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Higher Order Constitutional Dynamic Networks: [2×3] and [3×3] Networks Displaying Multiple, Synergistic and Competitive Hierarchical Adaptation

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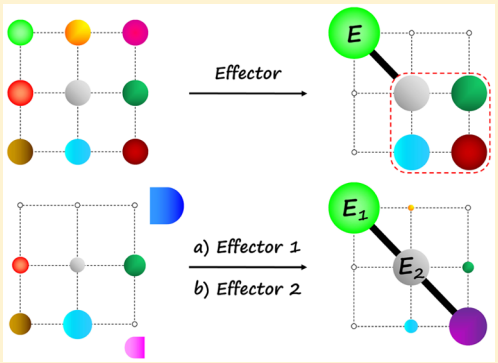
Supporting Information

ABSTRACT: The present study investigates the constitutional dynamic networks (CDNs) underlying dynamic covalent libraries (DCLs) that extend beyond the [2×2] case toward higher orders, namely [2×3] and [3×3] CDNs involving respectively six and nine constituents generated from the recombination of five and six components linked through reversible chemical reactions. It explores the behavior of such systems under the action of one or two effectors. More specifically and for the sake of proof of principle, it makes use of DCLs involving dynamic organic ligands and analyzes their single and double adaptive response under the action of one and two metal cation effectors. Thus, interconversions within [2×3] DCLs of six constituents (hydrazone, acylhydrazone, and imine ligands) give access to the generation of [2×3] CDNs of 3D trigonal prismatic type consisting of three [2×2] sub-networks and presenting specific responses to the application of Cu^{+} and Zn^{2+} metal cation effectors, in particular double agonistic amplification. More complex [3×3] CDNs based on nine ligand constituents of imine, hydrazone, and acylhydrazone types were also designed and subjected to the application of one or two effectors, e.g., Cu^{+} and Fe^{2+} metal cations, revealing novel types of adaptive behavior: (i) agonistic amplification between a single constituent and a full [2×2] sub-network, and (ii) agonistic amplification along a single diagonal connecting three constituents. Of special interest is also the dependence of the response of the system to hierarchical sequence of effector application, whereby initial interaction with Cu^{+} ions results in the destruction of the network, whereas the sequence Fe^{2+} followed by Cu^{+} yields a clean three-constituent DCL. Finally and strikingly, the present results also demonstrate that the increase in complexity of the system by introduction of an additional entity leads to a simpler output through dynamic competition between components.



1. INTRODUCTION

Constitutional dynamic libraries (CDLs)[1] of dynamic covalent[2] or non-covalent supramolecular type, formed respectively from the reaction or interaction of n with m components, may be represented in terms of [*n*×*m*] *constitutional dynamic networks* (CDNs)[1b−e,3,4] of order [*n*×*m*] that connect the interconverting constituents through agonistic and antagonistic relationships[1b−e,3] and define the *connectome* of the system.[1d,3e] Such CDLs respond to the application of chemical[5] or physical[6] agents by a redistribution of their constituents, thus displaying adaptive behavior. Sets of four constituents resulting from the recombination of four components linked through reversible chemical reactions form a *dynamic covalent library* (DCL) that is represented by a square network of order [2×2].[1b−e,3a−d,g] The response of such networks to a single agent (such as a metal cation) or their double adaptive responses to two orthogonal agents, i.e., photoselection and metalloselection, have been investigated.[3d] Interconversions between [2×2] DCLs located in two separate domains define 3D networks of square prismatic type, as is the case for the splitting of a single homogeneous solution into two separate liquid phases.[3e,f] Taking steps toward more complex systems[7] requires the exploration of DCLs of higher order containing a larger number of interconverting constituents and defining higher order networks, including networks of networks. Such connectomes lead to the emergence of novel features under coupling to multiple agents in the environment and responding to them in diverse fashions.

In the present study, we designed several higher order systems and investigated their multiple responses to several chemical effectors, displaying multiple sequential and hierarchical adaptation features. On the first stage, DCLs of six constituents, hydrazone, acylhydrazone, and imine ligands, were designed to give access to the generation of [2×3] CDNs consisting of three [2×2] sub-networks and presenting novel types of responses to the application of different metal cation effectors. In a further

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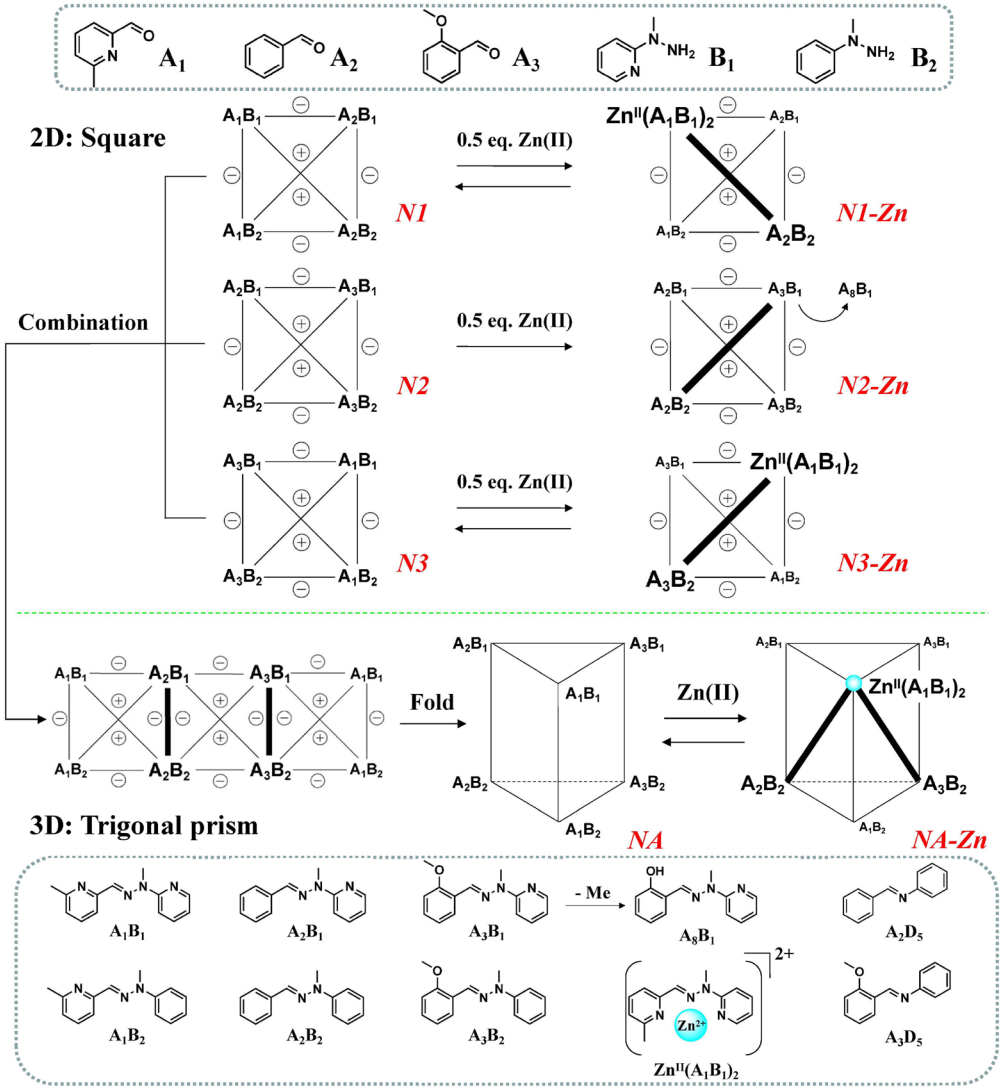
Scheme 1. Generation and Behavior of a 3D Trigonal Prismatic [2×3] CDN[a]



