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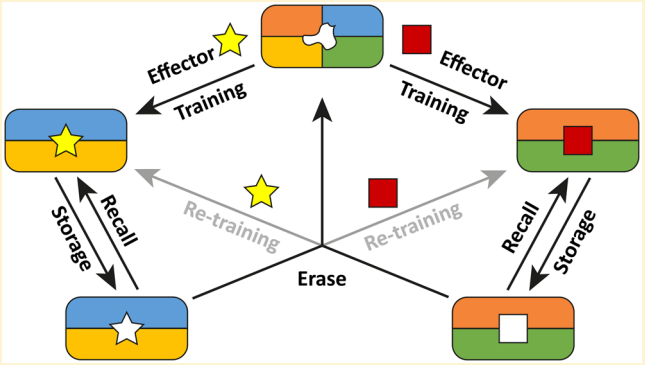
Training a Constitutional Dynamic Network for Effector Recognition: Storage, Recall, and Erasing of Information

Jan Holub, Ghislaine Vantomme,[†] and Jean-Marie Lehn*

Laboratoire de Chimie Supramoléculaire, Institut de Science et d'Ingénierie Supramoléculaires (ISIS), Université de Strasbourg, 8 allée Gaspard Monge, 67000 Strasbourg, France

Supporting Information

ABSTRACT: Constitutional dynamic libraries (CDLs) of hydrazones, acylhydrazones, and imines undergo reorganization and adaptation in response to chemical effectors (herein metal cations) via component exchange and selection. Such CDLs can be subjected to training by exposition to given effectors and keep memory of the information stored by interaction with a specific metal ion. The long-term storage of the acquired information into the set of constituents of the system allows for fast recognition on subsequent contacts with the same effector(s). Dynamic networks of constituents were designed to adapt orthogonally to different metal cations by up- and down-regulation of specific constituents in the final distribution. The memory may be erased by component exchange between the constituents so as to regenerate the initial (statistical) distribution. The libraries described represent constituational dynamic systems capable of acting as information storage molecular devices, in which the presence of components linked by reversible covalent bonds in slow exchange and bearing adequate coordination sites allows for the adaptation to different metal ions by constitutional variation. The system thus performs information storage, recall, and erase processes.



INTRODUCTION

The designed self-organization of well-defined supramolecular architectures from their components rests on the storage of the required molecular information in the covalent framework of the components and its processing at the supramolecular level through specific interactional algorithms.[1,2] A further step toward systems of increasing complexity consists of the implementation of constitutional dynamic chemistry (CDC)[3] and its adaptive features for the design of chemical learning systems that are not just programmed beforehand for a given process but can be trained toward the acquisition of a given function, such as remembering an agent to which it had been subjected. Training and learning involve progressive adaptation of a system, in effect a constitutional dynamic library (CDL), subjected to repetitive application of a physical stimulus or of a chemical effector, thus building up an adapted state and retaining it.[3d] The members of the CDL are linked in a constitutional dynamic network (CDN)[3c,d] that interconnects the constituents of the CDL through agonistic and antagonistic relationships, so that training and learning imply a progressive modification/adaptation of the connectome in response to various inputs/solicitations.

Herein, we demonstrate the implementation of a dynamic covalent library (DCL)[4] for performing a set of molecular information processing operations involved in the design of a prototypical chemical learning system, training the system through (repetitive) application of an effector for the recognition of that very effector. They comprise (i) imprinting of information in a constitutional state/distribution of a DCL by an effector; (ii) long-term retention of the stored information on removal of the effector; (iii) fast repetitive recognition of the agent; (iv) retraining of the system onto a different agent; and (v) final erasing of information with return to the initial "naive" DCL composition. For the sake of demonstration, the systems described below implement DCLs of ligand molecules, responding to the application of metal cation effectors, based on components related to those used in previous studies of metallo-selection and photoselection processes,[5] but adjusted here for the present purposes (Figure 1). The results are meant to provide a proof of principle of the ability of CDC to give access to higher levels of behavior of a chemical system[6] such as training and learning through adaptation by component selection.[3,S]

Rationale. The DCL training operations are accessible via changes between agonist/antagonist pairs of constituents within the CDN. Antagonists, that is, constituents (e.g., $^{3}\mathbf{A}^{1}\mathbf{C}$ and $^{3}\mathbf{A}^{1}\mathbf{D}$, Figure 1) that share a component ($^{3}\mathbf{A}$), are competitors. Enhancing the formation of one ($^{3}\mathbf{A}^{1}\mathbf{C}$) results in the reduction of the other ($^{3}\mathbf{A}^{1}\mathbf{D}$). On the other hand, agonists

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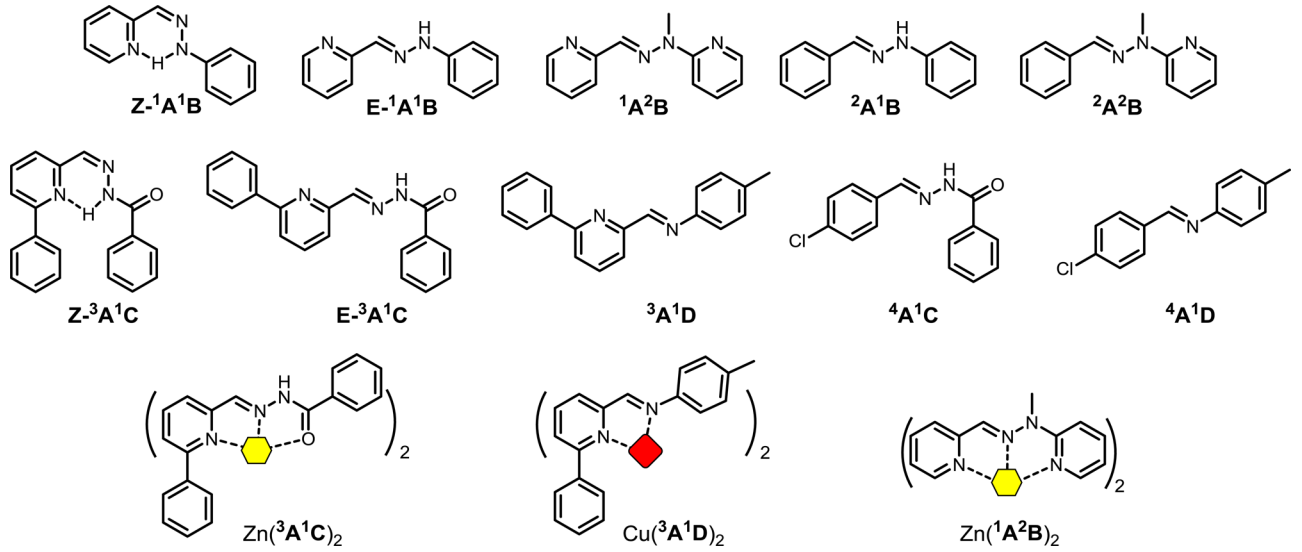

