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Adaptation in Constitutional Dynamic Libraries and Networks, Switching between Orthogonal Metalloselection and Photoselection Processes

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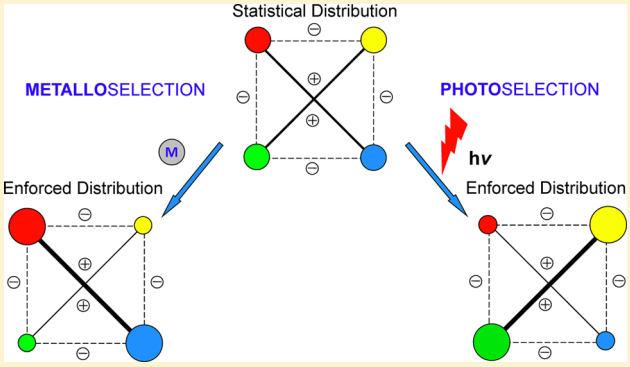
Supporting Information

ABSTRACT: Constitutional dynamic libraries of hydrazones $^{a}\mathbf{A}^{b}\mathbf{B}$ and acylhydrazones $^{a}\mathbf{A}^{c}\mathbf{C}$ undergo reorganization and adaptation in response to a chemical effector (metal cations) or a physical stimulus (light). The set of hydrazones [$^{1}\mathbf{A}^{1}\mathbf{B}$, $^{1}\mathbf{A}^{2}\mathbf{B}$, $^{2}\mathbf{A}^{1}\mathbf{B}$, $^{2}\mathbf{A}^{2}\mathbf{B}$] undergoes metalloselection on addition of zinc cations which drive the amplification of Zn($^{1}\mathbf{A}^{2}\mathbf{B}$)$_2$ by selection of the fittest component $^{1}\mathbf{A}^{2}\mathbf{B}$. The set of acylhydrazones [*E*-$^{1}\mathbf{A}^{1}\mathbf{C}$, $^{1}\mathbf{A}^{2}\mathbf{C}$, $^{2}\mathbf{A}^{1}\mathbf{C}$, $^{2}\mathbf{A}^{2}\mathbf{C}$] undergoes photoselection by irradiation of the system, which causes photoisomerization of *E*-$^{1}\mathbf{A}^{1}\mathbf{C}$ into *Z*-$^{1}\mathbf{A}^{1}\mathbf{C}$ with amplification of the latter. The set of acyl hydrazones [*E*-$^{1}\mathbf{A}^{1}\mathbf{C}$, $^{1}\mathbf{A}^{3}\mathbf{C}$, $^{2}\mathbf{A}^{1}\mathbf{C}$, $^{2}\mathbf{A}^{3}\mathbf{C}$] undergoes a *dual adaptation* via component exchange and selection in response to two orthogonal external agents: a chemical effector, metal cations, and a physical stimulus, light irradiation. *Metalloselection* takes place on addition of zinc cations which drive the amplification of Zn($^{1}\mathbf{A}^{3}\mathbf{C}$)$_2$ by selection of the fittest constituent $^{1}\mathbf{A}^{3}\mathbf{C}$. *Photoselection* is obtained on irradiation of the acylhydrazones that leads to photoisomerization from *E*-$^{1}\mathbf{A}^{1}\mathbf{C}$ to *Z*-$^{1}\mathbf{A}^{1}\mathbf{C}$ configuration with amplification of the latter. These changes may be represented by square constitutional dynamic networks that display up-regulation of the pairs of agonists ($^{1}\mathbf{A}^{2}\mathbf{B}$, $^{2}\mathbf{A}^{1}\mathbf{B}$), (*Z*-$^{1}\mathbf{A}^{1}\mathbf{C}$, $^{2}\mathbf{A}^{2}\mathbf{C}$), ($^{1}\mathbf{A}^{3}\mathbf{C}$, $^{2}\mathbf{A}^{1}\mathbf{C}$), (*Z*-$^{1}\mathbf{A}^{1}\mathbf{C}$, $^{2}\mathbf{A}^{3}\mathbf{C}$) and the simultaneous down-regulation of the pairs of antagonists ($^{1}\mathbf{A}^{1}\mathbf{B}$, $^{2}\mathbf{A}^{2}\mathbf{B}$), ($^{1}\mathbf{A}^{2}\mathbf{C}$, $^{2}\mathbf{A}^{1}\mathbf{C}$), (*E*-$^{1}\mathbf{A}^{1}\mathbf{C}$, $^{2}\mathbf{A}^{3}\mathbf{C}$), ($^{1}\mathbf{A}^{3}\mathbf{C}$, $^{2}\mathbf{A}^{1}\mathbf{C}$). The orthogonal dual adaptation undergone by the set of acylhydrazones amounts to a network switching process.



INTRODUCTION

On the way toward higher levels of complexity in chemical systems, constitutional dynamic chemistry (CDC)[1] gives access to constitutional dynamic libraries (CDLs) by the generation of chemical diversity on both the molecular and supramolecular levels through the exchange of components between the constituents of the system, implementing either reversible covalent reactions[1,2] or labile noncovalent interactions, respectively. CDC allows for variation and operates selection on dynamic constitutional diversity in response to the pressure of either chemical or physical agents to achieve adaptation of CDLs, thus enabling adaptive chemistry.[1,3−5] The set of dynamically interconverting constituents of a CDL forms a network, a constitutional dynamic network (CDN),[1,6] that can be represented in a schematic way by a weighted graph,[7] where the links between the constituents describe the relationships between the members of a set, their agonistic or antagonistic behavior, as well as their relative weights. CDNs are adaptive systems, as the weights of their vertices/nodes and of their connections/links respond to the application of a physical stimulus or a chemical effector, which may modify the CDL distribution by amplification/up-regulation of the responsive constituent(s) and its (their) agonist(s) and down-regulation of the antagonists.[6] On the molecular level, a CDL is based on constituents interconverting via reversible chemical reactions and is thus a dynamic covalent library (DCL). On the basis of previous work from our group,[8] pyridyl-hydrazones and pyridyl-acylhydrazones present the very attractive feature of being triple dynamic entities capable of undergoing: (1) *conformational dynamics* by shape switching on cation coordination to the NNN and NNO tridentate binding sites, respectively;[9] (2) *configurational dynamics* on *E* to *Z* photoisomerization stabilized by internal hydrogen bonding with the pyridine moiety;[10] (3) *constitutional dynamics*, by component exchange via the reversible C═N bond.[1,2]

We have investigated the ability of a DCL to undergo *double adaptation* by studying its response to two orthogonal agents: a chemical effector,[4] e.g., a metal cation, and a physical stimulus,[3] light irradiation. To this end, selection and adaptation have been analyzed for different DCLs of four constituents each, chosen among the hydrazones $^{a}\mathbf{A}^{b}\mathbf{B}$ and the acylhydrazones $^{a}\mathbf{A}^{c}\mathbf{C}$ shown in Figure 1, that were generated from the condensation

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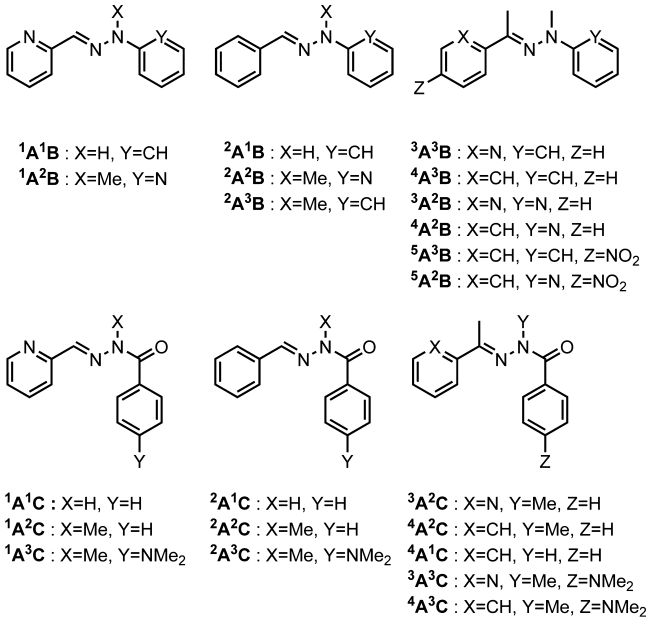


Figure 1. Structures of the hydrazones ^{a}A^{b}B and acylhydrazones ^{a}A^{c}C obtained by condensation of aldehydes and ketones with hydrazines and hydrazides. The fragments originating from the aldehyde and ketone components are designated by the letter **A**, the fragments originating from the hydrazines by the letter **B**, and those from the hydrazides by the letter **C**. All compounds are shown in the *E* configuration about the C=N double bond.