[a](*Top left*) Any two of benzaldehyde components among $\mathbf{A}_1$, $\mathbf{A}_2$, and $\mathbf{A}_3$ (1 equiv each, 30 mM) and the two hydrazines $\mathbf{B}_1$ and $\mathbf{B}_2$ (1 equiv each, 30 mM) with 5% (in volume) aniline as a catalyst were used to establish the three 2D [2×2] square CDNs (***N1***–***N3***). These CDNs formed from the four hydrazone constituents $\mathbf{A}_a\mathbf{B}_b$ are indicated with statistical distribution of constituents. (*Top right*) Adaptation of the ***N1*** and ***N3*** CDNs in response to the addition of zinc triflate with an amplification of $\mathbf{A}_1\mathbf{B}_1$ as its zinc complex and a simultaneous up-regulation of the corresponding agonists $\mathbf{A}_2\mathbf{B}_2$ and $\mathbf{A}_3\mathbf{B}_2$; the network **N3** is perturbed by the destruction of the constituent $\mathbf{A}_3\mathbf{B}_1$ by demethylation to $\mathbf{A}_8\mathbf{B}_1$. (*Middle*) Generation of the 3D [2×3] trigonal prismatic CDN ***NA*** by combination of the three 2D [2×2] square sub-networks into a linear array ***N1-N2-N3*** by superposition of the vertices linking the same constituents followed by folding along these common vertices; treatment of ***NA*** with Zn^{2+} cations leads to an adaptation with amplification of $\mathbf{A}_1\mathbf{B}_1$ as its zinc complex and a simultaneous up-regulation of the corresponding agonists $\mathbf{A}_2\mathbf{B}_2$ and $\mathbf{A}_3\mathbf{B}_2$ on two faces of the prism. The larger size and bold letters as well as the bold diagonal lines indicate simultaneous up-regulations of these agonistic constituents in response to the effector. (*Bottom*) Structures of the hydrazine constituents $\mathbf{A}_a\mathbf{B}_b$ and of the imines generated from aniline $\mathbf{D}_5$. The salicylaldehyde residue, produced by the demethylation side reaction, has been labeled $\mathbf{A}_8$. For the effect of Zn^{2+} binding to $\mathbf{A}_3\mathbf{B}_1$ and $\mathbf{A}_8\mathbf{B}_1$, see Figure S5a–c. The quantitative values of the constituent distributions are given in Table S1.

step, more complex [3×3] CDNs based on nine constituents were also designed and subjected to one effector or two effectors, revealing novel adaptive behaviors. The present work is meant to be a general demonstration of principle and an exploration of the behavior of dynamic systems of increasing complexity. It thus implements chemical entities derived from previous investigations in a logical development and paves the way for further studies. [Note: The general description of the CDNs is given in the main text, while the corresponding numerical data are provided in the Supporting Information (SI). In order to facilitate the perusal of the rather complicated sets of data, the representations of the network patterns shown in Schemes 1–5 highlight in a graphical way the main features of the constituent distributions and the changes they undergo in response to the effectors. The disposition of the numerical values in the tables given as SI follow the same organization of the network patterns, again to facilitate reading.]

2. RESULTS AND DISCUSSION

2.1. [2×3] CDN with One Effector: Construction of a 3D Network from Several 2D Networks. According to our previous studies, hydrazones may be implemented for the design

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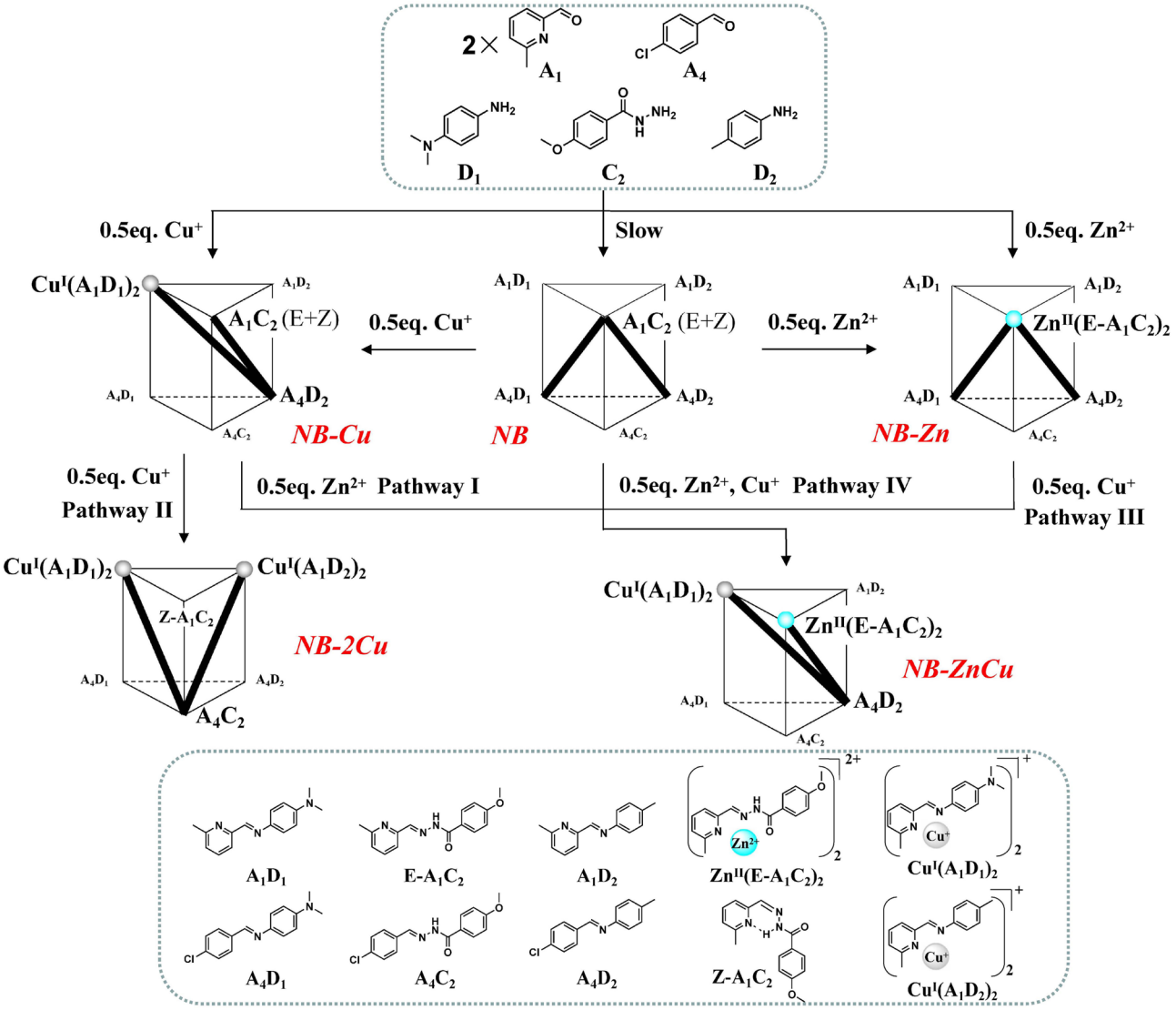
Scheme 2. Multiple and Sequential Adaptation in the [2×3] Trigonal Prismatic CDN of the Six Constituents Generated from (*top*) the Components (1 equiv each, 30 mM) A_4, D_1, C_2, and D_2 and A_1 (2 equiv) in Response to (*middle*) a Single Effector or (*bottom*) the Two Effectors Cu^+ and Zn^{2+} (0.5 equiv each)[a]