Figure 1. Structures of the dynamic covalent ligands forming the constitutional dynamic library (CDL) used in the present work. The fragments A, on one hand, and B, C, and D, on the other, are derived respectively from the aldehyde and the amine (hydrazine, top, or acylhydrazone, middle) components of the CDL. The complexes of the metal cations M are also shown (bottom).

(e.g., ^{3}**A**^{1}**C** and ^{4}**A**^{1}**D**, Figure 1) are constituents without common component. They are in a synergistic relationship; thus an increase of one (^{3}**A**^{1}**C**) enforces also the formation of the other one (^{4}**A**^{1}**D**) by agonist amplification.[3c,d]

The agonist/antagonist relationship in response to interaction with an effector, here a metal cation, is the key regulatory mechanism allowing the DCL to adjust its equilibrium composition by up- and down-regulation of its constituents.[3−5] Exposing the system to a second contact with the same effector leads to instant recognition in a fast recall process. Such a DCL can also be amenable to double (multiple) training toward different effectors (metal cations), and the information stored can be later erased through re-equilibration of the components. Depending on the conditions used, orthogonal switching between different constitutional states through metalloselection imprints different information represented by specific distributions of the constituents of the DCL enforced by a given effector/metal cation. It is important to note that in the present case the chemical information resides in a distribution of constituents, representing a constitutional engram,[7,8] rather than in a molecular shape/structure imprint in polymeric materials.[9] Furthermore, removal of the effector leads to an out-of-equilibrium constitutional state (see also ref 10) that retains the information about the effector. Memory corresponds to an out-of-equilibrium state. For the present purposes, the system has to combine (i) the ability to equilibrate the constituents of the DCL so as to be able to respond to the effector(s) by component exchange, (ii) with sufficient stability, that is, slow component exchange in given conditions, so as to retain the constituent distribution after removal of the effector(s). At least one constituent must present these features so as to allow for kinetic control of the system. Thus, imine-based constituents exchange too easily their components. On the other hand, hydrazone- and acylhydrazone-based constituents/ligands are much more reluctant to undergo component exchange, while still able to respond to an effector/metal cation. The presence of an hydrazone or acylhydrazone is thus of utmost importance for providing the kinetic barrier required for stabilizing the out-of-equilibrium states generated after removal of the effector/metal cation and thus preclude re-equilibration, that is, memory/information erasing. Such an effect may be described as agonist inhibition because, in the presence of both fast exchanging (imines) and slow exchanging constituents (hydrazones, acylhydrazones), the stability of one constituent also prevents re-equilibration of its kinetically less stable agonist.

On the basis of previous work from our group,[5] pyridyl-hydrazones and pyridyl-acylhydrazones present the very attractive feature of being triple dynamic entities, capable of long-term and short-term information storage,[5a] by undergoing (1) conformational dynamics by shape switching on cation coordination to the NNN and NNO tridentate binding sites, respectively;[5,11,12] (2) configurational dynamics on *E* to *Z* photoisomerization stabilized by internal hydrogen bonding with the pyridine moiety;[5,13] and (3) constitutional dynamics, by component exchange via the reversible C═N connection.[4,5] The DCLs of pyridyl-hydrazones, pyridyl-acylhydrazones, and pyridyl-imines studied here form networks represented as 2D square [2 × 2] CDNs in the schemes below. All of the metal cation-induced changes in constituent distributions were monitored by ^{1}H NMR spectroscopy and are shown in the Supporting Information.

RESULTS AND DISCUSSION

Training of a Dynamic Covalent Library of Hydrazones toward a Single Effector. *Imprinting and Storage of Information.* On the basis of previous results in our laboratory,[5] we first investigated the DCL of the four hydrazones ^{1}**A**^{1}**B**, ^{1}**A**^{2}**B**, ^{2}**A**^{1}**B**, and ^{2}**A**^{2}**B** (Figure 1). It was generated from a mixture of equimolar quantities of the two constituents ^{1}**A**^{1}**B** and ^{2}**A**^{2}**B** (0.6×10^{-5} mol, 10 mM each, through component randomization under metal ion catalysis (4:1 acetonitrile/water, 170 °C, MW, 20 min in the presence of $Sc(OTf)_3$ (2 mM)),[14] giving the full set of four constituents by component exchange with a distribution for ^{1}**A**^{1}**B**/^{1}**A**^{2}**B**/^{2}**A**^{1}**B**/^{2}**A**^{2}**B** in agreement within experimental error with the previously reported one (32/17/21/18%, respectively, and 12% hydrolysis).[5b] The ^{1}**A**^{1}**B** was present in the form of its *E* (60%) and *Z* (40%) isomers, and the total