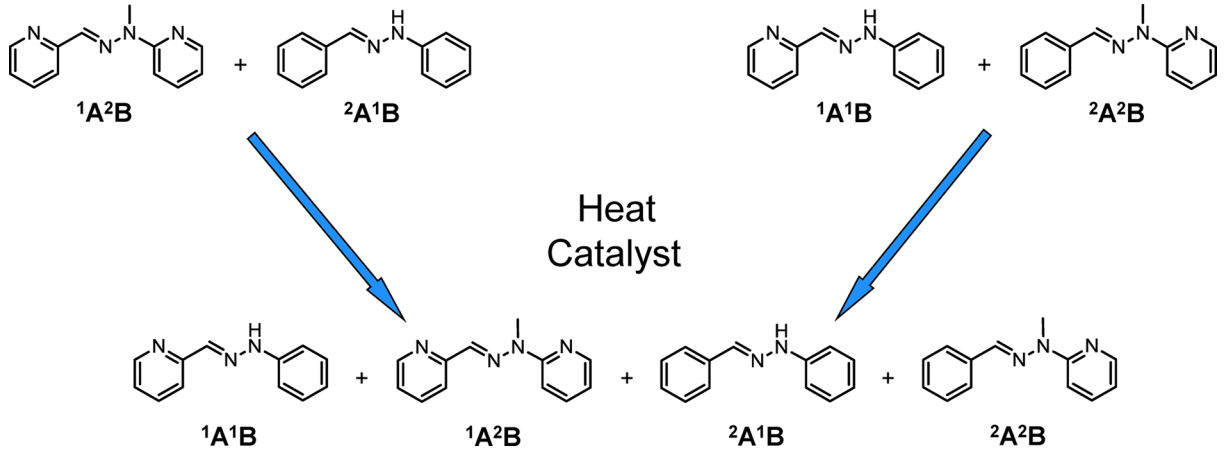
products of aldehydes or ketones (fragments ^{a}**A**) with hydrazines (fragments ^{b}**B**) or hydrazides (fragments ^{c}**C**). These sets of constituents were subjected either to interaction with metal cations or to light irradiation in conditions allowing for component exchange, thus leading to adaptation through orthogonal selection processes, respectively *metalloselection* (Schemes 2, 4, and 5) or *photoselection* (Schemes 3–5). They form square CDNs that undergo network switching in response to these two independent external agents.

RESULTS

1. Adaptation in a DCL of Hydrazones. *1.1. Component Exchange in the Two DCLs of Hydrazones [^{1}A^{1}B, ^{1}A^{2}B, ^{2}A^{1}B, ^{2}A^{2}B] and [^{3}A^{2}B, ^{3}A^{3}B, ^{4}A^{2}B, ^{4}A^{3}B].* On the basis of previous work in our laboratory,[8a] we first investigated the set of four hydrazones ^{1}A^{1}B, ^{1}A^{2}B, ^{2}A^{1}B, and ^{2}A^{2}B. It may be generated either by mixing equimolecular quantities of each individually synthesized constituent or by randomization of just two constituents, for example ^{1}A^{1}B and ^{2}A^{2}B, through component exchange (Scheme 1). Hydrazones are kinetically inert under neutral conditions as a result of C=N̄—N̄ conjugation which decreases the electrophilicity of the C=N bond, making them too stable for use in dynamic covalent libraries. Reported exchange processes feature hydrazones bearing electron-withdrawing groups.[11] To circumvent this problem, we investigated means of facilitating exchange of the carbonyl and hydrazine components of hydrazones. Three different exchange procedures via hydrolysis and recondensation were developed: (i) metal ion or acid catalysis under microwave heating, (ii) organocatalysis with aniline,[12] and (iii) introduction of methyl groups in order to twist and destabilize the hydrazone connection by steric strain. All the exchange reactions were monitored by ^{1}H NMR spectroscopy (see the figures in Supporting Information for exchange processes studied here).

1.1.1. Metal Ion Catalysis. Hydrazone exchange has been catalyzed by scandium(III) triflate,[4a,13] under intense microwave heating.[14] When a solution of the two hydrazones ^{1}A^{1}B and ^{2}A^{2}B (10 mM each) in 4:1 acetonitrile/water was heated to 170 °C in a microwave oven in the presence of scandium triflate (2 mM) during 20 min (under 12 bar), the full set of four constituents ^{1}A^{1}B, ^{1}A^{2}B, ^{2}A^{1}B, and ^{2}A^{2}B was formed by component exchange at the C=N site, with a distribution of 32/17/21/18% of ^{1}A^{1}B/^{1}A^{2}B/^{2}A^{1}B/^{2}A^{2}B together with 12% hydrolysis (see the ^{1}H NMR spectrum in Supporting Information, Figure S1).[14] The same distribution was generated starting from ^{2}A^{1}B and ^{1}A^{2}B in the same conditions. In both cases, ^{1}A^{1}B was present in both the *E* and *Z* configurations (63% and 37%, respectively). Furthermore, when either *E*-^{1}A^{1}B or *Z*-^{1}A^{1}B was subjected separately to these conditions for constitutional exchange, the same $^3/_2$ mixture of the two configurational isomers *E*-^{1}A^{1}B and *Z*-^{1}A^{1}B was obtained (Supporting Information Figures S2–S3). One may note that only benzaldehyde is formed during the exchange due to the greater sensitivity of its imines to hydrolysis compared to 2-pyridinecarboxaldehyde. This hydrazone exchange can also be catalyzed in the same conditions by addition of 20 mol % trifluoroacetic acid instead of scandium triflate. The component scrambling reaction is expected to proceed through a transimination, hydrolysis/recondensation process.

Scheme 1. Generation of the Set of Four Hydrazones ^{1}A^{1}B, ^{1}A^{2}B, ^{2}A^{1}B, and ^{2}A^{2}B by Component Exchange between Either ^{1}A^{2}B and ^{2}A^{1}B (Top Left) or ^{1}A^{1}B and ^{2}A^{2}B (Top Right) Giving the Same Statistical Distribution of the Dynamic Library



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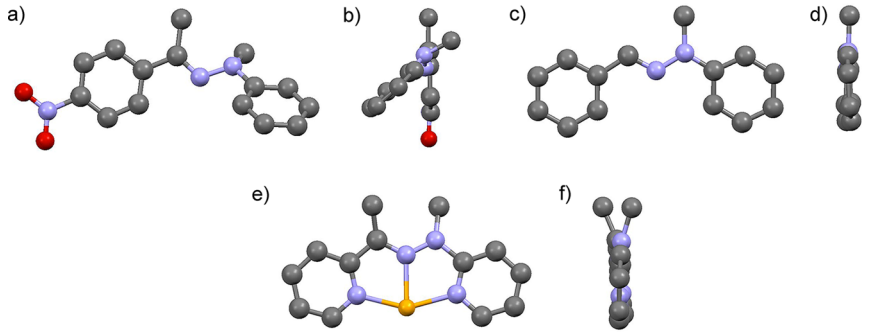