[a]The longer and shorter left and right arrows indicate respectively the additions of the effector Cu^+ (*top left*) or Zn^{2+} (*top right*) to the mixture of components or to the preformed DCL of constituents. A_1C_2 exists in *E* and *Z* forms (see SI for details). The larger size and bold letters as well as the bold diagonal lines indicate simultaneous up-regulation of these agonistic constituents in response to the effectors. See Table S2 for numerical values.

of adaptive libraries in view of their thermodynamic stability at equilibrium state and their ability to undergo reversible component exchange at the C═N bond facilitated by catalysts such as aniline.[3c,d,g] We here investigated the DCLs generated from any two aldehydes among A_1, A_2, and A_3 and the two hydrazines B_1 and B_2 (Scheme 1) in order to establish the three 2D [2×2] square sub-networks that may then be combined to construct the corresponding [2×3] full network. First, 1 equiv of each component was mixed with 5% (in volume) aniline D_5 used as organo-catalyst[3d,8] in CD_3CN. After heating at 78 °C for 17 h, the DCLs were cooled and subjected to ^1H NMR measurement for the analysis of the composition of the mixture of compounds generated. As shown in Scheme 1 (*top panel*), three DCLs of four hydrazone constituents, corresponding to the [2×2] square CDNs $A_1B_1/A_1B_2/A_2B_1/A_2B_2$ (*N1*), $A_2B_1/A_2B_2/A_3B_1/A_3B_2$ (*N2*), and $A_3B_1/A_3B_2/A_1B_1/A_1B_2$ (*N3*), were produced from condensation, transimination, hydrolysis, and recondensation of the respective **A** and **B** components. The quantitative values determined for all three DCLs were statistical within experimental error (Table S1, *top*; Figures S1, S2, and S5a).

When 0.5 equiv of zinc triflate was added, ***N1*** and ***N3***, which involve the only tridentate ligand A_1B_1, underwent reorganization to amplify the hydrazone A_1B_1 in the form of its $Zn^{II}(A_1B_1)_2$ complex as well as simultaneously its diagonally linked agonist A_2B_2 or A_3B_2 (agonist amplification;[1b−e] Scheme 1, *top right*; see Figures S3−S5 for NMR spectra) giving strongly modified distributions of 49%/1%/1%/49% for the $A_1B_1/A_1B_2/A_2B_1/A_2B_2$ ***N1-Zn*** network and 1%/49%/49%/1% for the $A_3B_1/A_3B_2/A_1B_1/A_1B_2$ ***N3-Zn*** network. Compared to the DCLs treated with scandium triflate (20%) as exchange catalyst, these systems (***N1*** and ***N3***) catalyzed by aniline display more pronounced amplifications as a result of less hydrolysis.[3d] However, the DCL with the constituents $A_2B_1/A_2B_2/A_3B_1/A_3B_2$ (*N2*), without the pyridine carboxaldehyde moiety A_1, exhibited a

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different behavior on addition of zinc cations compared to the libraries of ***N1*** and ***N3***. In this case, 10% of a byproduct was obtained, produced by an irreversible demethylation of the methoxyl group in $\mathbf{A_3B_1}$, giving $\mathbf{A_8B_1}$ and leading to a partial destruction of the network ***N3*** (Scheme 1, *top center*). In absence of the pyridine aldehyde component $\mathbf{A_1}$, required for the formation of a tridentate NNN binding site, the added Zn^{2+} cation favored binding to the free NN bidentate component $\mathbf{B_1}$, thus giving $Zn^{II}(\mathbf{B_1})_x$ complexes and increasing hydrolysis in the DCL. In separate experiments, the notable demethylation reaction of the O-methoxyl substituent of $\mathbf{A_3B_1}$ in the presence of Zn^{2+} and 5% aniline as catalyst was further investigated. As it is not central for the present purposes, the results are given in the SI (see Figure S5a−c for more details).

A [2×3] DCL was set up by mixing the separately equilibrated libraries of ***N1***, ***N2***, and ***N3*** in a NMR tube and re-equilibrating the mixture at 78 °C for 17 h. It contained the full set of six constituents $\mathbf{A_2B_1}/\mathbf{A_2B_1}/\mathbf{A_1B_1}/\mathbf{A_1B_2}/\mathbf{A_3B_1}/\mathbf{A_3B_2}$ with the distributions corresponding to a retention of the distributions present in the starting [2×2] DCLs (see Table S1; see Figure S6 for ^{1}H NMR spectrum). This [2×3] DCL may be represented by a trigonal prism-shaped 3D [2×3] network ***NA***, constructed by the connection and folding of the previous three 2D sub-networks along the vertices sharing the components $\mathbf{B_1}$ and $\mathbf{B_2}$ (Scheme 1, *middle left*). When 1 equiv Zn^{2+} was added, the strong binding of these effector cations to the tridentate NNN ligand $\mathbf{A_1B_1}$ drives the amplification of this constituent as its complex $Zn^{II}(\mathbf{A_1B_1})_2$ as well as the concomitant double up-regulation of its two agonists $\mathbf{A_2B_2}$ and $\mathbf{A_3B_2}$ located all three in the two [2×2] sub-networks sharing the $\mathbf{A_1B_1}$−$\mathbf{A_1B_2}$ edge of the trigonal prismatic [2×3] network. Simultaneously, $\mathbf{A_1B_2}$, which presents a triply antagonistic relationship, is strongly down-regulated, whereas this effect is weaker for $\mathbf{A_2B_1}$ and $\mathbf{A_3B_1}$, which are connected to only two antagonistic partners. The trapping of the Zn^{2+} cations by $\mathbf{A_1B_1}$ suppresses the demethylation of the $\mathbf{A_3B_1}$ constituent, thus preventing the destruction of the fragile $\mathbf{A_2A_3B_1B_2}$ sub-network. Compared to the simple [2×2] CDNs, the more complex integrated [2×3] network displays not only the expected reorganization of the constituents through *double agonist amplification* but also provides improved stability to the system by protecting it from degradation of one of its constituents, $\mathbf{A_3B_1}$ (Scheme 1, *middle right*; see Figure S7 for ^{1}H NMR spectrum).

Thus, remarkably, the larger DCL behaves in an improved fashion, presenting an increased stability with less sensitivity toward destructive perturbation by virtue of the relationships between constituents established within the more complex network.

2.2. [2×3] CDNs with Two Effectors: Multiple Adaptation. *2.2.1. Multiple Adaptation in a DCL of Imines and Acylhydrazones.* A further step consists in devising a CDN that would alternately respond to two different effectors, so that it may be driven along different pathways to the expression of multiple distributional patterns corresponding to different constitutional information. The design of such a CDN requires higher dimensionality than a 2D square network and involves two specific receptors, one for each of the two effectors operating in combination. To this end, two metal ion effectors Zn^{2+} and Cu^+ were utilized, in view of their different coordination features, and the former CDN, solely based on hydrazone constituents, was developed into a more complex imine/acylhydrazone mixed system.