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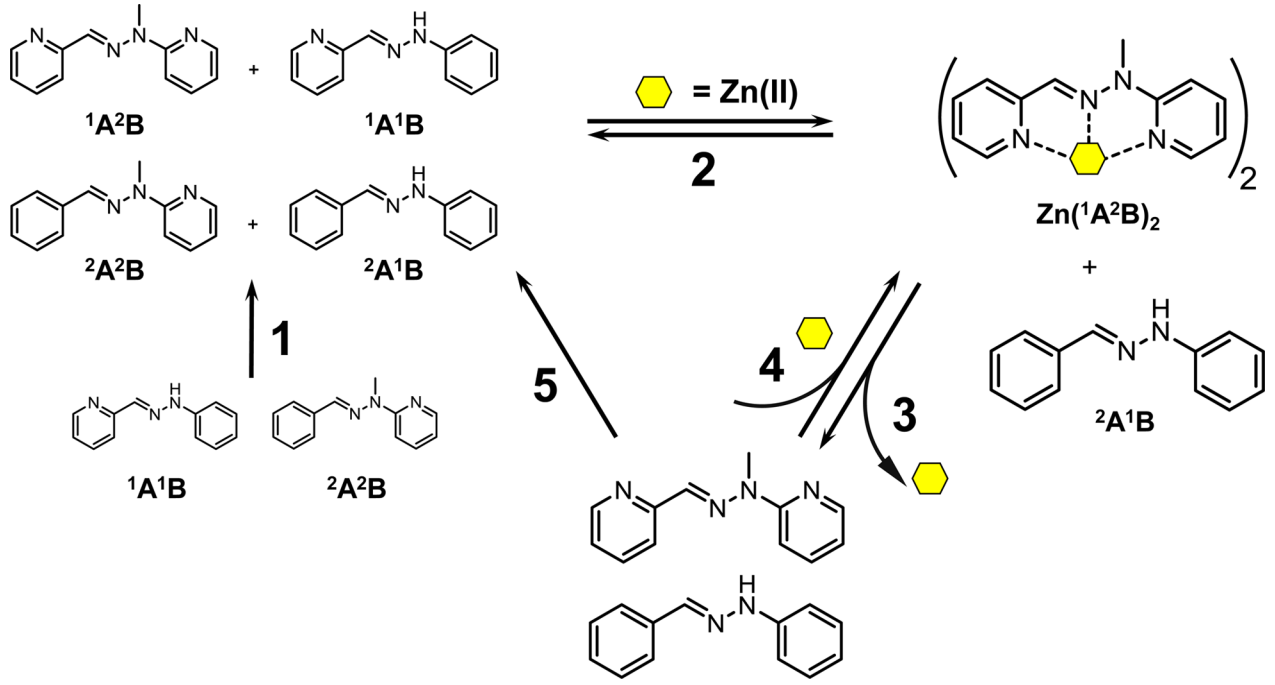
Scheme 1. Training of the Dynamic Covalent Library (DCL) of Four Hydrazone Constituents $^1A^1B$, $^1A^2B$, $^2A^1B$, and $^2A^2B$ for the Recognition of Zinc Cations[a]



[a](1) Generation of the complete set of four hydrazones by component exchange under Sc(III) metal ion catalysis and distribution of the constituents (below); (2) dynamic imprinting by metalloselection via the prime addition of zinc(II) cations and resulting distribution of the constituents (below) showing adaptation driven by the metal ion effector; (3) removal of both Zn(II) and Sc(III) cations by precipitation with potassium ferricyanide, with generation of an out-of-equilibrium state storing the information about the Zn(II) effector in the constitution of the system; (4) new addition of zinc(II) cations inducing a fast recall of the encoded information; and (5) erasing of the stored information. For clarity, only the major components are represented for each step. (bottom) Representation of the library adaptation as a square Constitutional Dynamic Network (CDN) showing agonist amplification and down-regulation of the antagonists. $^1A^1B$ is obtained as both *E* and *Z* (not shown) isomers; Zn(II) binding converts all *Z* into *E*. Error on % determination: ~±2%.

amount of both isomers was taken into an account when analyzing the mixture.

Metalloselection was used to imprint constitutional information into the system by changing the relative amounts of the constituents. Upon treatment with zinc(II) triflate, the DCL above underwent reorganization to a distribution of 14/29/38/11% for $^1A^1B/^1A^2B/^2A^1B/^2A^2B$, respectively, with 8% of hydrolysis, $^1A^2B$ being present as the complex $Zn(^1A^2B)_2$, and no mixed-ligand complexes were observed (see step 2 in Scheme 1, Figure 1, and Figure S27).[5b] Thus, both $^1A^2B$ and its agonist $^2A^1B$ were up-regulated, whereas the amounts of $^1A^1B$ and $^2A^2B$ decreased substantially. These changes amount to a storage of information in the constitutional distribution triggered by addition of zinc triflate ($Zn(OTf)_2$). The reaction time of these metallo-induced changes increased markedly when the temperature was decreased to about 12 h at 60 °C.

Starting from this distribution of $^1A^1B$, $Zn(^1A^2B)_2$, $^2A^1B$, and $^2A^2B$ obtained by metalloselection, removal of the zinc(II) cation from $Zn(^1A^2B)_2$ was achieved by addition of potassium ferricyanide (5 mM, 1 equiv with respect to Zn(II) ions), which resulted in precipitation of both the Zn(II) and the Sc(III) cations, thus removing all cations from the medium. Because the exchange between the hydrazones under these conditions is very slow, the DCL retained its composition unchanged (see step 3 in Scheme 1, Figure S28) and thus kept the encoded information in the form of the frozen distribution of constituents, which did not change at 25 °C for more than 7 days. It is important to note that the system is now in a kinetically trapped out-of-equilibrium state, as equilibration is precluded by the very slow component exchange.

Recognition of the Effector and Recall of the Information. To show that the system had been trained for recognition of the Zn(II) cation effector, zinc triflate (5 mM) was added again to the mixture above, resulting in the immediate regeneration of the $Zn(^1A^2B)_2$ complex with the preformed ligand constituent in the unchanged distribution obtained after removal of the cations (see above). The response of the system to this new addition of zinc cations took less than the time needed to measure the ^1H NMR spectrum (about 2 min) and to observe the formation of the complex $Zn(^1A^2B)_2$. This fast recall on second contact with zinc cations as compared to the first exposition results from the fact that the system does not need to modify its constitution, as it is optimized for binding zinc cations. It is probable that the time to form the zinc complex was less than a few seconds on this second exposition as compared to several hours for the first exposition under the same conditions. Thus, the renewed presentation of the effector zinc(II) to the system induced a fast recall of the encoded information, and showed that the system had been trained for recognition of the effector (see step 4 in Scheme 1).