Figure 2. Two views of the solid-state molecular structures of the methylated hydrazones ^{5}**A**^{3}**B**, ^{2}**A**^{3}**B**, and Zn(^{3}**A**^{2}**B**). (a) In ^{5}**A**^{3}**B**, the **phenyl**—**C**(CH_3)=$\bar{N}$— moiety lies in the plane of the figure while the =$\bar{N}$—$\bar{N}$(CH_3)—**phenyl** moiety is located in a plane making a dihedral angle of about 61°. (c) Solid-state molecular structure of the hydrazone ^{2}**A**^{3}**B** in the plane of the figure.[16] (b, d) Perpendicular views for ^{5}**A**^{3}**B** (b) and ^{2}**A**^{3}**B**[16] (d) showing clearly the torsion angle in ^{5}**A**^{3}**B**. (e) In the hydrazone ^{3}**A**^{2}**B** complexed with the zinc(II) cations, the **pyridine**—**C**(CH_3)=$\bar{N}$— moiety lies in the plane of the figure while the =$\bar{N}$—$\bar{N}$(CH_3)—**pyridine** moiety is located in a plane making a dihedral angle of about 39°. The carbon C6 and the nitrogen N3 are disordered. The complexes are bridged through $ZnCl_4^{2-}$ anions (Supporting Information Figure S6). (f) Perpendicular view for Zn(^{3}**A**^{2}**B**). Protons and chloride anions are omitted for clarity.

1.1.2. Organocatalysis. The hydrazone exchange has also been performed by organocatalysis, via the addition of aniline (10% in volume, about 100 equiv) to a 10 mM acetonitrile solution of the two hydrazones ^{1}**A**^{1}**B** and ^{2}**A**^{2}**B** in the presence of trifluoroacetic acid (2 mM). Component exchange occurred, and the equilibrium between the hydrazones ^{1}**A**^{1}**B**, ^{1}**A**^{2}**B**, ^{2}**A**^{1}**B**, and ^{2}**A**^{2}**B** was obtained after 1 day at 25 °C, giving a distribution of 32/21/21/26% of ^{1}**A**^{1}**B**/^{1}**A**^{2}**B**/^{2}**A**^{1}**B**/^{2}**A**^{2}**B**, respectively. No hydrolysis was observed in the NMR ^{1}H spectrum after the exchange (Supporting Information Figure S4). In this case, almost 50% of *E*-^{1}**A**^{1}**B** was converted into *Z*-^{1}**A**^{1}**B** indicating an *E*/Z interconversion mechanism in the course of the catalytic process. Other organocatalysts have also been tested for the exchange (see Supporting Information section S1.1.ii). One may note that organocatalysis by aniline or related compounds provides an entry into the equilibration of C=N based dynamic covalent libraries[12] in rather mild conditions, a feature that may have significant usefulness for a wide variety of adaptation/selection processes under the action of different effectors/stimuli and for systems of much greater complexity than the present ones.

1.1.3. Strain Activation in the DCL of Hydrazones ^{3}A^{2}B, ^{3}A^{3}B, ^{4}A^{2}B, and ^{4}A^{3}B. We hypothesized that steric strain caused by CH_3/CH_3 interaction on introduction of methyl groups at both the C=N carbon and the hydrazone —$\bar{N}$— sites would markedly twist the **C**=$\bar{N}$—$\bar{N}$ fragment,[15] thus decreasing conjugation within the **C**=$\bar{N}$—$\bar{N}$ fragment. As a result, one would expect an increase of the reactivity of the hydrazone bond, facilitating component exchange between C, N doubly methylated hydrazones such as ^{3}**A**^{3}**B** and ^{4}**A**^{2}**B**. These expectations were confirmed by the X-ray crystallographic determination of the solid-state molecular structure of the hydrazone ^{5}**A**^{3}**B** (a nitro group has been introduced so as to obtain a solid at 25 °C, as the hindered hydrazones ^{3}**A**^{2}**B**, ^{3}**A**^{3}**B**, ^{4}**A**^{2}**B**, and ^{4}**A**^{3}**B** are liquids at 25 °C, Figure 2). The dihedral angle between the planes containing the CH_3—**C**=$\bar{N}$ and the =$\bar{N}$—$\bar{N}$—CH_3 fragments in ^{5}**A**^{3}**B** amounts to 61°, compared to a torsion angle of only 2° in the corresponding **H**—**C**=$\bar{N}$—$\bar{N}$—CH_3 unit of ^{2}**A**^{3}**B**,[16] showing clearly the twist imposed in the hydrazone unit by the steric interaction between the two methyl groups. In addition, as a further indication of decreased conjugation, the —$\bar{N}$(CH_3)— nitrogen site is partially pyramidilized in ^{5}**A**^{3}**B** (N is located at a distance of 0.3 Å from the plane containing the three connected NCC atoms) whereas it is planar in ^{2}**A**^{3}**B**. An increase in reactivity on deconjugation is well-documented, for instance in the sensitivity of out-of-plane distorted amide groups to nucleophiles.[17] Indeed, a marked increase in component exchange rate between hydrazones was observed: when the two hydrazones ^{3}**A**^{3}**B** and ^{4}**A**^{2}**B** were mixed in 10 mM acetonitrile solution in the presence of scandium triflate (2 mM) at 60 °C during 8 h, the full set ^{3}**A**^{2}**B**, ^{3}**A**^{3}**B**, ^{4}**A**^{2}**B**, and ^{4}**A**^{3}**B** was formed (Supporting Information Figure S5). Thus, these hydrazones bearing sterically hindering methyl groups present a strain-activated reactivity closer to that of imines. For comparison, the hydrazones ^{1}**A**^{1}**B** and ^{2}**A**^{2}**B** did not show any component exchange at 60 °C in the same conditions.

The same methylated hydrazone exchange has also been performed by organocatalysis: aniline (10% in volume, about 100 equiv) was added to an acetonitrile solution of the two hydrazones ^{3}**A**^{3}**B** and ^{4}**A**^{2}**B** (10 mM each) in the presence of trifluoroacetic acid (2 mM). The exchange was observed, and the equilibrium between the hydrazones ^{3}**A**^{2}**B**, ^{3}**A**^{3}**B**, ^{4}**A**^{2}**B**, and ^{4}**A**^{3}**B** was obtained after 6 h at 60 °C. The presence of aniline did not induce an acceleration as important as that seen above, probably due to hindrance of aniline addition on the C=N carbon in the methylated hydrazones.

The deformation induced in the coordination site by the two methyl groups does however not preclude the formation of transition metal complexes by the tridentate ligand ^{3}**A**^{2}**B**. The X-ray crystallographic determination of the solid-state molecular structure of the hydrazone ^{3}**A**^{2}**B** complexed with zinc(II) cations shows a torsion angle of 39° between the planes of H_3C—**C**=$\bar{N}$ and the =$\bar{N}$—$\bar{N}$—CH_3 fragments (Figure 2e,f).

