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Protonic and Temperature Modulation of Constituent Expression by Component Selection in a Dynamic Combinatorial Library of Imines

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Abstract: The constitutional recomposition of a dynamic library of imines displays a complex behavior under the effect of two parameters, acidity and temperature. A qualitative analysis of the quantitative data is presented. The results illustrate the response of such a dynamic system to a physical stimulus (temperature) and a chemical effector (H^+), thus demonstrating its adaptive behavior under the pressure of external factors. They also point to the possibility of modulating a given functional property (optical, electronic, ionic) by constitutional recomposition induced by a specific trigger. Such features are of great interest for the development of stimuli-responsive, functional dynamic materials.

Keywords: acidity · dynamic combinatorial chemistry · imines · molecular diversity · stimuli-responsive systems

Introduction

Constitutional dynamic chemistry (CDC) deals with the generation of both molecular and supramolecular dynamic libraries of constituents by reversible connection between a set of basic building blocks.[1] It has been implemented specifically on the molecular level in the actively developing area of dynamic (covalent) combinatorial chemistry (DCC) based on recombination of molecular components linked through reversible covalent bonds.[2] At thermodynamic equilibrium, these libraries may contain all possible combinations of components in a well-defined ratio, although they may also just remain virtual depending on conditions.[2b] Such systems can be instructed by the presence of molecular targets, through an internal organization (self-recognition) or by means of an external one (species binding). As a result, the equilibrium is shifted to the over-expression of selected products by target recognition-directed self-assembly. Numerous investigations on DCC have been pursued by different groups over the last few years, showing in particular the wide potentialities of the seminal concept in various fields such as drug discovery;[2f,3] self-assembly of inorganic architectures, receptor generation, and substrate binding;[3–5] and catalyst screening.[6] However, CDC and, therefore, its molecular domain DCC are not limited to receptor generation for a substrate or substrate assembly by a receptor (RACS: receptor-assisted compound synthesis[2h]). CDC can also be applied to materials science, leading to the generation of dynamic materials of molecular or supramolecular nature,[1,2b,7] such as, in particular, dynamic polymers ("dynamers"), the monomeric components of which are connected by reversible covalent[8] or noncovalent[9] bonds.

The discrimination between the constituents of dynamic combinatorial libraries (DCLs) has centered on the utilization of molecular recognition as the driving force, due in particular to application in drug discovery. In the course of our investigations toward the design of adaptative chemical systems[1,2b,7b] that respond to environmental parameters, we have become interested in the potential offered by the possibility to drive constituent reorganization and amplification/selection, by means of component exchange in a DCL, by external physical (temperature, pressure, electric field) or chemical (protons, ions, molecules) triggers. Changes in the composition of the constituents of a DCL represent an adaptation of the dynamic system in response to the perturbation. Such effects are of special interest in the perspective of developing dynamic materials responding to environmental effectors. We have recently described the evolution of constitutional dynamic systems driven by the coordination of metal ions[10] or by a phase change, such as the formation of a stable hydrogel[11a] or of a solid.[11b]

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A DCL may be characterized by three main parameters:

1) The *conversion*, that is, the total amount of constituents generated with respect to the free components.
2) The *composition*, that is, the distribution or relative amounts of the different constituents that also represents the selectivity of the system.
3) The product of conversion and selectivity may be considered as defining the *expression* of a given constituent.[12]

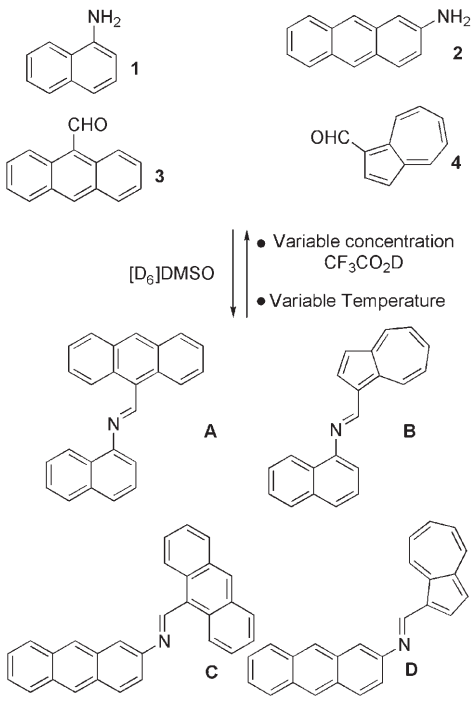
Changes in expression of the different constituents as a factor of external parameters represent an adaptation of the system to environmental conditions, such as medium (solvent), presence of interacting species (protons, metal ions, substrate molecules, etc.) or physical factors (temperature, pressure, electric or magnetic fields, etc.).