Erasing of the Information. The information stored into the composition of the CDL was erased by removal of the effector followed by heating, which promoted a restoration of the initial distribution of constituents (step 5, Scheme 1). The effector was again removed by addition of potassium ferricyanide (1 equiv with respect to Zn(II) ions) to precipitate the cation

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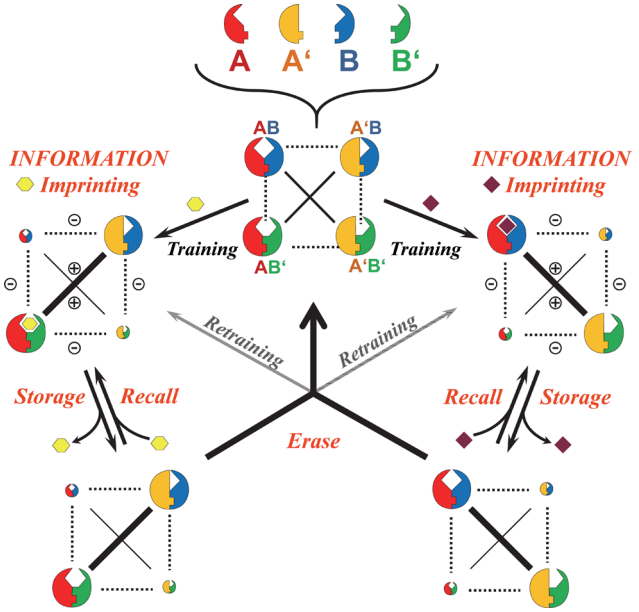
from its $Zn(^1A^2B)_2$ complex. Subsequent heating of the solution at 170 °C for 20 min in the microwave reactor in the presence of scandium triflate (2 mM) as exchange catalyst provided the same initial distribution of the four hydrazones $^1A^1B$, $^1A^2B$, $^2A^1B$, and $^2A^2B$, thus closing the circle and demonstrating the reversibility of all processes during information imprinting, storage, recall, and final erasing.

Double Training of a Dynamic Covalent Library of Imines and Acylhydrazones toward Two Different Effectors. *Searching for a Dual Responsive System – Strong Orthogonal Amplification of a Biased DCL. Setting the Stage.* A further step consists of devising a DCL that may respond to two different effectors, so that, on applying them, it may be trained to store different information and undergo switching between two orthogonal memory states (Scheme 2).

Scheme 2. Dual Responsive Dynamic Combinatorial Library System Displaying Amplification of Two Orthogonal Pairs of Agonists by Component Selection in Response to Two Different Metal Cations, Thus Undergoing Double Training with Network Switching[a]



[a]The DCL distributions on the bottom left and right represent orthogonal constitutional imprints, out-of-equilibrium states.

The design of such systems requires a slow component exchange between the constituents so as to retain the constituent selection obtained after removal of each of the two effectors, so as not to lose the information stored before reading it by a subsequent exposure to each effector. To achieve such double effector responsive and dual information storing dynamic system, the DCL must be based on components capable of generating constituents that respond specifically to each of the two effectors. To this end, a search for a DCL based on both imine and acylhydrazone ligand constituents, presenting respectively bidentate and tridentate binding subunits, was set up. It was surmised that such a DCL would be able to respond to metal cations presenting either tetrahedral or octahedral coordination geometry under metal-loselection.

Searching for a Suitable DCL. We first explored a DCL generated from the two aldehyde ^5A and ^6A, the diamine ^1E, and the hydrazide ^1C components (Scheme 3). It is expected to contain the four constituents $^5A^1C$, $^5A_2{}^1E$, $^6A^1C$, and $^6A_2{}^1E$, which could in principle respond to dual training by either Zn(II) and Cu(I) cations. [One should note that the rate of formation of the acylhydrazones is increased in the presence of aliphatic or aromatic amines (see Schemes 3 and 4). Indeed, amines act as nucleophilic catalysts for the formation of acylhydrazones (see ref 19). This was demonstrated here in the case of the formation of E-$^3A^1C$ from its components (^3A and ^1C), which was substantially faster (from days to hours) and occurred at room temperature (down from 70 °C) in the presence of a catalytic amount (~10%) of *p*-toluidine (see also E/Z isomerization of $^3A^1C$ in the Supporting Information).] When all four components ^1C, ^5A, ^6A (1.25×10^{-5} mol, 25 mM), and ^1E (0.625×10^{-5} mol, 12.5 mM) were mixed in a NMR tube in acetonitrile at 23 °C, the only components identified in the mixture after about 12 h were $^5A^1C$ (E form only; see Figures S1–S6 for more details on E and Z formation) and $^6A_2{}^1E$, indicating a strongly biased initial library. [The E/Z isomerization of $^3A^1C$ and $^5A^1C$ was studied in detail. All four isomers were observed and characterized by ^1H NMR (1D and 2D). E-$^3A^1C$ and Z-$^5A^1C$ were isolated in pure forms, and their transformation from one isomer to the other was achieved by various methods. The other two isomers were converted into their counterpart in solution. Details about the E/Z isomerization of these compounds are given in the Supporting Information. For another study on E/Z isomerization of acylhydrazones, see the literature.[18]] The origin of this bias may be attributed to the favored formation of the acylhydrazone $^5A^1C$ and to the stabilization of its agonist $^6A_2{}^1E$ by hydrogen bonding between the phenolic –OH and the imine –N=[15] (see also Figure S29). Both factors combine to drive the selection between constituents toward a strong amplification of the agonists $^5A^1C$ and $^6A_2{}^1E$ in a synergistic fashion even in the absence of any metal cation.

Addition of zinc cations led to partial destruction of the library due to extensive hydrolysis of the bis-imine $^6A_2{}^1E$.