1.2. Metalloselection in the Three DCLs of Hydrazones: [^{1}A^{1}B, ^{1}A^{2}B, ^{2}A^{1}B, ^{2}A^{2}B], [^{3}A^{2}B, ^{3}A^{3}B, ^{4}A^{2}B, ^{4}A^{3}B], and [^{3}A^{2}B, ^{3}A^{3}B, ^{5}A^{2}B, ^{5}A^{3}B]. The four hydrazones ^{1}**A**^{1}**B**, ^{1}**A**^{2}**B**, ^{2}**A**^{1}**B**, and ^{2}**A**^{2}**B** were selected to analyze the adaptation of the set in response to the addition of zinc cations. Pyridyl-hydrazones are known to form stable complexes with a variety of metal cations by coordination to the NNN tridentate site.[18] This is the case for the hydrazone ^{1}**A**^{2}**B**, compared to the other hydrazones which present only bidentate or monodentate sites. Hydrazones ^{1}**A**^{1}**B** and ^{2}**A**^{2}**B** (10 mM each) were treated with zinc(II) triflate (5 mM) under equilibrating conditions either with or without added scandium triflate (2 mM, see above) in 10 mM 4:1 acetonitrile/water solution and heated at 170 °C in the microwave oven during 20 min. In both cases, the dynamic library underwent

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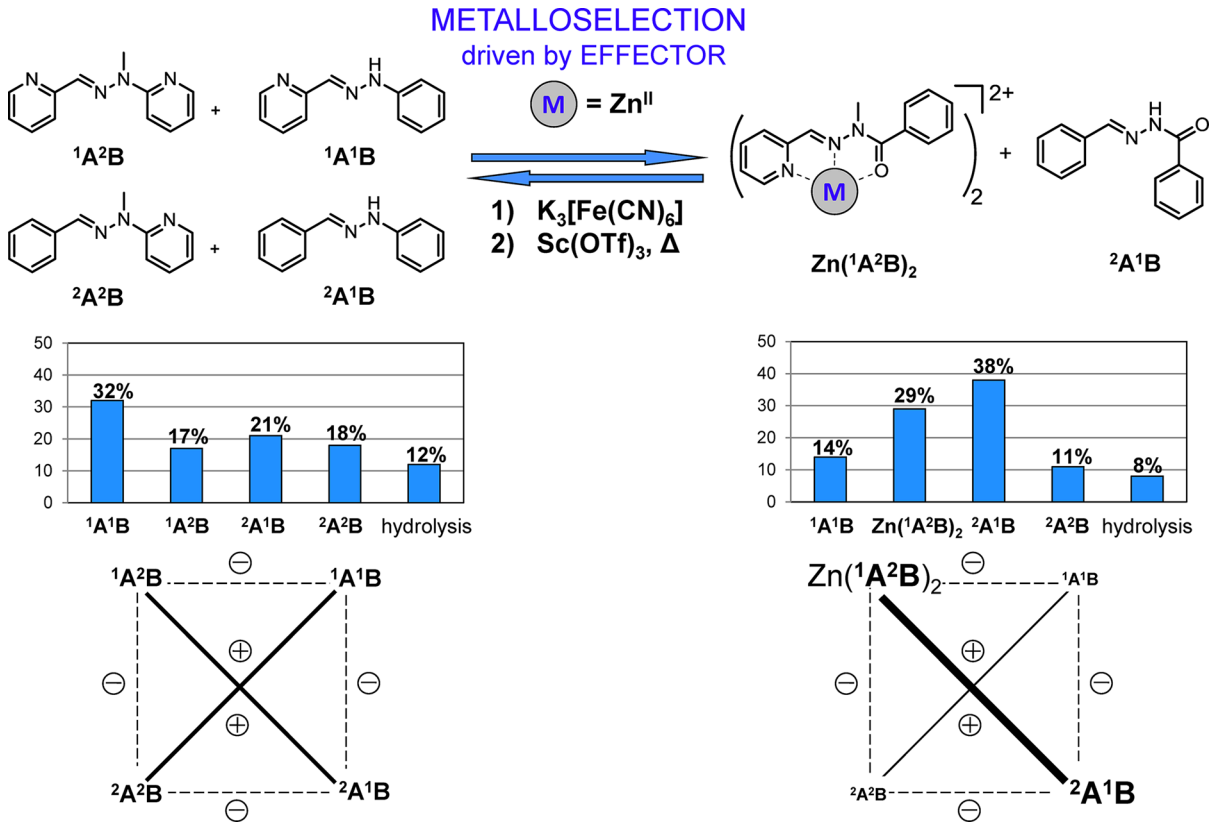
Scheme 2. (Top) Adaptation of the DCL of Four Hydrazone Constituents $^1A^1B$, $^1A^2B$, $^2A^1B$, $^2A^2B$ by Metalloselection of the A, B Fragments on Addition of Zinc Cations Driven by Amplification of the Fittest Constituent $^1A^2B$ That Forms the Most Stable Zinc Complex,[a] (Middle) Distribution of the Constituents of the DCL before (Middle Left) and after (Middle Right) Addition of the Zinc Cations Showing Adaptation Driven by an Effector, and (Bottom) Representation of the Library Adaptation as a Square CDN Showing Agonist Amplification and Down-Regulation of the Antagonists[b]



[a]For clarity, only the major components $Zn(^1A^2B)_2$ and $^2A^1B$ are represented on the right hand side. $^1A^2B$ is indicated as its Zn complex $Zn(^1A^2B)_2$. [b]Error on % determination: ~5%.

reorganization to amplify the hydrazone $^1A^2B$ in the form of its $Zn(^1A^2B)_2$ complex as well as simultaneously its agonist $^2A^1B$. The distribution obtained was 14/29/38/11% for the constituents $^1A^1B/^1A^2B/^2A^1B/^2A^2B$, respectively, together with 8% hydrolysis, with $^1A^2B$ being in the form of the complex $Zn(^1A^2B)_2$ (Scheme 2, Supporting Information Figure S8). The distribution of the constituents did not change by further heating. This set of hydrazones thus displays an amplification of both $^1A^2B$ (12%) and $^2A^1B$ (17%), whereas the amounts of $^1A^1B$ and $^2A^2B$ decrease markedly, representing the adaptation of the system to the addition of zinc triflate by metalloselection, as shown in Scheme 2. One may note that there was 8% hydrolysis, exclusively coming from the benzaldehyde moiety, and not the pyridine-2-carboxaldehyde. Furthermore, the fact that similar results were obtained with or without added scandium triflate indicates that, in the latter case, the zinc ions both facilitate the equilibration and are incorporated in the final set of products.

The metalloselection on this same set of four hydrazones $^1A^1B$, $^1A^2B$, $^2A^1B$, and $^2A^2B$ was also studied in milder conditions, by means of organocatalysis with aniline to establish equilibration conditions. Hydrazones $^1A^1B$ and $^2A^2B$ (10 mM each) were treated with zinc(II) triflate (5 mM) in the presence of aniline (10% in volume, about 100 equiv) in acetonitrile solution and heated at 80 °C during 6 h. The dynamic library underwent again reorganization as presented above giving a distribution 4/45/44/7% for the constituents $^1A^1B/^1A^2B/^2A^1B/^2A^2B$, respectively, with almost no hydrolysis, with $^1A^2B$ being in the form of the complex $Zn(^1A^2B)_2$ (Supporting Information Figure S9).

The adaptation of the set of methylated hydrazones $^3A^2B$, $^3A^3B$, $^4A^2B$, and $^4A^3B$ under metalloselection in the presence of zinc cations could be achieved at lower temperature (60 °C overnight) without added catalyst, in line with the easier component exchange in these hydrazones (see above). It gave the same selection and amplification of $Zn(^3A^2B)_2$ and $^4A^3B$. The distribution obtained was 42/5/6/47% for the constituents $^3A^2B/^3A^3B/^4A^2B/^4A^3B$, respectively, together with almost no hydrolysis, with $^3A^2B$ being in the form of the complex $Zn(^3A^2B)_2$ (Supporting Information Figure S10). The distribution of the constituents did not change on further heating. The addition of mercury or lead cations led to similar results. However, this system will not be further described, because it cannot be used for photoselection due to the absence of N−H bond to stabilize the *Z* photoisomer by hydrogen bonding (see below).

