is stable until the application of a stimulus, that activates the communication between the dynamic processes. In such a way, the initial system was transformed into a completely different one, and concomitantly, the original supramolecular and luminescent properties were cancelled, and new ones emerged. Remarkably, one of the emerging properties is anion affinity, due to NH groups attached to the tetrazine ring, which constitutes an unexplored moiety to build anion receptors.

The strategy reported herein represents a powerful alternative to manage molecular complexity in order to implement function, and it could find applicability in sensing or in systems chemistry.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: self-sorting · dynamic covalent chemistry · tetrazine · aromatic substitution · nonequilibrium processes

[1] N. Pearcy, N. Chuzhanova, J. J. Crofts, *J. Theor. Biol.* **2016**, *406*, 99–104.
[2] L. Yue, S. Wang, S. Lilienthal, V. Wulf, F. Remacle, R. D. Levine, I. Willner, *J. Am. Chem. Soc.* **2018**, *140*, 8721–8731.
[3] A. Ma'ayan, et al., *Science* **2005**, *309*, 1078–1083.
[4] U. S. Bhalla, P. T. Ram, R. Iyengar, *Science* **2002**, *297*, 1018–1023.
[5] J. Solà, C. Jimeno, I. Alfonso, *Chem. Commun.* **2020**, *56*, 13273–13286.
[6] G. Ashkenasy, T. M. Hermans, S. Otto, A. F. Taylor, *Chem. Soc. Rev.* **2017**, *46*, 2543–2554.
[7] R. F. Ludlow, S. Otto, *Chem. Soc. Rev.* **2008**, *37*, 101–108.
[8] F. B. L. Cougnon, J. K. M. Sanders, *Acc. Chem. Res.* **2012**, *45*, 2211–2221.
[9] J. Li, P. Nowak, S. Otto, *J. Am. Chem. Soc.* **2013**, *135*, 9222–9239.
[10] R. A. R. Hunt, S. Otto, *Chem. Commun.* **2011**, *47*, 847–858.
[11] P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652–3711.
[12] *Dynamic Combinatorial Chemistry* (Ed: B. L. Miller), John Wiley & Sons, Inc., Hoboken, NJ **2010**.
[13] *Dynamic Combinatorial Chemistry* (Eds: J. N. H. Reek, S. Otto), Wiley-VCH, Weinheim, Germany **2010**.
[14] S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem. Int. Ed.* **2002**, *41*, 898–952.
[15] Y. Jin, C. Yu, R. J. Denman, W. Zhang, *Chem. Soc. Rev.* **2013**, *42*, 6634–6654.

[16] R. L. E. Furlan, S. Otto, J. K. M. Sanders, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4801–4804.
[17] Y. Pérez-Fuertes, A. M. Kelly, A. L. Johnson, S. Arimori, S. D. Bull, T. D. James, *Org. Lett.* **2006**, *8*, 609–612.
[18] A. M. Kelly, Y. Pérez-Fuertes, S. Arimori, S. D. Bull, T. D. James, *Org. Lett.* **2006**, *8*, 1971–1974.
[19] R. J. Sarma, S. Otto, J. R. Nitschke, *Chem. Eur. J.* **2007**, *13*, 9542–9546.
[20] M. Hutin, G. Bernardinelli, J. R. Nitschke, *Chem. Eur. J.* **2008**, *14*, 4585–4593.
[21] S. Hagihara, H. Tanaka, S. Matile, *J. Am. Chem. Soc.* **2008**, *130*, 5656–5657.
[22] N. Christinat, R. Scopelliti, K. Severin, *Angew. Chem. Int. Ed.* **2008**, *47*, 1848–1852.
[23] Z. Rodriguez-Docampo, S. Otto, *Chem. Commun.* **2008**, 5301–5303.
[24] A. G. Orrillo, A. M. Escalante, R. L. E. Furlan, *Chem. Commun.* **2008**, 5298–5300.
[25] B. Icli, N. Christinat, J. Tönnemann, C. Schüttler, R. Scopelliti, K. Severin, *J. Am. Chem. Soc.* **2009**, *131*, 3154–3155.
[26] M. von Delius, E. Geertsema, D. A. Leigh, *Nat. Chem.* **2010**, *2*, 96–101.