We report here a study of the *simultaneous* modulation of these three parameters of a DCL by both protonation and temperature, through expression of different constituents, by means of component selection driven by chemical and/or physical stimuli. It implements sets of imine constituents, as imine formation from amino and carbonyl groups represents a reversible covalent reaction playing a widespread role in chemical, biological, and material sciences.[2–4,8–11]

Imine formation has been very extensively studied (see below) as have multiple equilibria. The aim of the present investigation is to describe the response of sets of compounds, linked and interconverting through multiple equilibria to effectors by expression of different constituents, as an illustration of the behavior of complex constitutionally dynamic chemical systems.

Results

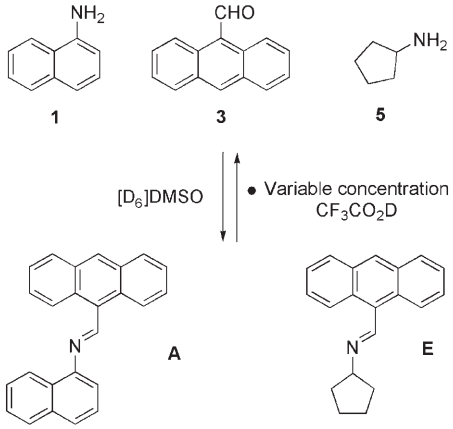
A dynamic set of aromatic imines **A**–**D** was generated from a stoechiometric mixture of 1-naphtylamine (**1**), 2-aminoanthracene (**2**), 9-anthracene carboxaldehyde (**3**), and 1-azulenecarboxaldehyde (**4**; Scheme 1). These components were chosen in view of the different emission properties of the imine products formed, so as to provide a dynamic emissive library presenting modulation of a physical property, that is, light emission, and not just library composition.



Scheme 1. Dynamic library of the four components **1**–**4** and the four constituents **A**–**D**. The study was performed using a concentration of 5.12×10^{-2} M for each component **1**–**4**.

In addition, to highlight the role of the basicity of the amines in such DCLs of imines, a simpler three-component set has been studied; it involves a stoichiometric mixture of an aromatic amine **1**, an aliphatic amine, cyclopentylamine (**5**) and the aldehyde **3**, generating the imines **A** and **E** (Scheme 2).

Generation of the dynamic library of imines A–D: The (partial) condensation of the components **1**–**4** (each 5×10^{-2} M in [D_6]DMSO; Scheme 1) into the four possible imine products



Scheme 2. Dynamic library formed by the three components **1**, **3**, **5** and the two constituents **A**, **E**.

Abstract in French: *Une bibliothèque combinatoire dynamique d'imines présente un comportement complexe sous l'action de deux paramètres: concentration en protons et température. Une analyse qualitative des données quantitatives est présentée. Les résultats illustrent les possibilités offertes par les changements de constitution en réponse à des stimuli physiques (T) ou chimiques (H^+), et ils démontrent l'adaptation de tels systèmes sous la pression de paramètres environnementaux. Cette modulation de la constitution permet également d'envisager la modulation d'une propriété fonctionnelle donnée (optique, électronique, ionique) par variation des stimuli imposés. Une telle approche présente un intérêt particulier pour le développement de matériaux dynamiques fonctionnels adaptatifs.*

A–**D** and the distribution of all these compounds were followed by ^{1}H NMR spectroscopy as a function of temperature and proton (CF_3CO_2D) concentration (Figure 1). The

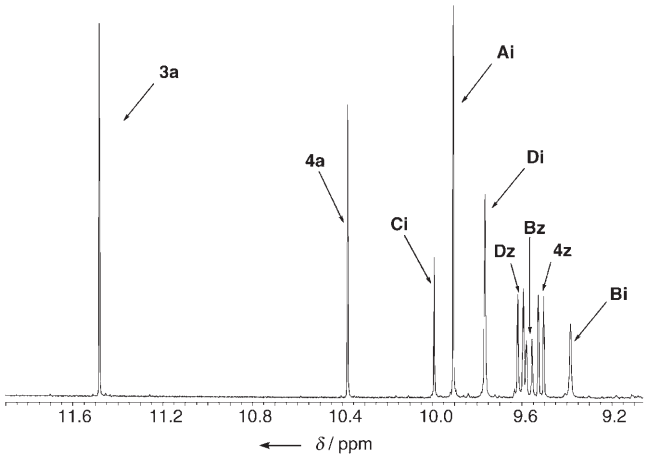


Figure 1. 400 MHz proton NMR spectrum of the DCL generated from components **1**–**4** in [D_6]DMSO at 40 °C, for $[CF_3CO_2D] = 2.07\times10^{-1}$ M. The signals marked **3a** and **4a** correspond to the aldehyde signals of compounds **3** and **4**, respectively. The signals marked **Ai**, **Bi**, **Ci**, and **Di** represent the imine signals for compounds **A**, **B**, **C**, and **D**, respectively. The signals marked **4z**, **Bz**, and **Dz** are the H(2) signals of the azulene group for compounds **4**, **B**, and **D**, respectively.