1.3. Attempts for Photoselection in the DCL of Hydrazones [$^1A^1B$, $^1A^2B$, $^2A^1B$, $^2A^2B$]. A number of experiments have been performed with the aim of inducing photoselection by photogeneration of *Z*-$^1A^1B$ from the *E*-$^1A^1B$ form within the set of hydrazones $^1A^1B$, $^1A^2B$, $^2A^1B$, and $^2A^2B$. However, on irradiation of a solution of the preformed hydrazones (10 mM each in 4:1 acetonitrile/water; see experimental details in the Supporting Information) no amplification of *Z*-$^1A^1B$ by *E*-$^1A^1B$ to *Z*-$^1A^1B$ conversion was obtained in the scandium triflate

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catalyzed equilibrating conditions (see above, section 1.1.1). In fact, the hydrazone exchange gave the same 3/2 *E*/*Z* mixture as in absence of irradiation (see Supporting Information). Attempts to increase the quantity of *Z* isomer by irradiation of the solution in these conditions directly inside the microwave oven were unsuccessful (Supporting Information Figure S11−S12). Photoselection in conditions of hydrazone exchange through organocatalysis by aniline (see above section 1.1.2) also failed. It thus appears that light-induced photoselection by *E*-^{1}**A**^{1}**B** to *Z*-^{1}**A**^{1}**B** conversion is incompatible with the conditions required for component exchange.

As no photoselection could be achieved with the hydrazones ^{a}**A**^{b}**B**, we turned our attention to the acylhydrazones ^{a}**A**^{c}**C**.

2. Adaptation in a DCL of Acylhydrazones. *2.1. Component Exchange in the Two DCLs of Acylhydrazones [^{1}A^{1}C, ^{1}A^{2}C, ^{2}A^{1}C, ^{2}A^{2}C] and [^{1}A^{1}C, ^{1}A^{3}C, ^{2}A^{1}C, ^{2}A^{3}C].* A number of examples of acylhydrazone exchange in the presence of Brönsted acid catalyst have been described in the literature.[3c,4c,d,9b,19] Thus, component exchange among acylhydrazones appears to take place more easily than for hydrazones. Indeed, conjugation of the hydrazone —$\bar{\mathrm{N}}$— site with the carbonyl group may be expected to decrease its conjugation with the **C**=$\bar{\mathbf{N}}$ bond, which thus becomes more reactive toward nucleophiles/water. On the other hand, a goal of the present study was to design a DCL that would be susceptible to achieve *both* metalloselection and photoselection. To this end, DCLs based on different components were explored.

First, when the two acylhydrazones ^{1}**A**^{2}**C** and ^{2}**A**^{1}**C** were mixed in 10 mM 3:2 acetonitrile/water solution in the presence of scandium triflate (2 mM) at 60 °C during 12 h, exchange occurred, yielding the full set ^{1}**A**^{1}**C**, ^{1}**A**^{2}**C**, ^{2}**A**^{1}**C**, and ^{2}**A**^{2}**C** in an almost statistical distribution of constituents: 25/23/28/22%, respectively, with 2% hydrolysis (Supporting Information Figure S13). No change was observed on further heating. The same distribution was obtained when starting from ^{1}**A**^{1}**C** and ^{2}**A**^{2}**C**. In both cases, ^{1}**A**^{1}**C** was obtained as a mixture of the *E* and *Z* configurations (respectively, 75% and 25%). Again, component exchange among acylhydrazones could be achieved in much milder conditions under organocatalysis by the addition of aniline (1% in volume, about 10 equiv). It went to thermal equilibrium after just 2 h at 25 °C, and the expected statistical distribution was obtained: 27/23/27/21% of ^{1}**A**^{1}**C**/^{1}**A**^{2}**C**/^{2}**A**^{1}**C**/^{2}**A**^{2}**C**, respectively, with only 2% hydrolysis (Supporting Information Figure S14). Again, the *E* and *Z* configurations were obtained for ^{1}**A**^{1}**C** (respectively, 48% and 52%).

However, in the ^{1}**A**^{1}**C**, ^{1}**A**^{2}**C**, ^{2}**A**^{1}**C**, ^{2}**A**^{2}**C** set, the metal cation complexation ability of ^{1}**A**^{1}**C** and ^{1}**A**^{2}**C** may be too similar to allow for any significant metalloselection. In order to increase the metal cation binding ability of the NNO coordination site of one of the constituents (see below, section 2.4), a DCL containing a benzhydrazide component bearing a *para*-dimethylamino substituent was studied. Thus, in the same conditions as above, in the presence of scandium triflate, the two acylhydrazones ^{1}**A**^{3}**C** and ^{2}**A**^{1}**C** underwent exchange, yielding the full set ^{1}**A**^{1}**C**, ^{1}**A**^{3}**C**, ^{2}**A**^{1}**C**, and ^{2}**A**^{3}**C** in an almost statistical distribution of constituents: 24/25/20/23%, respectively, with 8% hydrolysis (Supporting Information Figure S15). The *E* and *Z* configurations were obtained for ^{1}**A**^{1}**C** in the same proportions as above. The same distribution was obtained when starting from ^{1}**A**^{1}**C** and ^{2}**A**^{3}**C**. Again, in the presence of aniline, thermal equilibrium was reached after just 1 h at 25 °C, giving the expected statistical distribution with equal amounts of the four constituents: 26/25/23/24% of ^{1}**A**^{1}**C**/^{1}**A**^{3}**C**/^{2}**A**^{1}**C**/^{2}**A**^{3}**C**, respectively, with only 2% hydrolysis (Supporting Information Figure S16). Again, both the *E* and *Z* configurations were obtained for ^{1}**A**^{1}**C** as above. One may note that here, also, hydrolysis in the course of the exchange gives only benzaldehyde, in view of the greater sensitivity of its acylhydrazones ^{2}**A**^{1}**C** and ^{2}**A**^{3}**C** compared to those of 2-pyridinecarboxaldehyde.

2.2. Strain Activation in the DCL of Acylhydrazones ^{3}A^{3}C, ^{3}A^{2}C, ^{4}A^{3}C, and ^{4}A^{2}C. The activation of exchange by strain achieved for hydrazones (see above) has also been tested in the present case of acylhydrazones. The introduction of a methyl group at both the C=N carbon and the acylhydrazone —$\bar{\mathrm{N}}$— sites induces again a pronounced twist in the **C**=$\bar{\mathbf{N}}$—$\bar{\mathbf{N}}$—**C**=**O** fragment, as confirmed by the X-ray crystallographic determination of the solid-state molecular structure of ^{4}**A**^{2}**C** (Figure 3). The dihedral angle between the $\mathbf{H_3C}$—**C**=$\bar{\mathbf{N}}$ and the =$\bar{\mathbf{N}}$—$\bar{\mathbf{N}}$—$\mathbf{CH_3}$ found in ^{4}**A**^{2}**C** amounts to a torsion of 126°, about twice larger than in the hydrazone ^{5}**A**^{3}**B**, due to the conjugation of the acylhydrazone —$\bar{\mathrm{N}}$— site with the carbonyl group, which reduces the conjugation within the **C**=$\bar{\mathbf{N}}$—$\bar{\mathbf{N}}$ fragment, increasing the single bond character to the N−N bond and allowing for a larger twist angle. As a consequence, in 3:2 acetonitrile/water solution in the presence of scandium triflate (2 mM) at 60 °C during 12 h full hydrolysis took place and in pure acetonitrile component exchange of the hindered acylhydrazones ^{3,4}**A**^{2,3}**C** was observed, but together with 50% hydrolysis (Supporting Information Figure S17). The very large amount of hydrolysis is indicative of the instability of these methylated acylhydrazones compared to the nonmethylated ones.