On the other hand, addition of the copper(I) cation caused the strong amplification of the opposite agonist pair $^5A^1E$ and $^6A^1C$ via formation of the Cu($^5A_2{}^1E$) complex (characterized by its NMR data and its particularly clean ESI mass spectrum; see Figures S33–S35). Thus, a remarkable change of constituent expression had taken place with a very pronounced difference between the effects of the two different cations and an orthogonal switching of the DCL constituents with respect to both the initial DCL and its composition in the presence of Zn(II) cations (see also Figures S32 and S36). However, in view of both the extensive hydrolysis brought about by the addition of the Zn(II) cations and the initial bias of the DCL, further exploration toward a suitable system was conducted.

H-bonding was eliminated by exchanging salicylaldehyde (^6A) first for benzaldehyde and later to further reduce hydrolysis, for 4-chlorobenzaldehyde (^4A). Replacing the aliphatic amine by an aromatic amine (*p*-toluidine) then reduced the level of metal-induced hydrolysis to one-half of the previous one. A final adjustment consisted of exchanging 6-methyl-2-pyrydinecarboxaldehyde (^5A) for 6-phenyl-2-pyridinecarboxaldehyde (^3A), as it might enhance binding of copper(I), considering the known increase in stability of the copper(I) complexes from 6,6′-dimethyl-2,2′-bipyridine to 6,6′-diphenyl-2,2′-bipyridine.[16]

The new CDL was then generated from an equimolar mixture of the four components: 6-phenylpyridine-2-carbox-

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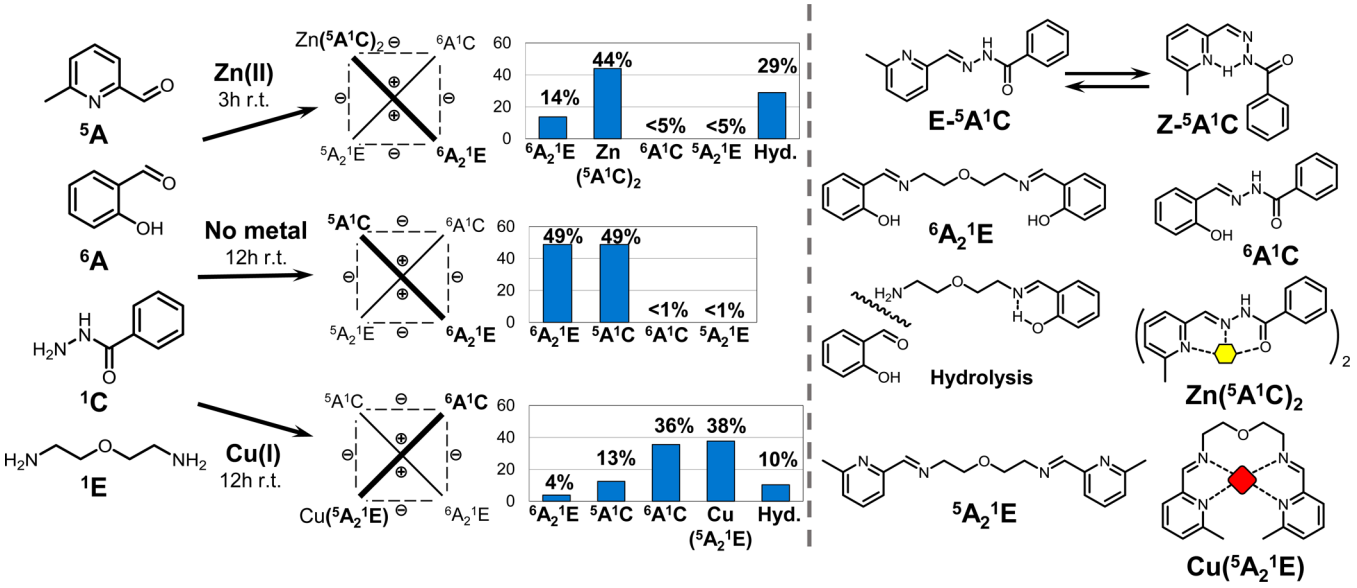
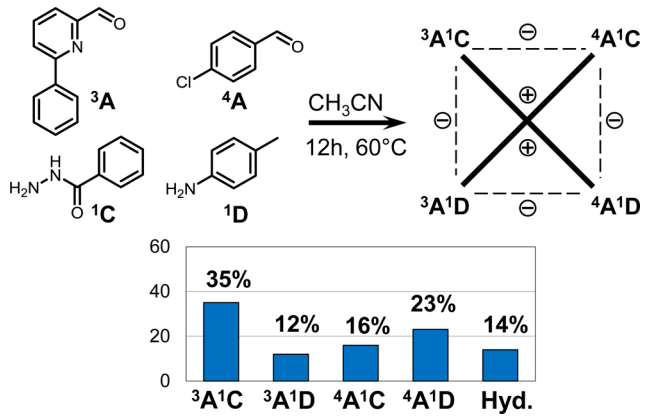
Scheme 3. Distribution of the Four Constituents of the DCL $^{5}A^{1}C$, $^{5}A_{2}{}^{1}E$, $^{6}A^{1}C$, and $^{6}A_{2}{}^{1}E$ without Any Metal (Middle), after Zn(II) Addition (Top), and after Cu(I) Addition (Bottom) Showing the Biased Initial Distribution (Middle) and Extensive Hydrolysis of $^{6}A_{2}{}^{1}E$ (Top)[a]



[a](a) The component $^{5}A^{1}C$ can exist in *E* and *Z* forms (see Figures S1–S6 for details). (b) Error on determination ~±2%.

Scheme 4. Distribution of the Constituents of the Optimized DCL Generated from the Components in the Absence of Metal Cations[a]



[a]The amount of $^{3}A^{1}C$ indicated is the sum of the *E* and *Z* forms of this constituent.

aldehyde (^{3}A), 4-chlorobenzaldehyde (^{4}A), benzhydrazide (^{1}C), and *p*-toluidine (^{1}D) (1.25 × 10^{-5} mol each, 25 mM) in acetonitrile, heated at 60 °C for 12 h to achieve equilibration. Four constituents $^{3}A^{1}C$, $^{3}A^{1}D$, $^{4}A^{1}C$, and $^{4}A^{1}D$ were obtained with a distribution of 35/12/16/23%, respectively, together with 14% hydrolysis (Scheme 4, Figures S37–S40). The elevated level of hydrolysis of $^{4}A^{1}D$ is part of the equilibrium and could not be avoided. Moreover, the presence of the two configurational isomers of $^{3}A^{1}C$ (*E*-$^{3}A^{1}C$ (40%) and *Z*-$^{3}A^{1}C$ (60%), confirmed by 2D NMR; see Figures S13–S20) was observed, and both were taken into account. DCLs of the same composition (within experimental error ~±2%) can be generated starting from a mixture either of the four components or of pairs of agonist constituents.