[27] M. von Delius, E. Geertsema, D. A. Leigh, D.-T. D. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 16134–16145.
[28] A. M. Escalante, A. G. Orrillo, R. L. E. Furlan, *J. Comb. Chem.* **2010**, *12*, 410–413.
[29] N. Sakai, S. Matile, *J. Am. Chem. Soc.* **2011**, *133*, 18542–18545.
[30] K. D. Okochi, Y. Jin, W. Zhang, *Chem. Commun.* **2013**, *49*, 4418–4420.
[31] G. Sforazzini, R. Turdean, N. Sakai, S. Matile, *Chem. Sci.* **2013**, *4*, 1847–1851.
[32] J. F. Teichert, D. Mazunin, J. W. Bode, *J. Am. Chem. Soc.* **2013**, *135*, 11314–11321.
[33] A. Wilson, G. Gasparinia, S. Matile, *Chem. Soc. Rev.* **2014**, *43*, 1948–1962.
[34] F. Schaufelberger, L. Hu, O. Ramström, *Chem. Eur. J.* **2015**, *21*, 9776–9783.
[35] L. Rocard, A. Berezin, F. De Leo, D. Bonifazi, *Angew. Chem. Int. Ed.* **2015**, *54*, 15739–15743.
[36] M. E. Bracchi, D. A. Fulton, *Chem. Commun.* **2015**, *51*, 11052–11055.
[37] S. Kassem, A. T. L. Lee, D. A. Leigh, A. Markevicius, J. Solà, *Nat. Chem.* **2016**, *8*, 138–143.
[38] W. Drożdż, C. Bouillon, C. Kotras, S. Richeter, M. D. Barboiu, S. Clément, A. R. Stefankiewicz, S. Ulrich, *Chem. Eur. J.* **2017**, *23*, 18010–18018.
[39] S. Erbas-Cakmak, S. P. D. Fielden, U. Karaca, D. A. Leigh, C. T. McTernan, D. J. Tetlow, M. R. Wilson, *Science* **2017**, *358*, 340–343.
[40] C. Bouillon, Y. Bessin, F. Poncet, M. Gary-Bobo, P. Dumy, M. Barboiu, N. Bettache, S. Ulrich, *J. Mater. Chem. B* **2018**, *6*, 7239–7246.
[41] W. Drożdż, A. Walczak, A. R. Stefankiewicz, *Org. Lett.* **2021**, *23*, 3641–3645.
[42] I. Marić, L. Yang, X. Li, G. M. Santiago, C. G. Pappas, X. Qiu, J. A. Dijksman, K. Mikhailov, P. Rijn, S. Otto, *Angew. Chem. Int. Ed.* **2023**, *62*, e202216475.
[43] J. Leclaire, L. Vial, S. Otto, J. K. M. Sanders, *Chem. Commun.* **2005**, 1959–1961.
[44] A. G. Orrillo, A. M. Escalante, R. L. E. Furlan, *Chem. Eur. J.* **2016**, *22*, 6746–6749.
[45] B. M. Matysiak, P. Nowak, I. Cvrtila, C. G. Pappas, B. Liu, D. Komáromy, S. Otto, *J. Am. Chem. Soc.* **2017**, *139*, 6744–6751.
[46] A. G. Orrillo, A. La-Venia, A. M. Escalante, R. L. E. Furlan, *Chem. Eur. J.* **2018**, *24*, 3141–3146.
[47] Y. Hai, H. Zou, H. Ye, L. You, *J. Org. Chem.* **2018**, *83*, 9858–9869.
[48] A. G. Orrillo, A. M. Escalante, M. Martínez-Amezaga, I. Cabezudo, R. L. E. Furlan, *Chem. Eur. J.* **2019**, *25*, 1118–1127.
[49] M. Martínez-Amezaga, A. G. Orrillo, R. L. E. Furlan, *Chem. Sci.* **2019**, *10*, 8338–8347.
[50] H. Zou, Y. Hai, H. Ye, L. You, *J. Am. Chem. Soc.* **2019**, *141*, 16344–16353.
[51] H. Zheng, C. Ni, H. Chen, D. Zha, Y. Hai, H. Ye, L. You, *ACS Omega* **2019**, *4*, 10273–10278.