As in the case of the hydrazones above, the strain-induced twist within the **C**=$\bar{\mathbf{N}}$—$\bar{\mathbf{N}}$ fragment is reduced by metal ion

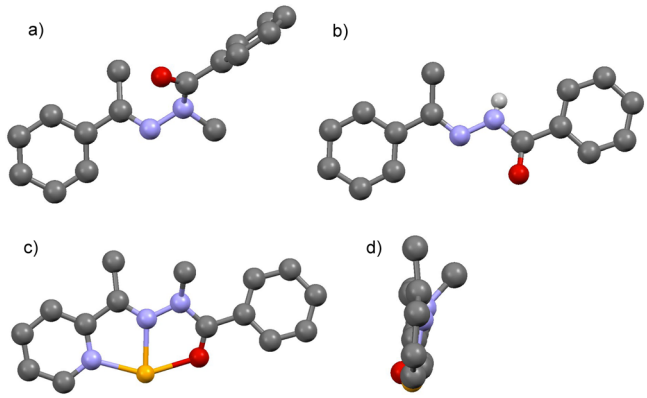

Figure 3. Views of the solid-state molecular structures of the acylhydrazones ^{4}**A**^{2}**C**, ^{4}**A**^{1}**C**,[20] and Zn(^{3}**A**^{2}**C**). (a) ^{4}**A**^{2}**C**: The **phenyl**—**C**($\mathbf{CH_3}$)=$\bar{\mathbf{N}}$— moiety lies in the plane of the figure while the =$\bar{\mathbf{N}}$—$\bar{\mathbf{N}}$($\mathbf{CH_3}$)—**C**(=**O**)—**phenyl** moiety is located in a plane making a dihedral angle of about 126°. (b) ^{4}**A**^{1}**C**:[20] The **phenyl**—**C**($\mathbf{CH_3}$)=$\bar{\mathbf{N}}$— moiety lies in the plane of the figure while the =$\bar{\mathbf{N}}$—$\bar{\mathbf{N}}$**H**—**C**(=**O**)—**phenyl** moiety is located in a plane making a dihedral angle of about 18°, showing clearly a smaller torsion angle than in ^{4}**A**^{2}**C**. (c) Zn(^{3}**A**^{2}**C**): The **pyridine**—**C**($\mathbf{CH_3}$)=$\bar{\mathbf{N}}$— moiety lies in the plane of the figure while the =$\bar{\mathbf{N}}$—$\bar{\mathbf{N}}$($\mathbf{CH_3}$)—**C**(=**O**)—**phenyl** moiety is located in a plane making a dihedral angle of about 45°. (d) Perpendicular view for Zn(^{3}**A**^{2}**C**). See Supporting Information Figure S18 for a structure of the corresponding Pb(^{3}**A**^{2}**C**) complex. Protons and tetrafluoroborate counterions are omitted for clarity.

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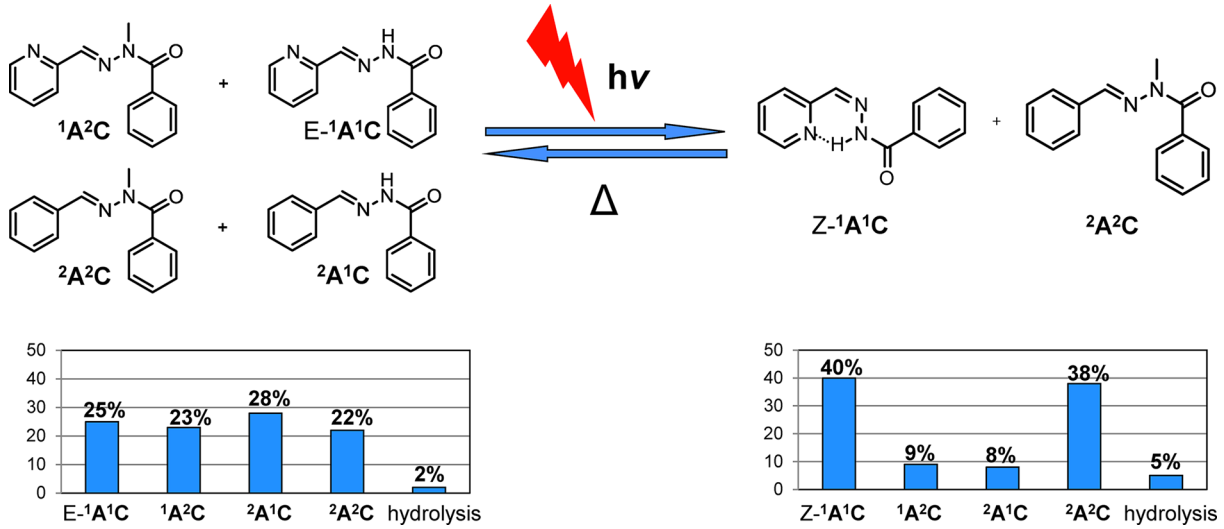
Scheme 3. Adaptation of the DCL of Four Constituents E-^{1}A^{1}C, ^{1}A^{2}C, ^{2}A^{1}C, and ^{2}A^{2}C by Photoselection of the A, C Fragments on Light Irradiation Driven by Amplification of the Fittest Constituent ^{1}A^{1}C That Forms the Metastable Z Isomer[a] with (Bottom) Distribution of the Constituents of the DCL before (Left) and after (Right) Light Irradiation[b]



[a]For clarity, only the major components Z-^{1}A^{1}C and ^{2}A^{2}C are represented on the right hand side. [b]Error on % determination: ~5%.

coordination, as found in the solid molecular structure in the acylhydrazone complex Zn(^{3}A^{2}C) (Figure 3).

2.3. Photoselection in the DCL of the Acylhydrazones [E-^{1}A^{1}C, ^{1}A^{2}C, ^{2}A^{1}C, ^{2}A^{2}C]. Photoselection was first investigated on the set of parent acylhydrazones E-^{1}A^{1}C, ^{1}A^{2}C, ^{2}A^{1}C, and ^{2}A^{2}C. On the basis of earlier results,[8] in this set, only the E-^{1}A^{1}C is expected to undergo photoisomerization, due to the presence of both the N−H bond and the pyridine N site, which allow for the formation of an internal hydrogen bond stabilizing the Z isomer. On the other hand, this set does not perform metalloselection (see below). A 3:2 acetonitrile/water solution of the two acylhydrazones ^{1}A^{2}C and ^{2}A^{1}C (10 mM each) was treated with a catalytic amount of scandium triflate (2 mM) to achieve equilibration conditions, and the mixture was irradiated at 25 °C. After 4 h of irradiation, a change in the composition of the library was observed in the ^{1}H NMR spectrum of the solution. 99% of the acylhydrazone E-^{1}A^{1}C was isomerized into Z-^{1}A^{1}C, and the equilibrating library had undergone reorganization to promote the metastable state Z-^{1}A^{1}C. The distribution of the library constituents obtained was 40/9/8/38% of Z-^{1}A^{1}C/^{1}A^{2}C/^{2}A^{1}C/^{2}A^{2}C, respectively, with 5% hydrolysis (Supporting Information Figure S19, Scheme 3). With respect to the distribution obtained without irradiation, 25/23/28/22% for ^{1}A^{1}C/^{1}A^{2}C/^{2}A^{1}C/^{2}A^{2}C, respectively (see above section 2.1), the present data represent a photoinduced amplification (by about 15%) of *both* Z-^{1}A^{1}C and its agonist ^{2}A^{2}C in the DCL and define its response/adaptation to irradiation by light with generation of a new distribution of constituents.

2.4. Metalloselection and Photoselection in the DCL of Acylhydrazones [E-^{1}A^{1}C, ^{1}A^{3}C, ^{2}A^{1}C, ^{2}A^{3}C]. 2.4.1. Metalloselection. Pyridyl-acylhydrazones bind metal cations by their tridentate NNO coordination site.[21] In order to achieve metalloselection in a DCL of acylhydrazones, the metal cation must select between NNO units presenting different binding abilities, due, for instance, to the presence of substituents that modify the interaction strength of the carbonyl oxygen site. Indeed, when a 1/1 mixture of the only slightly different ^{1}A^{2}C and ^{1}A^{1}C was treated with 0.5 equiv of zinc salt, almost the same amounts of the two complexes Zn(^{1}A^{2}C)$_2$ (about 45%) and Zn(^{1}A^{1}C)$_2$ (about 55%) were obtained, indicating no significant preference for either coordination site.