Dual Responsive Information Processing within a CDL: Training, Storage, Recall, Erasing, and Retraining. Training of the DCL generated above is achieved by subjecting it to the action of a given metal cation, thus generating a specific distribution of the constituents, which encodes/stores the information about that particular metal cation. Removal of the metal thereafter conserves the specific distribution, leaving the cation-free system prepared for subsequent operations of recall, retraining, or erasing.

Operating on Cation 1, Zn(II). Training. When the initial mixture of four components was subjected to addition of $Zn(OTf)_2$ (0.5 equiv, 0.625 × 10^{-5} mol, 12.5 mM), the octahedral coordination to the cation promoted the formation of the tridentate ligand constituent $^{3}A^{1}C$ as its complex $Zn(^{3}A^{1}C)_2$, and as a consequence the amount of its agonists $^{4}A^{1}D$ increased as well (Scheme 5). The formation of the Zn library required heating to 60 °C for 3 h leading to full amplification of only one agonist pair (one diagonal of the square network; Scheme 5) with the composition: Zn-($^{3}A^{1}C$)$_2$/$^{3}A^{1}D$/$^{4}A^{1}C$/$^{4}A^{1}D$/hydrolysis = 50/<1/<1/36/12% (see also Figures S43–S45). For identification purposes, the zinc complex $Zn(^{3}A^{1}C)_2$, as well as the copper complex $Cu(^{3}A^{1}D)_2$, below have been separately prepared and characterized (see Figures S41, S42 and S51, S52).

Storage. The removal of the zinc cations turned out to be particularly challenging because of the presence of the N–H group in the acylhydrazone moiety and of the Lewis acidity of the zinc cation.

The acylhydrazone N–H group becomes easily ionizable upon binding of the zinc cation, resulting in a complex acido–basic equilibrium and hard to resolve mixtures upon decomplexations. Further, demetalation reagents (e.g., hexacyclen) may interfere with the subsequent steps (retraining, recall, erasing), or are insoluble in pure acetonitrile (e.g., $K_3[Fe(CN)_6]$), or catalyze fast re-equilibration (erasing the information). After considerable exploration, the most suitable reagent proved to be the bis-tetraethylammonium salt of EDTA, $(NEt_4)_2EDTAH_2$. It forms strong complexes with the Zn(II) cations, which precipitate from the mixture, thus

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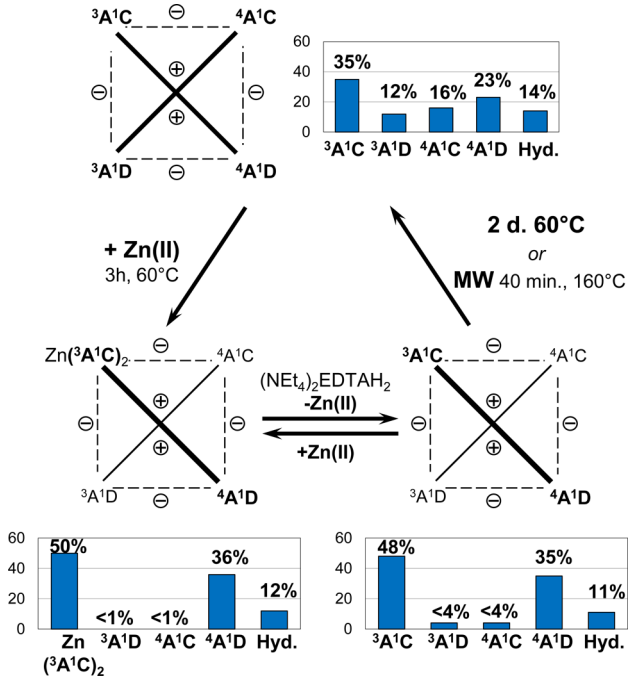
Scheme 5. Formation of the Zn(II)-Trained DCL Distribution by Addition of $Zn(OTf)_2$ to a Mixture of the Four Constituents $^3A^1C$, $^3A^1D$, $^4A^1C$, and $^4A^1D$ (Training; Left Top to Bottom), Which on Cation Removal Mainly Retains Its Composition in the Metal-Free DCL (Information Storage; Bottom Left to Right); Recall by Addition of Zinc(II) (Bottom Right to Left); and Erasing of the Metal-Free DCL by Heating (Right Bottom to Top) with Return to the Thermodynamically Driven Initial State



eliminating both the metal ion and the complexing agent from the medium. However, a slight excess was needed to ensure that no Zn(II) remained in solution, as traces were found to catalyze re-equilibration of the metal-free state, thus substantially decreasing the lifetime of the cation-free out-of-equilibrium state. Indeed, the slightly higher levels of $^3A^1D$ and $^4A^1C$ observed after demetalation may be attributed to this zinc-catalyzed equilibration during the demetalation/precipitation step (see Figure S48). When care is taken of this factor, the out-of-equilibrium state is stable (less than 10% change) for about 12 h (see NMR spectra in Figure S49).

Recall. After removal of the Zn(II) cations, the system is now trained and prepared for the repeated zinc recognition, which is expected to be much faster than the initial complexation where equilibration of the DCL had first to take place. Indeed, the readdition of the zinc cations resulted in direct fast return to the previous complexed state (recall) in a much shorter time (less than the 2 min required to perform the NMR measurement) than the initial training step (3 h) (see also above) (Scheme 5; see Figure S48).