[52] J. Mao, Y. Hai, H. Ye, L. You, *J. Org. Chem.* **2020**, *85*, 5351–5361.
[53] Z. Li, L. Zhang, Y. Zhou, D. Zha, Y. Hai, L. You, *Eur. J. Org. Chem.* **2022**, *2022*, e202101461.
[54] L. You, *Chem. Commun.* **2023**, *59*, 12943–12958.
[55] One of the libraries in antiparallel dynamic chemistry (reversible communication), can be coupled to an additional (third) irreversible reaction. However, that is actually a kinetic self-sorting of one of the libraries, and it is conceptually different to an irreversible interconnection between libraries. See: a) P. Vongvilai, O. Ramström, *J. Am. Chem. Soc.* **2009**, *131*, 14419–14425; b) T. Puangsamlee, O. Š Miljanić, *Org. Lett.* **2020**, *22*, 5900–5904.
[56] K. Osowska, O. Š Miljanić, *Synlett* **2011**, *12*, 1643–1648.
[57] K. Osowska, O. Š Miljanić, *J. Am. Chem. Soc.* **2011**, *133*, 724–727.
[58] K. Osowska, O. Š Miljanić, *Angew. Chem. Int. Ed.* **2011**, *50*, 8345–8349.
[59] R. C. Lirag, K. Osowska, O. Š Miljanić, *Org. Biomol. Chem.* **2012**, *10*, 4847–4850.
[60] C.-W. Hsu, O. Š Miljanić, *Chem. Commun.* **2016**, *52*, 12357–12359.
[61] Q. Ji, R. C. Lirag, O. Š Miljanić, *Chem. Soc. Rev.* **2014**, *43*, 1873–1884.
[62] C.-W. Hsu, O. Š Miljanić, *Angew. Chem. Int. Ed.* **2015**, *54*, 2219–2222.
[63] S. Lee, A. Yang, T. P. Moneypenny II, J. S. Moore, *J. Am. Chem. Soc.* **2016**, *138*, 2182–2185.
[64] E. A. Neal, S. M. Goldup, *Angew. Chem. Int. Ed.* **2016**, *55*, 12488–12493.
[65] F. Schaufelberger, O. Ramström, *J. Am. Chem. Soc.* **2016**, *138*, 7836–7839.
[66] T. Marchetti, D. Frezzato, L. Gabrielli, L. J. Prins, *Angew. Chem. Int. Ed.* **2023**, *62*, e202307530.
[67] M. Sakulsombat, Y. Zhang, O. Ramström, *Top. Curr. Chem.* **2012**, *322*, 55–86.
[68] P. Vongvilai, M. Angelin, R. Larsson, O. Ramström, *Angew. Chem. Int. Ed.* **2007**, *46*, 948–950.
[69] T. Santos, D. S. Rivero, Y. Pérez-Pérez, E. Martín-Encinas, J. Pasán, A. H. Daranas, R. Carrillo, *Angew. Chem. Int. Ed.* **2021**, *60*, 18783–18791.
[70] D. S. Rivero, R. E. Paiva-Feener, T. Santos, E. Martín-Encinas, R. Carrillo, *Macromolecules* **2021**, *54*, 10428–10434.
[71] M. D. Perretti, Y. Pérez-Pérez, K. Soler-Carracedo, E. Martín-Encinas, C. Alonso, J. Scoccia, R. Carrillo, *Chem. Commun.* **2022**, *58*, 5518–5521.
[72] A. M. Tallon, Y. Xu, G. M. West, C. W. am Ende, J. M. Fox, *J. Am. Chem. Soc.* **2023**, *145*, 16069–16080.
[73] See also: K. Gavriel, D. C. A. van Doeselaar, D. W. T. Geers, K. Neumann, *RSC Chem. Biol.* **2023**, *4*, 685–691.
[74] R. Sheyi, A. Sharma, A. El-Faham, B. G. de la Torre, F. Albericio, *Aust. J. Chem.* **2020**, *73*, 352–356.
[75] S. Sandanayake, S. J. Langford, *Aust. J. Chem.* **2014**, *67*, 1264–1269.