In contrast, a marked difference in metal cation binding ability may be expected to exist between the acylhydrazones ^{1}A^{1}C and ^{1}A^{3}C, resulting from the presence on the ^{3}C fragment of an electron donor *para*-dimethylamino group expected to increase the basicity of the carbonyl and thus the strength of its interaction with a metal cation. Indeed, the electron donor effect of the dimethylamino group was confirmed by the comparison of the IR spectra of ^{1}A^{3}C and ^{1}A^{1}C. The C═O stretching frequency of the ^{1}A^{3}C carbonyl group is at 1645.4 cm^{-1}, which is about 2.5 cm^{-1} smaller than that in ^{1}A^{2}C, in agreement with electron donation into the C═O bond of ^{1}A^{3}C. As a consequence, treating a 1/1 mixture of ^{1}A^{3}C and ^{1}A^{1}C with 0.5 equiv of zinc salt showed the almost exclusive formation of Zn(^{1}A^{3}C)$_2$ (about 85%) with respect to Zn(^{1}A^{1}C)$_2$, demonstrating the strong effect of the *para*-dimethylamino group in the former.

Metalloselection was then studied on the DCL of acylhydrazones ^{1}A^{1}C, ^{1}A^{3}C, ^{2}A^{1}C, and ^{2}A^{3}C by the addition of zinc triflate (5 mM) in 3:2 acetonitrile/water solution. No catalyst was needed, as the zinc cations act both as catalyst and effector (see also section 1.2). As discussed above, in this set, the zinc cation should form the most stable complex with ^{1}A^{3}C compared to ^{1}A^{1}C. Indeed, at 25 °C, the dynamic library had underdone reorganization in 12 h (or less) to promote the acylhydrazone forming the Zn(^{1}A^{3}C)$_2$ complex (Supporting Information Figure S23). The distribution obtained was 9/41/36/12% for the constituents ^{1}A^{1}C/^{1}A^{3}C/^{2}A^{1}C/^{2}A^{3}C, respectively, with 2% hydrolysis, ^{1}A^{3}C being in the form of the complex Zn(^{1}A^{3}C)$_2$ (Scheme 4, left). It did not change on further heating. These percentages indicate an up-regulation of 17% of ^{1}A^{3}C and 13% of its agonist ^{2}A^{1}C and a down-regulation of the two antagonists and represent an adaptation of the DCL to the addition of zinc triflate by amplification of both Zn(^{1}A^{3}C)$_2$ and ^{2}A^{1}C (see Scheme 5, left).

The same metalloselection on the DCL of acylhydrazones ^{1}A^{1}C, ^{1}A^{3}C, ^{2}A^{1}C, and ^{2}A^{3}C was studied in milder conditions

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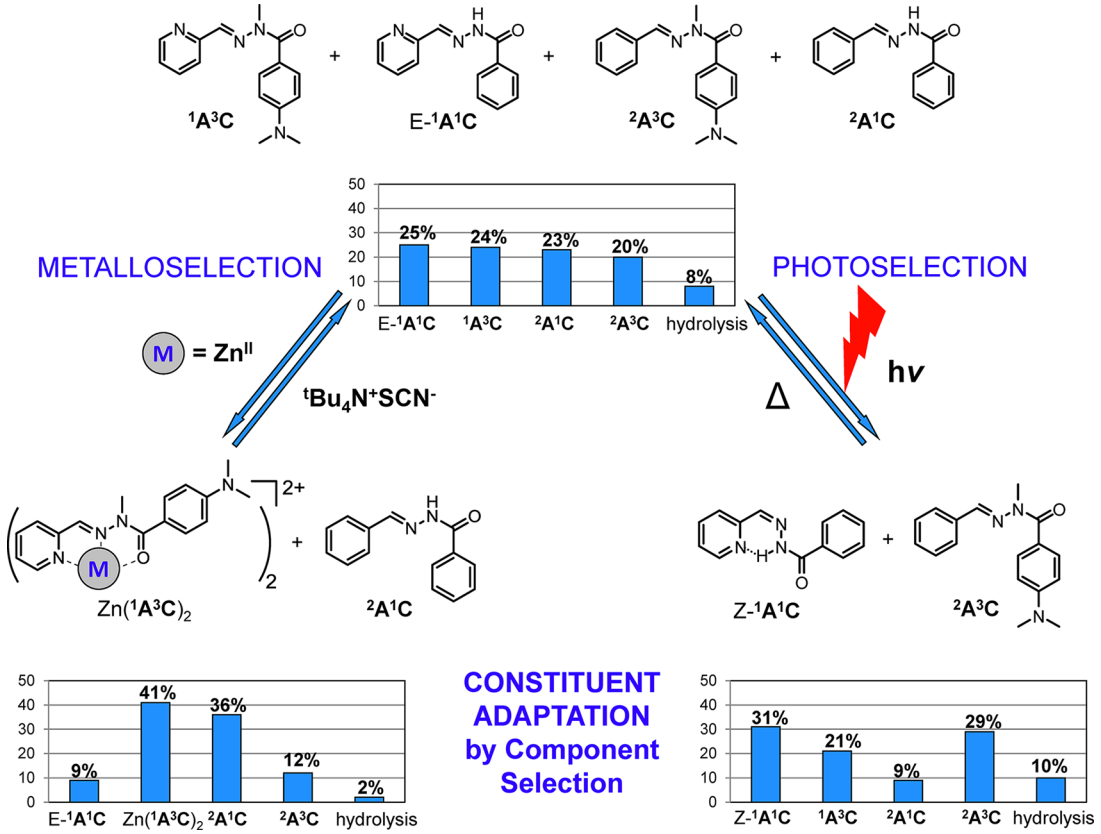
Scheme 4. Adaptation of the DCL of Four Acylhydrazone Constituents *E*-^{1}A^{1}C, ^{1}A^{3}C, ^{2}A^{1}C, and ^{2}A^{3}C by Modification of the Distributions under (Left) Metalloselection on Addition of Zinc(II) Metal Cation via the Formation of the Fittest Complex Zn(^{1}A^{3}C)$_2$ and (Right) Photoselection by Photoisomerization of *E*-^{1}A^{1}C into *Z*-^{1}A^{1}C on Light Irradiation and Distribution of the Constituents of the DCL before (Middle) and after Metalloselection (Bottom Left) and after Photoselection (Bottom Right)[a]



[a] ^{1}A^{3}C is indicated as its Zn complex Zn(^{1}A^{3}C)$_2$. For clarity, only the structures of the major components are represented on the right and left hand sides. For the CDN representation, see Scheme 5. Error on % determination: ~5%.

under organocatalysis with aniline. The acylhydrazones ^{1}A^{1}C and ^{2}A^{3}C (10 mM each) were treated with zinc(II) triflate (5 mM) under equilibrating conditions in the presence of aniline (1% in volume, about 10 equiv) in 10 mM acetonitrile solution and left at 25 °C during 30 min (Supporting Information Figure S24). The dynamic library underwent reorganization to promote the acylhydrazone Zn(^{1}A^{3}C)$_2$ and its agonist ^{2}A^{1}C, in a way similar to that described above.

2.4.2. Photoselection. In order to achieve *both* metallo and photoselection on *the same* system, irradiation was conducted on the DCL that showed metalloselection in response to the binding of zinc cations (see Scheme 4, left). Thus, irradiation for 4 h at 25 °C of a 3:2 acetonitrile/water solution of equimolar amounts (10 mM each) of the acylhydrazones ^{1}A^{3}C and ^{2}A^{1}C, containing scandium triflate (2 mM) as catalyst to achieve equilibrating conditions, transformed quantitatively *E*-^{1}A^{1}C into *Z*-^{1}A^{1}C, producing the set of four constituents *Z*-^{1}A^{1}C/^{1}A^{3}C/^{2}A^{1}C/^{2}A^{3}C in a distribution of 31/21/9/29%, respectively, together with 10% hydrolysis (Scheme 4, right), as observed by ^{1}H NMR (Supporting Information Figure S25). Further irradiation caused more hydrolysis. This distribution indicates an overall amplification of the two agonists *Z*-^{1}A^{1}C and ^{2}A^{3}C by about 7%. It represents the response of a DCL to the application of light as an orthogonal stimulus with respect to metal cation binding. The amplification observed is smaller than that obtained for metalloselection (see above), probably as a consequence of the larger amount of hydrolysis, itself related to the donor effect of the *para*-dimethylamino group of ^{3}C, which may be expected to render the C═N function in ^{1}A^{3}C more susceptible to hydrolysis.