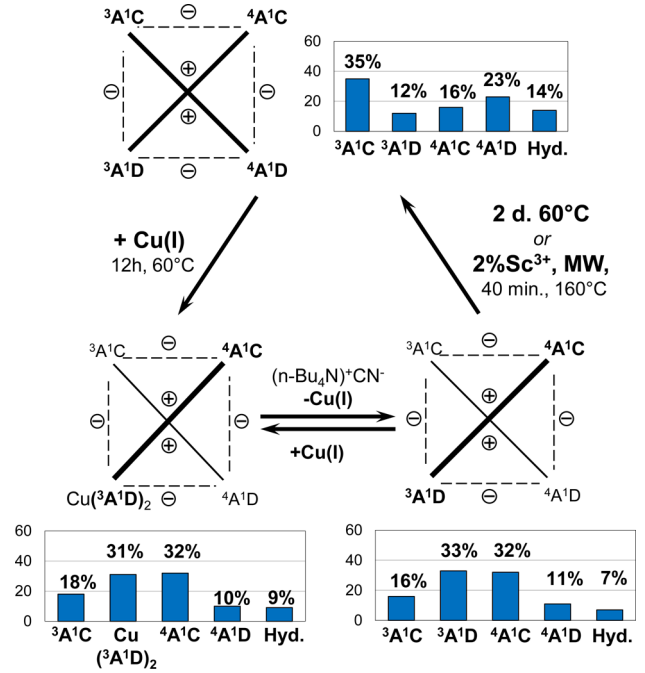
Erasing. This metal-free state of the DCL is a kinetically trapped out-of-equilibrium state and is stable for 12 h at 23 °C, due to the sluggishness of component exchange of the acylhydrazone $^3A^1C$ member of the library (see above). Indeed, harsh conditions are needed for erasing the information and returning to the thermodynamically stable state, the initial distribution of constituents, that is, heating the mixture for several days at 60 °C or applying microwave irradiation (40 min, 160 °C, 270 W) (see Figures S39, S40, and S49).

Retraining. Finally, the addition of Cu(I) triflate (CuOTf, 0.5 equiv, 0.625×10^{-5} mol, 12.5 mM) to the out-of-equilibrium state followed by heating at 60 °C for 12 h retrains the system from the zinc-trained/selected DCL composition directly into the copper-trained/selected one without the need to pass through an erasing step (see Scheme 7 and Figure S50).

Operating on Cation 2, Cu(I), Scheme 6. The corresponding steps can also be achieved with the second cation Cu(I). Treatment of the same starting mixture with CuOTf (0.5 equiv, 0.625×10^{-5} mol, 12.5 mM) followed by equilibration at 60 °C for 12 h led again to a marked change in composition of the CDL, driven this time by formation of the tetra-coordinated complex $Cu(^3A^1D)_2$ (Figure 1).

It thus resulted in the amplification of both the Cu(I) ligand $^3A^1D$ and its agonist $^4A^1C$, that is, the constituents linked by the network diagonal orthogonal to the previous zinc-selected diagonal. The distribution obtained was 18/31/32/10/9% for $^3A^1C/Cu(^3A^1D)_2/^4A^1C/^4A^1D$/hydrolysis, respectively

Scheme 6. Formation of the Cu(I)-Trained DCL Distribution by Addition of CuOTf to a Mixture of the Four Constituents $^3A^1C$, $^4A^1D$, $^3A^1D$, and $^4A^1C$ (Training; Left Top to Bottom), Which on Cation Removal Mainly Retains Its Composition in the Metal-Free DCL (Information Storage; Bottom Left to Right); Recall by Addition of Cu(I) (Bottom Right to Left); and Erasing of the Metal-Free DCL by Heating (Right Bottom to Top) with Return to the Thermodynamically Driven Initial State



(Scheme 6 and Figures S53, S54). Even though the constituent $^3A^1C$ can possibly bind Cu(I) in the same way as $^3A^1D$, the ^1H NMR does not show any direct binding (no significant shift of signals) as well as no signals of possible mixed-ligand complexes.

The Cu(I)-imprinted cation-free DCL can thereafter be generated by addition of NBu_4CN, leading to precipitation of CuCN from the mixture. The resulting out-of-equilibrium state