The derivatives of benzaldehyde $\mathbf{A_1}$ and $\mathbf{A_4}$ were selected as components in the DCL, using 2 equiv of $\mathbf{A_1}$ to generate the two constituents, acting respectively as specific receptors for the two effectors. Compared to the unsubstituted $\mathbf{A_2}$ and the methoxyl-substituted $\mathbf{A_3}$, the utilization of *p*-chloro substitution in $\mathbf{A_4}$ led to a reduction of hydrolysis within the DCL on formation and exchange of the imine and acylhydrazone constituents. On the other hand, for the amine components of the network, the hydrazine compounds were replaced by the aromatic amines $\mathbf{D_1}$ and $\mathbf{D_2}$ and the hydrazide $\mathbf{C_2}$ so as to adapt to the multiresponsive transformations of the DCL. The *p*-dimethylamino substitution of $\mathbf{D_1}$ might not only reduce the level of hydrolysis because of its strong electron-donating effect, but also enhance the binding of Cu^+ ion compared to the methyl-substituted $\mathbf{D_2}$, considering the known increase in stability of the copper complex.[9]

The new DCL was then generated from a mixture of the five components, $\mathbf{A_4}$, $\mathbf{D_1}$, $\mathbf{C_2}$, and $\mathbf{D_2}$ (30 mM for 1 equiv each) and 2 equiv of $\mathbf{A_1}$ in CD_3CN, heated at 60 °C for 51 h to reach the equilibrium. Six expected constituents $\mathbf{A_1D_1}$, $\mathbf{A_1C_2}$, $\mathbf{A_1D_2}$, $\mathbf{A_4D_1}$, $\mathbf{A_4C_2}$, and $\mathbf{A_4D_2}$ were obtained and confirmed by NMR determination (see Scheme 2, network ***NB***, and Table S2, *middle center*; Figure S8a,b), giving a biased distribution of 20%/31%/14%/13%/3%/11% with 8% hydrolysis. The origin of this bias may be attributed to the favored formation of acylhydrazone $\mathbf{A_1C_2}$ (in *E* and *Z* forms, *E*-$\mathbf{A_1C_2}$ 9%, *Z*-$\mathbf{A_1C_2}$ 22%, confirmed by 2D NMR shown in Figure S9a−c and both taken into account).[10] As a consequence, the percentages of its dual diagonal agonists, $\mathbf{A_4D_1}$ and $\mathbf{A_4D_2}$, were amplified on the side faces $\mathbf{A_1A_4D_1C_2}$ and $\mathbf{A_1A_4C_2D_2}$ of the 3D trigonal prismatic network. Meanwhile, $\mathbf{A_4C_2}$, involved in a triply antagonistic relationship, was sharply down-regulated. No additional catalyst was needed because the aniline-type components $\mathbf{D_1}$ and $\mathbf{D_2}$ themselves acted as catalysts during the exchange reactions. Starting from this initial DCL, its constitutional variations induced by four sequential pathways of cation additions were investigated: (I) Cu^+ followed by Zn^{2+}; (II) Cu^+ followed by another addition of the same amount of Cu^+; (III) Zn^{2+} followed by Cu^+; and (IV) Zn^{2+} and Cu^+ added together.

Pathway I. When the starting mixture of six constituents (***NB***) was subjected to $Cu^I(OTf)$ (0.5 equiv, 15 mM), the DCL underwent reorganization to amplify the imine constituent $\mathbf{A_1D_1}$ as expected, in the form of its tetrahedral complex $Cu^I(\mathbf{A_1D_1})_2$ acting as the second driving force besides the formation of the stable acylhydrazone constituent $\mathbf{A_1C_2}$ and favored by its electron-donating dimethylamino substitution compared to the other bidentate constituent $\mathbf{A_1D_2}$. As a consequence, the constituent $\mathbf{A_4D_2}$, the common agonist of $\mathbf{A_1C_2}$ and of the complex $Cu^I(\mathbf{A_1D_1})_2$, as well as $\mathbf{A_1C_2}$ (as *E*-$\mathbf{A_1C_2}$ 8% and *Z*-$\mathbf{A_1C_2}$ 18%) maintained their original up-regulation, giving a new expression of double diagonal agonistic amplification located on the two side-faces $\mathbf{A_1A_4D_1D_2}$ and $\mathbf{A_1A_4C_2D_2}$ of the trigonal prismatic network. Furthermore, the same distribution could also be obtained directly by equilibration of the starting mixture of the five components, $\mathbf{A_4}$, $\mathbf{D_1}$, $\mathbf{C_2}$, $\mathbf{D_2}$ and 2 equiv of $\mathbf{A_1}$ in the presence of 0.5 equiv Cu^+ ion, due to the thermodynamic control of the DCL (network ***NB-Cu*** shown in Scheme 2 and Table S2, *middle left*; see Figure S10a,b for spectral data). Subsequent addition of $Zn^{II}(OTf)_2$ into this Cu^+-pretreated network ***NB-Cu*** promoted the generation of the octahedral complex $Zn^{II}(E\text{-}\mathbf{A_1C_2})_2$, due to the preferential binding between Zn^{2+} ion and the only tridentate ligand constituent $\mathbf{A_1C_2}$, which displayed in addition a configurational adaptation from the starting *E*/*Z* mixed isomers of $\mathbf{A_1C_2}$ to fully *E* in the complex. However, the original

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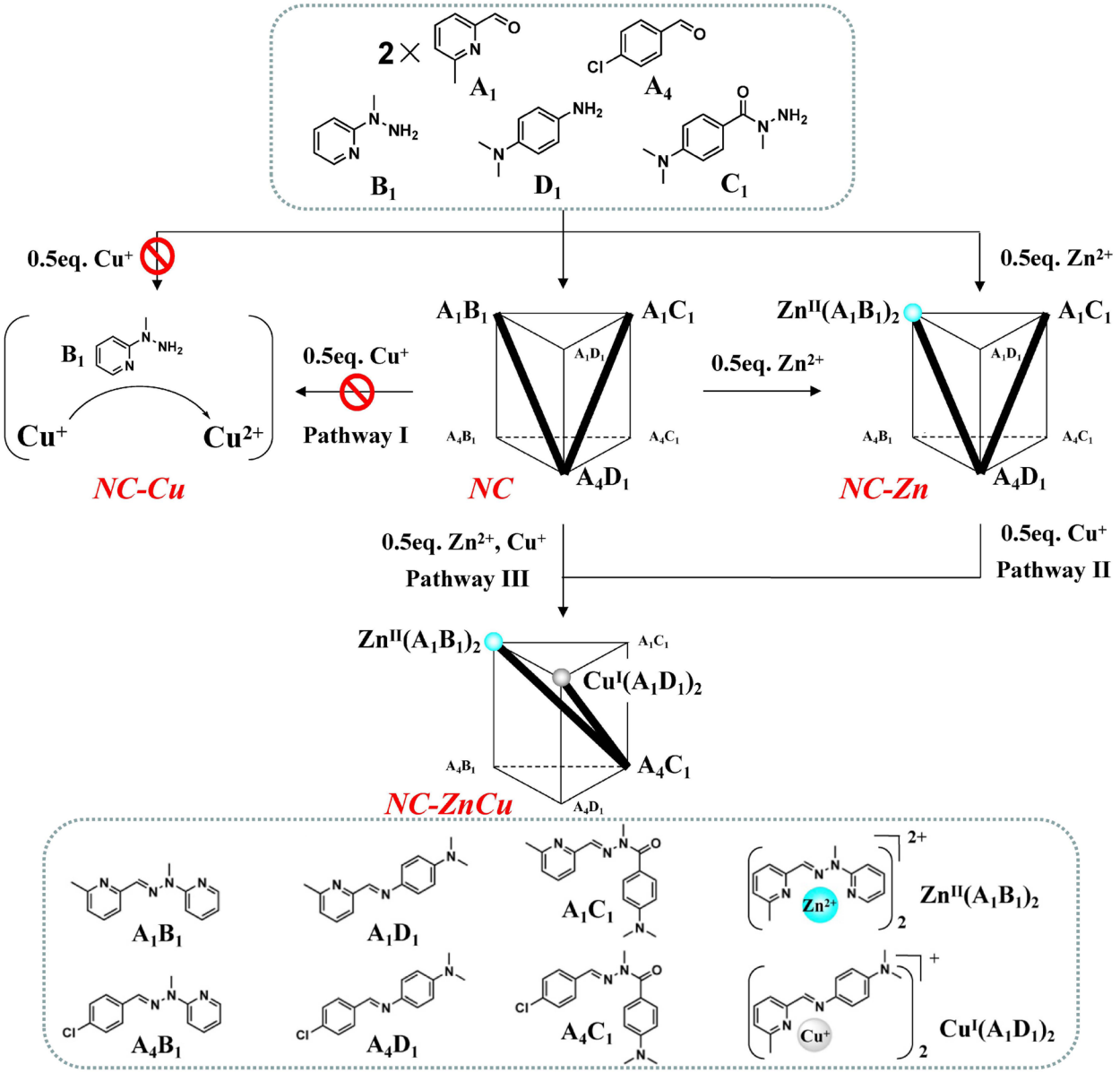
Scheme 3. Hierarchical Adaptation in the 3D Trigonal Prismatic CDN Representing the Response of the DCL Generated from (*top*) the Components (1 equiv each, 30 mM) A_4, B_1, D_1, and C_1 and A_1 (2 equiv) to (*middle*) a Single Effector or (*bottom*) the Two Effectors Cu^+ and Zn^{2+} (0.5 equiv each)[a]