[76] D. L. Boger, R. P. Schaum, R. M. Garbaccio, *J. Org. Chem.* **1998**, *63*, 6329–6337.

[77] S. C. Benson, L. Lee, L. Yang, J. K. Snyder, *Tetrahedron* **2000**, *56*, 1165–1180.
[78] C. Canovas, M. Moreau, J.-M. Vrigneaud, P.-S. Bellaye, B. Collin, F. Denat, V. Goncalves, *Bioconjugate Chem.* **2019**, *30*, 888–897.
[79] See the Supporting Information.
[80] Only under harsher conditions, thiols could be exchanged at a reasonable rate. See the Supporting Information.
[81] The experiments shown in this manuscript were carried out with specific thiols and phenols, and butylamine, which were chosen merely due to the speed of the reactions and to the position of the NMR peaks, to obtain the clearest spectra possible, in order to properly follow the reaction by ^{1}H NMR . It is worth mentioning that other compounds were equally successfully self-sorted. All the other experiments can be found in the Supporting Information.
[82] M. Ciaccia, R. Cacciapaglia, P. Mencarelli, L. Mandolini, S. Di Stefano, *Chem. Sci.* **2013**, *4*, 2253–2261.
[83] M. Ciaccia, S. Pilati, R. Cacciapaglia, L. Mandolini, S. Di Stefano, *Org. Biomol. Chem.* **2014**, *12*, 3282–3287.
[84] D. Del Giudice, M. Valentini, G. Melchiorre, E. Spatola, S. Di Stefano, *Chem. Eur. J.* **2022**, *28*, e202200685.
[85] Unfortunately, reaction cannot be initially set up in DMSO-d_6 because it is known the lack of reactivity of dichlorotetrazine in such solvent, probably due to solubility issues. See reference 69.
[86] E. Moulin, G. Cormos, N. Giuseppone, *Chem. Soc. Rev.* **2012**, *41*, 1031–1049.
[87] C. Jia, D. Qi, Y. Zhang, K. Rissanen, J. Li, *ChemSystemsChem* **2020**, *2*, e2000019.
[88] M. Lafuente, J. Solà, I. Alfonso, *Angew. Chem. Int. Ed.* **2018**, *57*, 8421–8424.
[89] M. Kołodziejski, A. R. Stefankiewicz, J.-M. Lehn, *Chem. Sci.* **2019**, *10*, 1836–1843.
[90] A. Jiménez, R. A. Bilbeisi, T. K. Ronson, S. Zarra, C. Woodhead, J. R. Nitschke, *Angew. Chem. Int. Ed.* **2014**, *53*, 4556–4560.
[91] F. B. L. Cougnon, A. R. Stefankiewicz, S. Ulrich, *Chem. Sci.* **2024**, *15*, 879–895.
[92] B. Odell, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, D. J. Williams, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1547–1550.
[93] Q.-Z. Zhou, X.-K. Jiang, X.-B. Shao, G.-J. Chen, M.-X. Jia, Z.-T. Li, *Org. Lett.* **2003**, *5*, 1955–1958.
[94] P. R. Ashton, D. Philp, N. Spencer, J. F. Stoddart, D. J. Williams, *J. Chem. Soc. Chem. Commun.* **1994**, 181–184.
[95] http://supramolecular.org.
[96] D. B. Hibbert, P. Thordarson, *Chem. Commun.* **2016**, *52*, 12792–12805.
[97] D. Schultz, J. R. Nitschke, *Chem. Eur. J.* **2007**, *13*, 3660–3665.
[98] H.-B. Liu, Q. Zhang, M.-X. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 6536–6540.
[99] S.-Y. Zhuang, Y. Cheng, Q. Zhang, S. Tong, M.-X. Wang, *Angew. Chem. Int. Ed.* **2020**, *59*, 23716–23723.
[100] S. Valiyaveettil, J. F. J. Engbersen, W. Verboom, D. N. Reinhoudt, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 900–901.
[101] N. Lau, L. N. Zakharov, M. D. Pluth, *Chem. Commun.* **2018**, *54*, 2337–2340.
[102] L. Chen, S. N. Berry, X. Wu, E. N. W. Howe, P. A. Gale, *Chem* **2020**, *6*, 61–141.

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