For both DCLs, ^{1}A^{1}C/^{1}A^{2}C/^{2}A^{1}C/^{2}A^{2}C (section 2.3) and ^{1}A^{1}C/^{1}A^{3}C/^{2}A^{1}C/^{2}A^{3}C (this section, above), photoselection in conditions of acylhydrazone exchange through organocatalysis by aniline failed, as both configurations *E* and *Z* of ^{1}A^{1}C were generated (48% and 52%, respectively), as in the case of the hydrazones (see section 1.3).

2.5. Reversible Metalloselection and Photoselection with the DCL of Acylhydrazones [^{1}A^{1}C, ^{1}A^{3}C, ^{2}A^{1}C, ^{2}A^{3}C]. For completeness, the reversibility of the selection processes investigated has been studied. Starting first from the mixture of *Z*-^{1}A^{1}C and ^{2}A^{3}C obtained via photoselection, heating at 80 °C regenerates the original complete library, with *Z* to *E* thermal-back conversion and acylhydrazone equilibration. Subsequently, the addition of zinc cations and heating gives the same metalloselection as observed previously with simultaneous amplification of the Zn(^{1}A^{3}C)$_2$ and ^{2}A^{1}C agonist constituents.

Conversely, starting from the distribution obtained by metalloselection, decomplexation of Zn(^{1}A^{3}C)$_2$ was achieved by addition of tetrabutylammonium thiocyanate (2 equiv with respect to Zn^{II} ions), which coordinates the zinc cations more

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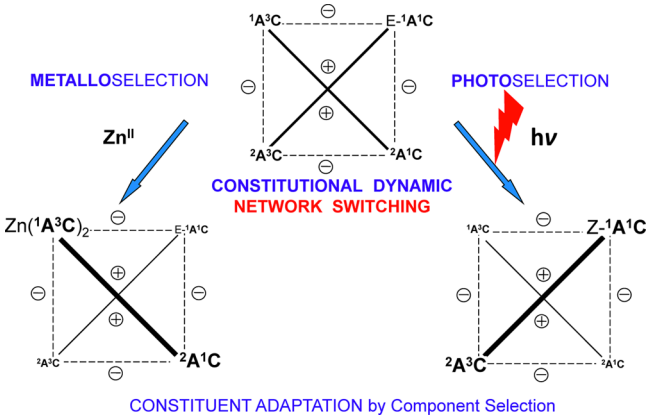
Scheme 5. Weighted Graph Representation of the Square CDN of E-^{1}A^{1}C, ^{1}A^{3}C, ^{2}A^{1}C, and ^{2}A^{3}C Constituents[a]



[a]The adaptation to addition of metal cation, metalloselection, is represented by the selection and amplification of the Zn(^{1}A^{3}C)$_2$ and ^{2}A^{1}C diagonal (left). The adaptation to photoirradiation, photoselection, is represented by the selection and amplification of the Z-^{1}A^{1}C and ^{2}A^{3}C diagonal (right). The diagonals and edges of the square link respectively agonistic (+) and antagonistic (−) constituents. ^{1}A^{3}C is indicated in the form of its complex Zn(^{1}A^{3}C)$_2$.

strongly. The mixture was then irradiated for 4 h at 25 °C in the presence of scandium triflate (0.2 equiv) as catalyst, and an increase of the constituents Z-^{1}A^{1}C and ^{2}A^{3}C on the orthogonal diagonal was observed, yielding the same library distribution as previously obtained by photoselection. Reversibility was also achieved by the addition of potassium hexacyanoferrate (1 equiv with respect to Zn^{II} ions) instead of tetrabutylammonium thiocyanate, with however 10% more hydrolysis.

These results establish the reversibility of the two selection processes, interconverting two different constituent distributions via the intermediate formation of the complete library, and confirm the possibility to switch between metalloselection and photoselection.

2.6. CDN Representation of the Metalloselection and Photoselection Processes. The processes reported herein concern CDLs of four members. They form CDNs that can be represented as square weighted graphs,[7] where vertices correspond to the four constituents while diagonals and edges describe, respectively, agonistic and antagonistic relationships between the members of a set. The relative weights of the vertices and links respond to the application of a chemical effector, metal ions, or of a physical stimulus, light, in an adaptive fashion.

Thus, the set of four acylhydrazones E-^{1}A^{1}C, ^{1}A^{3}C, ^{2}A^{1}C, and ^{2}A^{3}C forms a square CDN responding both to metal cations and light. The comparison of the variation in constituent distribution obtained for metalloselection (Scheme 5, left) and photoselection (Scheme 5, right) on the respective application of metal cations and of light irradiation reveals an up-regulation of the agonists located on the two different diagonals, respectively, [Zn(^{1}A^{3}C)$_2$ and ^{2}A^{1}C] and [Z-^{1}A^{1}C and ^{2}A^{3}C], together with a down-regulation of the corresponding antagonists [E-^{1}A^{1}C and ^{2}A^{3}C] and [^{1}A^{3}C and ^{2}A^{1}C]. This behavior corresponds to the operation of an orthogonal network switching (see also ref 6d) in response to two different agents by constitutional selection (Scheme 5).

In the case of the four hydrazones studied above, only metalloselection on addition of zinc triflate could be obtained (section 1.2). The corresponding square CDN displays an up-regulation of Zn(^{1}A^{2}B)$_2$ together with its agonist ^{2}A^{1}B and a down-regulation of the two antagonists ^{1}A^{1}B and ^{2}A^{2}B, as shown in Scheme 2.

CONCLUSIONS

The results described above achieve the modulation of a CDL by two different agents, a further step in the design and operation of complex adaptive networks. They present a number of features that lead to the following conclusions: (1) CDLs of hydrazones and acylhydrazones have been generated through component exchange reactions implementing different types of catalytic processes involving metal ions, organocatalyst, and strain activation. (2) The CDL of the four acylhydrazones E-^{1}A^{1}C, ^{1}A^{3}C, ^{2}A^{1}C, and ^{2}A^{3}C undergoes adaptation by orthogonal constitutional response to two external agents: the addition of metallic cation and light irradiation (Schemes 4 and 5). *Metalloselection* is observed on addition of zinc cations which drive the amplification of Zn(^{1}A^{3}C)$_2$ by selection of the fittest constituent ^{1}A^{3}C, with simultaneous reorganization increasing the amount of agonist ^{2}A^{1}C and decreasing the amounts of the antagonists ^{1}A^{1}C and ^{2}A^{3}C. *Photoselection* proceeds by irradiation of the system, leading to photoisomerization of E-^{1}A^{1}C into Z-^{1}A^{1}C with amplification of the latter, up-regulation of ^{2}A^{3}C and down-regulation of ^{1}A^{3}C and ^{2}A^{1}C. (3) The adaptation processes are reversible via the intermediate restoration of the full library. (4) This CDL forms a square CDN that displays network switching as it undergoes orthogonal adaptation in response to metallo- and photoselection. (5) The overall distribution of constituents within a CDN and its regulation may be considered as an information storage and processing system depending on and characteristic of the agent(s) acting on it. The information can be erased via the reversibility of the process. Moreover, one may note that, on removal of the effector/stimulus, the system enters an out-of-equilibrium state where it keeps memory of the encoded information, thus ensuring fast recall on renewed presentation of the agent. Such work is being pursued in this laboratory.

ASSOCIATED CONTENT

Supporting Information

Synthesis and analysis of compounds, ^{1}H NMR spectra, and X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.. CCDC 1006337−1006347 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interest.

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