[a]The larger size and bold letters as well as the bold diagonal line indicate simultaneous up-regulation of these agonistic constituents in response to the effectors. The longer and shorter left and right arrows indicate respectively the additions of the effector Cu^+ (*top left*) or Zn^{2+} (*top right*) to the mixture of components or to the preformed DCL of constituents. The network in brackets ***NC-Cu*** (*middle left*) is partially destroyed by oxidation of Cu^+ to Cu^{2+} facilitated by coordination of the latter to $\mathbf{B_1}$. See Table S3 for numerical values.

distribution was not strongly affected, as $\mathbf{A_1C_2}$ (E + Z) was already strongly amplified in the parent DCL (see network ***NB-ZnCu*** in Scheme 2 and Table S2, *bottom right*).

Pathway II. On the other hand, further addition of another 0.5 equiv of Cu^+ into ***NB-Cu*** gives another change in the distribution of the DCL by amplification the newly formed copper complex $Cu^I(\mathbf{A_1D_2})_2$. Consequently, the constituent $\mathbf{A_4C_2}$, the common double diagonal agonist of the two copper complexes $Cu^I(\mathbf{A_1D_1})_2$ and $Cu^I(\mathbf{A_1D_2})_2$, underwent a significant up-regulation from 7% to 19%. Engaged in triply antagonistic relationships, all the E-$\mathbf{A_1C_2}$ was consumed, and interestingly, Z-$\mathbf{A_1C_2}$ survived (9% left) the down-regulation of $\mathbf{A_1C_2}$ owing to the stabilization of the Z isomer by an internal hydrogen bond (network ***NB-2Cu*** in Scheme 2, *bottom left*; see Figure S12a.b for ^{1}H NMR spectra). This case showed another expression of conformational, configurational, and constitutional adaptation besides network ***NB-ZnCu***.

Pathway III. When the initial network ***NB*** was first treated with 0.5 equiv of Zn^{2+}, the DCL kept a distribution quite similar to the initial one (network ***NB-Zn***, 16%/33%/14%/11%/2%/14% respectively for constituents $\mathbf{A_1D_1}$/$\mathbf{A_1C_2}$/$\mathbf{A_1D_2}$/$\mathbf{A_4D_1}$/$\mathbf{A_4C_2}$/$\mathbf{A_4D_2}$ with about 10% hydrolysis and with $\mathbf{A_1C_2}$ mainly in its coordinated E form, 29%). Addition of Cu^+ into this Zn^{2+}-pretreated CDN resulted in the same distribution as ***NB-ZnCu***, showing a fourth type of adaptation (Figures S11 and S13 for ^{1}H NMR data).

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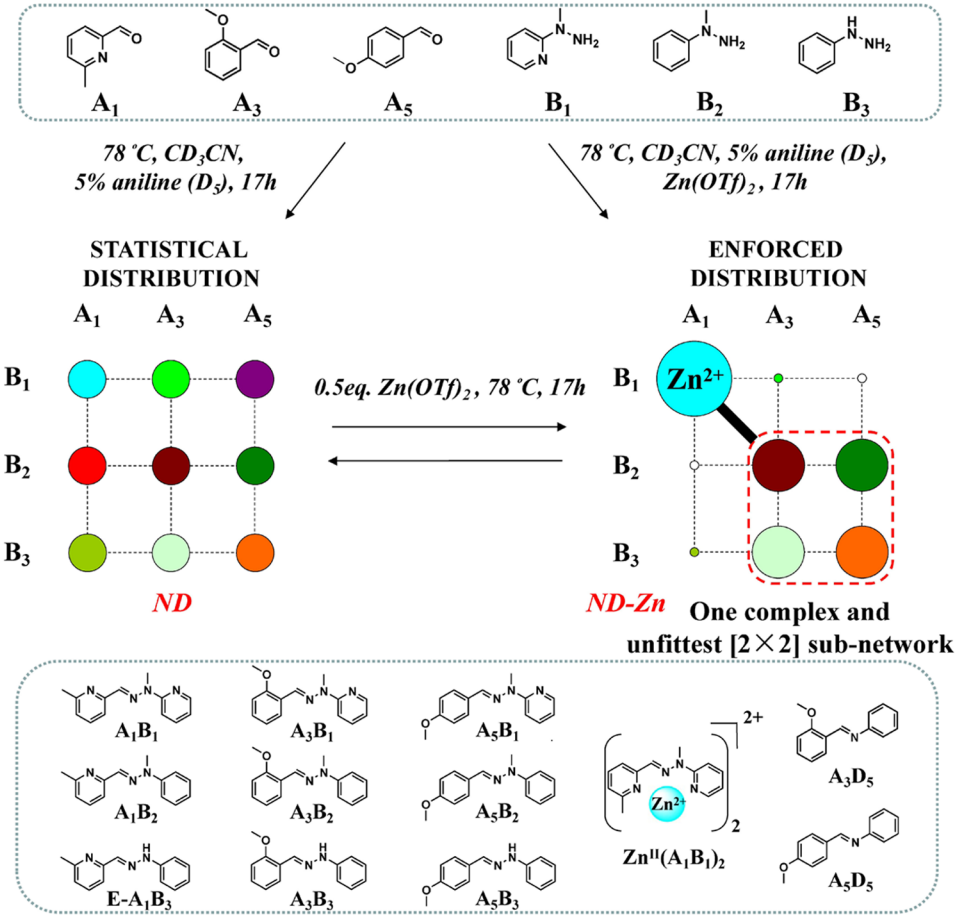
Scheme 4. Graphical Representation of the Adaptation of a [3×3] CDN of the Nine Constituents Generated from the Six Components (*top*) A_1, A_3, A_5, B_1, B_2, and B_3 (1 equiv each, 30 mM) with 5% (in Volume) Aniline as a Catalyst in CD_3CN as Weighted Graphs Corresponding to a DCL of Nine Hydrazones as Constituents under the Pressure of an Effector Zn^{2+} ion, Leading to the Constitutional Variation of the System from (*left*) an Approximately Statistical Distribution to (*right*) an Enforced Distribution Displaying (*bottom*) the Effector-Enhanced Fittest Constituent A_1B_1 in the Form of Its $Zn^{II}(A_1B_1)_2$ Complex and a Square [2×2] Sub-network as Unfittest Agonist of Four Amplified Constituents $A_3B_2/A_3B_3/A_5B_2/A_5B_3$[a]



[a]See Table S4 for numerical values.

Pathway IV. As expected, the same distribution was also obtained on simultaneous treatment with Zn^{2+} and Cu^{+} together from the start.[11]

The six component DCL thus led to diverse constitutional expressions on adaptation in response to the individual effectors Cu^{+} and Zn^{2+} and their synergistic action.