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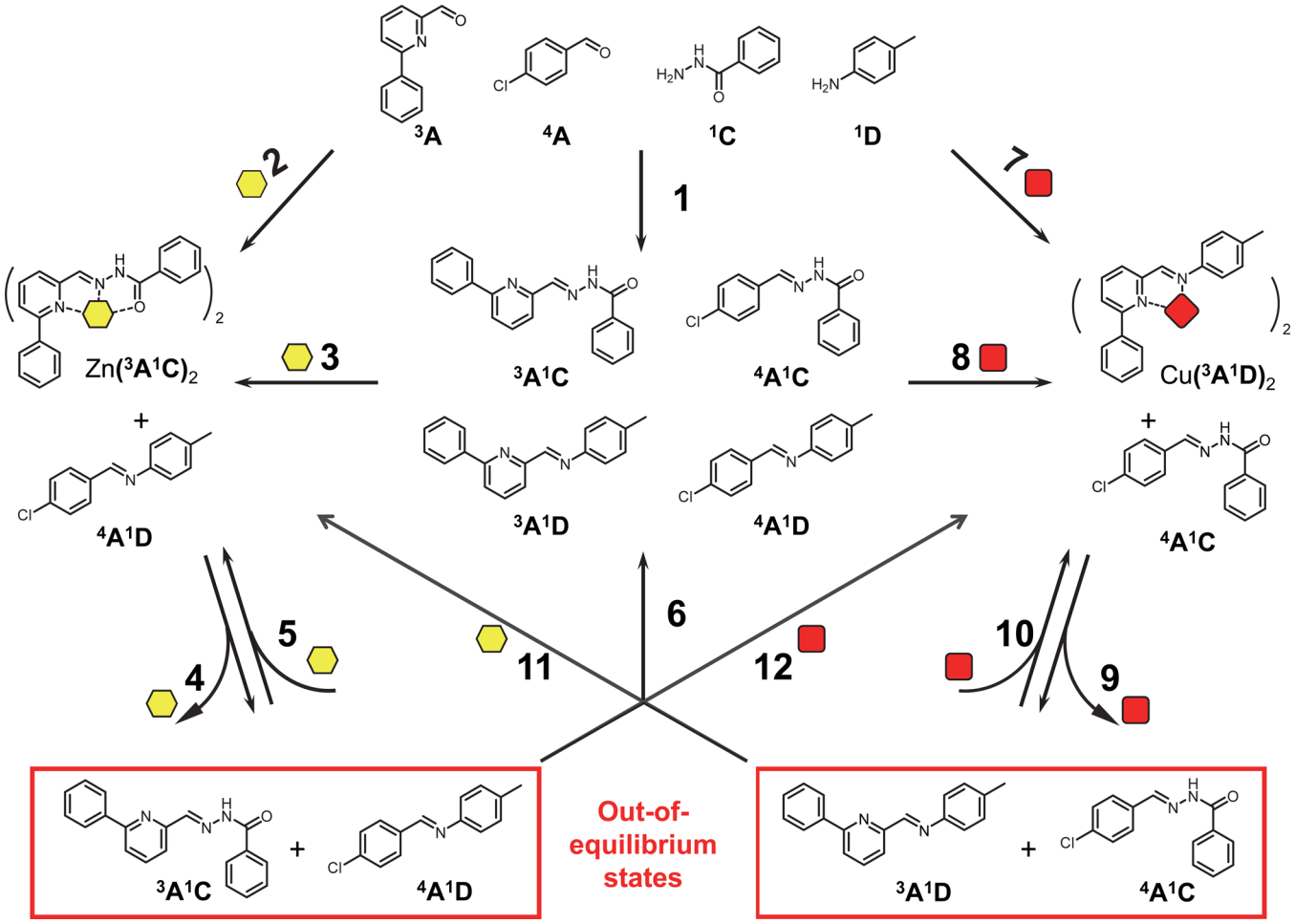
Scheme 7. Representation of All of the Transformations Performed by the Dual Responsive Dynamic Covalent System Based on the DCL $^{3}A^{1}C$, $^{4}A^{1}D$, $^{3}A^{1}D$, and $^{4}A^{1}C$[a]



[a](1) DCL generation from the components; 12 h, 60 °C, CH_3CN; (2,3) adaptation/training of the system on Zn(II) effector; 0.5 equiv of $Zn(OTf)_2$, 3 h, 60 °C; (4) Zn(II) removal by $[(Et_4)N]_2EDTAH_2$; retention of the distribution imprint/information storage at rt for 12 h; (5) fast information recall; re-addition of 0.5 equiv of $Zn(OTf)_2$; (6) information/imprint erase; MW, 40 min, 160 °C; (7,8) adaptation/training of the system on Cu(I); 0.5 equiv of CuOTf, 12 h, 60 °C; (9) Cu(I) removal by $(n\text{-}Bu)_4NCN$; retention of the distribution imprint/information storage at rt for 12 h; (10) fast information recall; re-addition of 0.5 equiv of $Zn(OTf)_2$; (11) direct retraining on Zn(II); 0.5 equiv of $Zn(OTf)_2$, 3 h, 60 °C; (12) direct retraining on Cu(I); 0.5 equiv of CuOTf, 12 h, 60 °C; [$^{3}A^{1}C$, $^{4}A^{1}D$] (bottom left) and [$^{3}A^{1}D$, $^{4}A^{1}C$] (bottom right) represent constitutional imprints, out-of-equilibrium states.

is then stable (less than 10% change) for up to 2 days (see NMR spectra in Figure S56).

The reverse process on readdition of Cu(I) is immediate (time between mixing and measuring the NMR spectrum; less than 2 min as compared to 12 h for the initial training step). (See Figure S55.) Thermodynamic equilibration and erasing of the Cu(I) imprint can be achieved by microwave irradiation (40 min, 160 °C, 270 W, +2% $Sc(OTf)_3$). (See Figures S40 and S56.) Finally, addition of zinc triflate to an out-of-equilibrium Cu-free Cu-DCL results in the direct formation of the Zn-DCL with complete retraining (change of the distribution) and switching of the CDN (see Figures S57 and S58).

Thus, the full circle of transformations involved in dual training and information processing based on the same DCL has been achieved, demonstrating the reversibility of all paths and the interconversion of all states of the full network as summarized in Scheme 7.

CONCLUSION

For both DCLs investigated above, different equilibrium distributions of constituents characterizing different constitutional states (Zn-DCL and Cu-DCL) are reached, along different training operations, depending on the applied stimulus (metal cation). The system exhibits long re-equilibration time at room temperature, allowing it to retain, in the related metal-free states, the information stored by training on application of the metal. These out-of-equilibrium states allow for fast recomplexation/detection of the metal effector, as the DCL is already in the preprepared state, demonstrating fast recall. On introduction of another effector/metal cation, the distribution of the constituents adapts for the recognition of this other effector. Finally, subjecting an out-of-equilibrium informed distribution to equilibrating conditions leads to the restoration of the initial state of thermodynamic equilibrium, thus erasing the information stored in the DCL on any effector previously applied. The present results thus display a full circle training/

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erasing process based on the generation of constitutional dynamic engrams[7] and operating via CDNs.

It is worth stressing that, whereas usually DCC searches for fast component exchange and constituent equilibration in a DCL, here a slow process is required to retain the trained, informed out-of-equilibrium state, highlighting the virtues of slowness (which may also apply to other cases)!

One may surmise that a more complex DCL based on more components of various structural types would generate a great variety of interconvertible constituents, which, when subjected to given effectors, would produce different distribution patterns within the higher order dynamic network underlying the DCL, thus yielding a constitutional fingerprint/engram, a specific distribution of constituents for each effector. Such multicomponent and multiresponsive constitutional dynamic networks provide avenues toward chemical systems[6] of increasing complexity.[17]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05785.

Experimental details, NMR spectra, and synthetic procedures (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*lehn@unistra.fr

Present Address

†Institute for Complex Molecular Systems and Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands.

Notes

The authors declare no competing financial interest.

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