2.2.2. Competitive Hierarchical Adaptation in a DCL of Imines, Acylhydrazones, and Hydrazones. For the purpose of reaching higher complexity, a six constituent DCL that included imines, acylhydrazones, and hydrazones was set up, and the response of its [2×3] CDN to two effectors was investigated. Besides keeping the aldehydes $\mathbf{A}_1$ and $\mathbf{A}_4$, hydrazine $\mathbf{B}_1$ and aniline $\mathbf{D}_1$ were chosen as components aimed at forming ligand constituents for binding of Zn^{2+} and Cu^{+}, respectively. The hydrazide $\mathbf{C}_1$ was expected to form NNO or NO coordination sites that would be not only weaker Zn^{2+} binders than an NNN site formed by hydrazone ligands but also potentially weaker Cu^{+} binders than the bidentate NN site provided by imine ligands generated from anilines. In addition, by suppressing the risk of ionization of the N−H site, such an *N*-methylated hydrazide has a lower risk of interference with the binding of Zn^{2+} to hydrazones compared to the non-methylated hydrazide $\mathbf{C}_2$.

Based on these considerations, $\mathbf{A}_4$, $\mathbf{B}_1$, $\mathbf{D}_1$, and $\mathbf{C}_1$ (30 mM each) together with 2 equiv of $\mathbf{A}_1$ (Scheme 3, *top*) were mixed in a NMR tube with CD_3CN as solvent. These components may generate a set of six constituents $\mathbf{A}_1\mathbf{B}_1$, $\mathbf{A}_1\mathbf{D}_1$, $\mathbf{A}_1\mathbf{C}_1$, $\mathbf{A}_4\mathbf{B}_1$, $\mathbf{A}_4\mathbf{D}_1$, and $\mathbf{A}_4\mathbf{C}_1$. However, after equilibrating at 78 °C for 26 h, the solution contained a mixture of mainly three constituents identified as $\mathbf{A}_1\mathbf{B}_1$, $\mathbf{A}_4\mathbf{D}_1$, and $\mathbf{A}_1\mathbf{C}_1$, forming a strongly biased initial DCL. This bias may be attributed to the favored formation of the hydrazone $\mathbf{A}_1\mathbf{B}_1$ and of the acylhydrazone $\mathbf{A}_1\mathbf{C}_1$ together with the corresponding amplification of their common agonist $\mathbf{A}_4\mathbf{D}_1$ on side-faces $\mathbf{A}_1\mathbf{A}_4\mathbf{B}_1\mathbf{D}_1$ and $\mathbf{A}_1\mathbf{A}_4\mathbf{D}_1\mathbf{C}_1$ of the trigonal prismatic network ***NC*** (Scheme 3, *middle center*; Figure S14a,b). This DCL was subjected to treatment by Cu^{+} and Zn^{2+} effectors along three pathways.

Pathway I. First addition of Cu^{+} caused the destruction of this DCL due to the oxidation of Cu^{+} to Cu^{2+} favored by the binding of the latter to the component $\mathbf{B}_1$ during the component exchange (network ***NC-Cu*** in Scheme 3 and Table S3, *middle left*; see Figure S15 for the details).

Pathway II. On the other hand, addition of Zn^{2+} alone did not greatly affect the original biased distribution, as it preferentially bound the constituent ligand $\mathbf{A}_1\mathbf{B}_1$ that was already strongly

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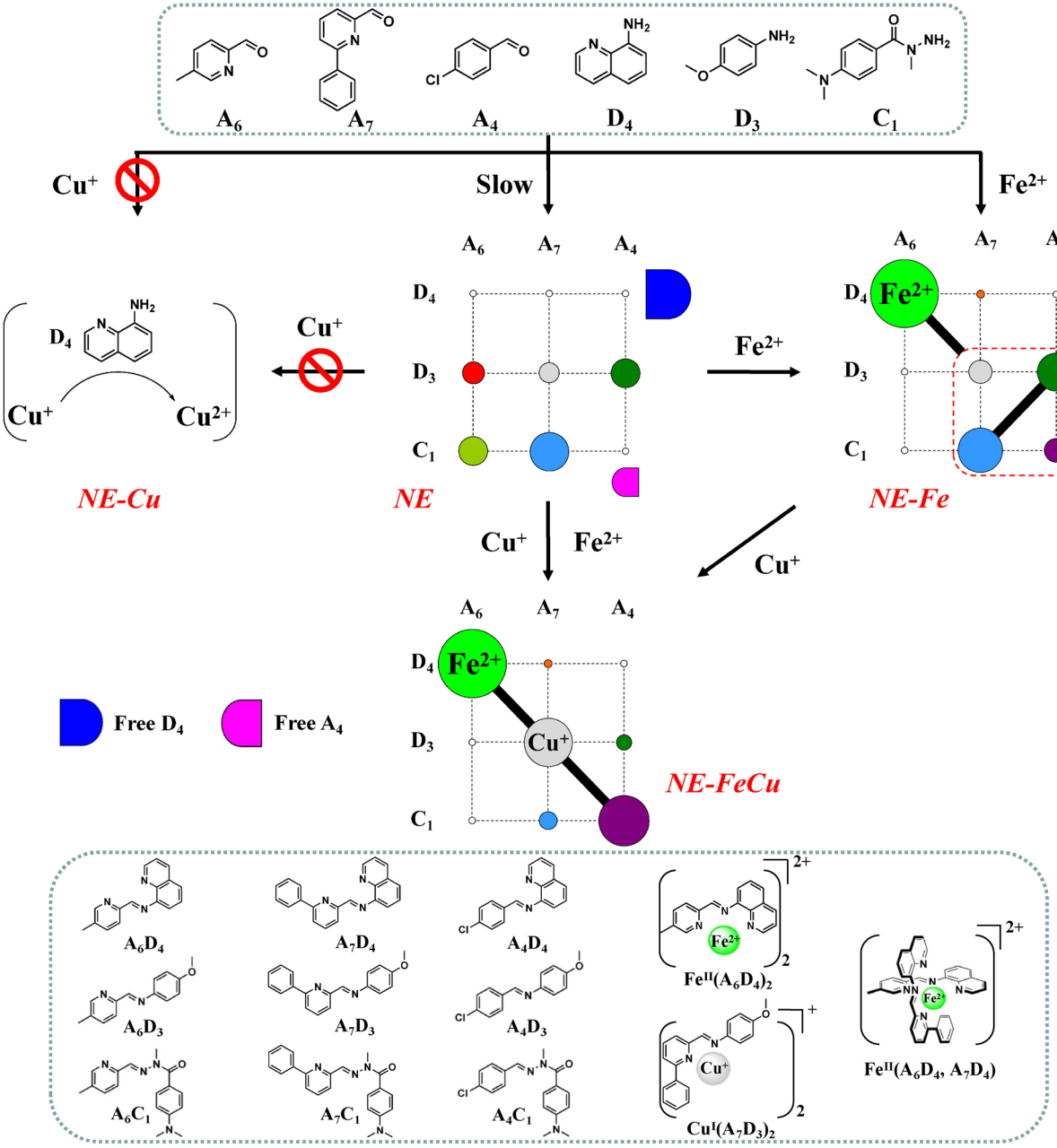
Scheme 5. Weighted Graph Representation of the Adaptation of the [3×3] CDN of a DCL of Nine Constituents Formed from a Mixture of Six Components of (*top*) A_6, A_7, A_4, D_4, D_3, and C_1 (1 equiv each, 30 mM) in Response to (*middle*) a Single Effector or (*bottom*) the Two Effectors Fe^{2+} and Cu^{+} (0.5 equiv each)[a]



[a]The size of the colored circles grossly represents the amounts of the corresponding constituents on the network. For clarity, only the dominant free components D_4 and A_4 are represented in form of colored arches located out of the network *NE*. The longer and shorter left and right arrows indicate respectively the addition of the effector Cu^{+} (*top left*) or Fe^{2+} (*top right*) to the mixture of components or to the preformed DCL of constituents. The network in brackets ***NE-Cu*** (*middle left*) is partially destroyed by oxidation of Cu^{+} to Cu^{2+} facilitated by coordination of the latter to D_4. See Table S5 for numerical values.

amplified in the initial biased DCL (network ***NC-Zn*** in Scheme 3 and Table S3, *middle right*; see Figure S16a,b for ^{1}H NMR spectra). However, subsequent addition of Cu^{+} into this mixture led to a pronounced constitutional change, and what is even more interesting, such Zn^{2+}-pretreated DCL and its network survived the addition of Cu^{+} ion because B_1 was already trapped and isolated from the dynamic exchange process by the formation of the complex $Zn^{II}(A_1B_1)_2$. In this case, constituents A_1B_1 and A_1D_1 were amplified via formation of their respective complexes $Zn^{II}(A_1B_1)_2$ and $Cu^{I}(A_1D_1)_2$ as well as simultaneously their common agonist A_4C_1 (network ***NC-ZnCu*** in Scheme 3 and Table S3, *bottom*; see Figure S17a,b for ^{1}H NMR spectra).

Pathway III. Addition of both Zn^{2+} and Cu^{+} together to the initial network ***NC*** led to the same distribution, indicating also that the interaction of the Zn^{2+} ions with the DCL supersedes that of the Cu^{+} ions.

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Thus, treating the original library with effectors Zn^{2+} and Cu^{+} either in fixed order (first zinc and second copper) or at the same time avoids the destruction of the DCL caused by Cu^{+} oxidation when it is added first, pointing to a hierarchical relationship between the two effectors. Comparison of pathways I, II, and III demonstrates that the two effectors operate in a synergistic way: Cu^{+} required Zn^{2+} to trap the $\mathbf{B}_1$ constituent, while Zn^{2+} needed the assistance of Cu^{+} to generate a novel state of the library, in a sort of "co-evolution" of the DCL.[12]

2.3. [3×3] CDN with One Effector: Amplification of the Unfittest Sub-network. A further step toward complex adaptive systems was to investigate the behavior of an even larger [3×3] network formed by a DCL of nine hydrazone constituents first in response to a single effector (see Scheme 4). The components $\mathbf{A}_1$ and $\mathbf{B}_1$ that form the only NNN tridentate constituent for effector Zn^{2+} were used as the driving force for the adaptation, and the components $\mathbf{A}_3$, $\mathbf{A}_5$, $\mathbf{B}_2$, and $\mathbf{B}_3$, not containing the pyridine group, were selected as the other components. The six-component mixture (1 equiv, 30 mM each) was reacted at 78 °C for 17 h in CD_3CN containing 5% aniline (in volume) as catalyst to reach thermal equilibrium. These components underwent condensation, transamination, and recondensation reactions, giving an almost statistical distribution of 12%/8%/12%/9%/10%/12%/12%/9%/7% respectively for $\mathbf{A}_1\mathbf{B}_1/\mathbf{A}_1\mathbf{B}_2/\mathbf{A}_1\mathbf{B}_3/\mathbf{A}_3\mathbf{B}_1/\mathbf{A}_3\mathbf{B}_2/\mathbf{A}_3\mathbf{B}_3/\mathbf{A}_5\mathbf{B}_1/\mathbf{A}_5\mathbf{B}_2/\mathbf{A}_5\mathbf{B}_3$ with a total of 9% hydrolysis over all nine constituents (network ***ND***, in which $\mathbf{A}_1\mathbf{B}_3$ mainly exists in *E* form; see Scheme 4 and Table S4, *middle left*; ^{1}H NMR spectra shown in Figure S18a,b). When 0.5 equiv (15 mM) of Zn^{2+} was added into this DCL, it reorganized to amplify the fittest ligand constituent $\mathbf{A}_1\mathbf{B}_1$ in the form of its $Zn^{II}(\mathbf{A}_1\mathbf{B}_1)_2$ complex and to up-regulate simultaneously four constituents $\mathbf{A}_3\mathbf{B}_2/\mathbf{A}_3\mathbf{B}_3/\mathbf{A}_5\mathbf{B}_2/\mathbf{A}_5\mathbf{B}_3$, together with a total of 3% hydrolysis (network ***ND-Zn***, Scheme 4 and Table S4, *middle right*; ^{1}H NMR spectra shown in Figure S19a,b). In this case, it was the 2D square network $\mathbf{A}_3\mathbf{A}_5\mathbf{B}_2\mathbf{B}_3$, showing an approximate statistical distribution and representing an "unfittest" sub-network, that acted as the agonist to the fittest constituent $\mathbf{A}_1\mathbf{B}_1$ and was amplified in concert with the adaptation of this [3×3] CDN toward the single effector Zn^{2+}.

The behavior of the present system provides the first example of evolution of a CDN in which a full [2×2] sub-CDN occupies the "unfittest" ecological niche (see refs 1c–e).

2.4. [3×3] CDN with Two Effectors: Hierarchical Adaptation. In the studies described above, we chose different amines (hydrazines and hydrazides providing NN and NO binding sites as well as anilines providing a single N binding site) for condensation with the same pyridine-2-carboxaldehyde $\mathbf{A}_1$. The mixture produced ligand constituents, presenting tridentate NNN and NNO or bidentate NN coordination subunits, that selectively formed complexes with Zn^{2+} and Cu^{+}, respectively, based on their different coordination features. For the purpose of construction of a [3×3] network that would respond to two effectors, three aldehyde components, two pyridyl-aldehydes $\mathbf{A}_6$ and $\mathbf{A}_7$ with markedly different steric hindrance features together with $\mathbf{A}_4$, were chosen to generate, in combination with the amino-components $\mathbf{C}_1$, $\mathbf{D}_3$, and $\mathbf{D}_4$, a DCL of nine constituents that would contain two ligand constituents presenting preferential binding for two different metal cation effectors. [One may note that the 8-aminoquinoline component provides a tridentate NNN coordination site on reaction with a pyridine-2-carboxaldehyde, while presenting exchange rates of imine-type compounds, which are much faster than those involving hydrazone NNN sites derived from hydrazines.] These components were selected on the basis of preliminary experiments exploring binding affinities of metal cations and ligands. We first observed the almost exclusive formation of $Fe^{II}(\mathbf{A}_6\mathbf{D}_4)_2$ with respect to $Fe^{II}(\mathbf{A}_7\mathbf{D}_4)_2$ through self-sorting from a mixture of $\mathbf{A}_6$, $\mathbf{A}_7$ and $\mathbf{D}_4$ (30 mM each) treated with 0.5 equiv of $Fe^{II}(BF_4)_2$, indicating that there was a strong metalloselection by Fe^{2+} ions in favor of $\mathbf{A}_6$ with respect to $\mathbf{A}_7$ on condensation with 8-aminoquinoline $\mathbf{D}_4$, resulting from the steric hindrance introduced by the phenyl ring in $\mathbf{A}_7$ on formation of the octahedral complex (Figure S20a–c, including 7% mixed ligand complex $Fe^{II}(\mathbf{A}_6\mathbf{D}_4, \mathbf{A}_7\mathbf{D}_4)$, which was confirmed by the mass spectrometric analysis shown in SI). On the other hand, the *p*-methoxy-substituted aniline $\mathbf{D}_3$ was selected to generate the second constituent for preferential coordination with Cu^{+} instead of $\mathbf{D}_1$ and $\mathbf{D}_2$, to take advantage of its clear methoxyl proton signal in the ^{1}H NMR spectra. Moreover, another preliminary experiment involving the components $\mathbf{A}_6$, $\mathbf{A}_7$, and $\mathbf{D}_3$ showed that the bidentate ligand ($\mathbf{A}_7\mathbf{D}_3$) was a preferential choice for Cu^{+} binding as compared to $\mathbf{A}_6\mathbf{D}_3$, in line with the known stability of tetrahedral Cu^{+} complexes with ligands bearing a phenyl ring in α position with respect to a coordinating pyridyl nitrogen site[13] (Figure S21a,b). Consequently, one might expect Fe^{2+} and Cu^{+} to pick up the constituents $\mathbf{A}_6\mathbf{D}_4$ and $\mathbf{A}_7\mathbf{D}_3$ orthogonally, if the preconstructed [2×2] sub-network coming from a mixture of $\mathbf{A}_6$, $\mathbf{A}_7$, $\mathbf{D}_3$ and $\mathbf{D}_4$ was treated simultaneously with *both* Fe^{2+} and Cu^{+} effectors. In order to extent such a [2×2] sub-network into a [3×3] network, a third pair of components, aldehyde $\mathbf{A}_4$ and amine $\mathbf{C}_1$, was selected in consideration of the reactivity of their condensation reaction and the low risk of interference with the two cation effectors.

Heating an equimolar mixture of all six components $\mathbf{A}_6$, $\mathbf{A}_7$, $\mathbf{A}_4$, $\mathbf{D}_4$, $\mathbf{D}_3$, and $\mathbf{C}_1$ (30 mM each) in CD_3CN at 60 °C for 5 h, produced initially a [2×2] square sub-network $\mathbf{A}_6\mathbf{D}_3/\mathbf{A}_7\mathbf{D}_3/\mathbf{A}_6\mathbf{C}_1/\mathbf{A}_7\mathbf{C}_1$. Subsequently as a function of time, $\mathbf{A}_4\mathbf{D}_3$ formed and increased gradually by condensation from the free $\mathbf{A}_4$ and $\mathbf{D}_3$ over a long time (at least 28 h) and higher temperature (78 °C) for equilibration. After equilibration, large amounts of the free components $\mathbf{A}_4$ and $\mathbf{D}_4$ (20% and 32%, respectively) were obtained as a result of their comparatively low reactivity in the imine formation reaction (network ***NE*** in Scheme 5 and Table S5, *middle center*; and Figure S23a,b), in agreement with the results from the competition experiments (Figure S22).

As expected, on addition of 15 mM $Fe^{II}(BF_4)_2$ to this preformed DCL the difference of steric hindrance between $\mathbf{A}_6$ and $\mathbf{A}_7$ led to a strong metalloselection (see Figure S20a), with generation of the octahedral coordination complex $Fe^{II}(\mathbf{A}_6\mathbf{D}_4)_2$, in preference to the complex containing the corresponding $\mathbf{A}_7$ component, with very pronounced amplification of this ligand at the expenses of the antagonist constituents containing either $\mathbf{A}_6$ or $\mathbf{D}_4$ as well as by the almost full incorporation of the free $\mathbf{D}_4$, which was unreacted in the starting library. As a consequence, the square sub-network $\mathbf{A}_7\mathbf{A}_4\mathbf{D}_3\mathbf{C}_1$ underwent overall up-regulation driven by the amplification of its $\mathbf{A}_6\mathbf{D}_4$ agonist, resulting also in the concomitant marked increase of $\mathbf{A}_4\mathbf{C}_1$ due to the condensation of free $\mathbf{A}_4$ with the $\mathbf{C}_1$ liberated in the process by down-regulation of the $\mathbf{A}_6\mathbf{C}_1$ antagonist. This agonist amplification between a single entity and a square sub-network is similar to that discussed above (see Scheme 4, *middle right*, network ***ND-Zn***). Furthermore, the distribution in this $\mathbf{A}_4\mathbf{A}_7\mathbf{C}_1\mathbf{D}_3$ sub-network of the Fe^{2+}-treated DCL showed a bias in favor of the $\mathbf{A}_7\mathbf{C}_1$-$\mathbf{A}_4\mathbf{D}_3$ diagonal (network ***NE-Fe*** in Scheme 5 and Table S5, *middle right*; see Figure S24a,b for ^{1}H NMR data). Thereafter, when this ***NE-Fe*** DCL was further treated with Cu^{+}, the square

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sub-network $\mathbf{A_7A_4D_3C_1}$ underwent an amplification of the opposite diagonal $\mathbf{A_7D_3}-\mathbf{A_4C_1}$ driven by the formation of the complex $Cu^{I}(\mathbf{A_7D_3})_2$. A very pronounced up-regulation (from lower than 1% to 24%) of $\mathbf{A_4C_1}$, resulting from its double agonistic relationship to both complexes $Fe^{II}(\mathbf{A_6D_4})_2$ and $Cu^{I}(\mathbf{A_7D_3})_2$, was achieved in a *single operation* when the initial DCL was treated simultaneously with Fe^{2+} and Cu^{+} (Scheme 5 and Table S5, *bottom center*; see Figure S25a,b for NMR data). On the other hand, first addition of Cu^{+} led to the destruction of the starting network, which may be attributed to the fact that strong binding of free $\mathbf{D_4}$ and Cu^{2+} promoted the oxidation of Cu^{+} (see Figure S26 for more details; see also the similar case of ***NC-Cu***, Scheme 4). As an extension of the results obtained from the [2×3] network above, the present [3×3] network displays the behavior of a hierarchical system through competitive effectors and constituents, where operation of the full connectome results in a much higher degree of control of the DCL via the underlying CDN.

Thus, increased complexity allows for (1) implementation of *sequential addition* of different effectors; (2) *increased efficiency* (higher yield) of imine formation, from about of 32% uncondensed free components (of both aldehyde and amine type) in ***NE*** to 4% in ***NE-Fe*** and to only 3% in ***NE-FeCu*** (see Table S5, *middle* and *bottom*); and (3) *higher selectivity* in constituent formation (which can be expressed by the increase in the sum of the % of constituents $\mathbf{A_6D_4}-\mathbf{A_7D_3}-\mathbf{A_4C_1}$ on the diagonal from only 10% for ***NE***, to 55% for ***NE-Fe*** and 80% for ***NE-FeCu***) corresponding to a strong reduction of multiplicity of the entities present in the dynamic system through competition between components.[12b,14]

3. CONCLUSION

The present study has explored dynamic covalent libraries comprising six and nine interconverting constituents in thermodynamic equilibrium and forming constitutional dynamic networks of respectively [2×3] and [3×3] order. It has revealed novel adaptive behaviors of these DCLs in response to the application of one or two effectors. Although they specifically implement ligand molecules and metal cation effectors, the features displayed are of broad significance, as they represent a demonstration of principle for the emergence of higher order adaptive properties, namely,

- *multiple agonistic and antagonistic* regulation
- *agonist amplification* involving a single constituent and a sub-network or a diagonal of three constituents
- *synergistic operation* of several agonists
- *conditional response* of the system on the *hierarchical sequence* of effector application

Finally and strikingly, the present results also demonstrate that an *increase in complexity* of the system by introduction of an additional entity (constituent or effector) may result in a *simpler output*, with higher efficiency and selectivity through dynamic competition between entities.[3g,14]

Steps toward systems of increasing complexity[15] require the exploration of DCLs of higher order containing a larger number of interconverting constituents and defining higher order networks, including networks of networks. Such connectomes lead to the emergence of novel features under coupling to multiple agents in the environment and responding to them in diverse fashions, thus revealing novel behaviors toward the implementation of adaptive chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b13072.

Experimental details, NMR spectra, and synthetic procedures, including Tables S1−S5 and Figures S1−S26 (PDF)

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Notes

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