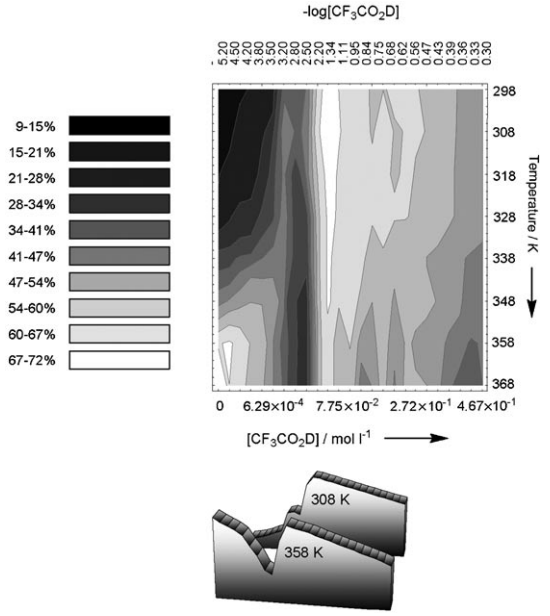


Figure 2. Top: Conversion surface for the 4/4 DCL (**1**–**4**, **A**–**D**) as a function of temperature and CF_3CO_2D concentration. The following concentrations of CF_3CO_2D were used: $c = 0$; 6.29×10^{-6}; 3.10×10^{-5}; 6.29×10^{-5}; 1.57×10^{-4}; 3.14×10^{-4}; 6.29×10^{-4}; 1.57×10^{-3}; 3.15×10^{-3}; 6.29×10^{-3}; 4.50×10^{-2}; 7.75×10^{-2}; 1.10×10^{-1}; 1.42×10^{-1}; 1.75×10^{-1}; 2.07×10^{-1}; 2.39×10^{-1}; 2.72×10^{-1}; 3.00×10^{-1}; 3.37×10^{-1}; 3.69×10^{-1}; 4.02×10^{-1}; 4.34×10^{-1}; 4.67×10^{-1}; 4.99×10^{-1} M. Bottom: Cross sections at 308 K and 358 K.

constituents **A**–**D** were also synthesized separately and their different well-resolved and easily identifiable ^{1}H NMR signals provided an unambiguous assignement for the products in the mixture. This allowed an accurate analysis of the composition.

At first, to establish the reversibility of the overall process in the conditions used, we performed two kinetic experiments at two concentrations of acid CF_3CO_2D: 6.29×10^{-5} M and 7.75×10^{-2} M. At the lowest concentration, a stable distribution pattern of the products ($\mathbf{A} < \mathbf{C} < \mathbf{D} \ll \mathbf{B}$) was established in less than 24 h at 298 K. Heating the reaction mixture to 338 K in the NMR probe gave a change in the distribution pattern which stabilized after three hours to $\mathbf{A} \ll \mathbf{D} < \mathbf{B} < \mathbf{C}$. Cooling back to 298 K, the equilibrium was reached after 48 h, showing a composition close to that obtained before heating. Increasing the acid concentration provided the same observation regarding the reversibility of the system, but with a faster rate and different distribution patterns: $\mathbf{C} \ll \mathbf{D} < \mathbf{A} < \mathbf{B}$ at 298 K and $\mathbf{B} \sim \mathbf{C} \sim \mathbf{D} < \mathbf{A}$ at 338 K.[13]

Temperature and protonic modulation of global conversion in the DCL (1–4, A–D): We first studied in detail the global conversion *C* of the starting materials **1**–**4** into the four imines **A**–**D** (Scheme 1).[13] Determination of the amounts of the four imine constituents **A**–**D** of the DCL yielded the conversion surface of the set as a contour map according to the variations of temperature (every 10 degrees from 298 K to 368 K)[14] and CF_3CO_2D concentration (25 different values between 0 M and 4.99×10^{-1} M; Figure 2).

The remaining compounds are unconverted starting materials. It is clearly apparent that while the system has only a small number of components, its behavior is nevertheless already rather complex.

One may distinguish five main regions in the conversion diagram as a function of temperature (*T*) and acidity [H^+]:

1) A low *C* (10–20 %) region at low *T* and low [H^+]; it may be considered as a "virtual"[2b] domain, in which the potential imine products are only weakly expressed.
2) As *T* is increased from 298 K to 368 K at low [H^+], *C* increases dramatically to a high *C* (70 %) region.
3) A decrease of *C* is observed at all *T* as [H^+] is progressively increased, generating a valley.
4) From the valley a ridge of high *C* (60–70 %) is reached at all *T* as [H^+] is further increased (7.75×10^{-2} M < $[CF_3CO_2D] < 1.10\times10^{-1}$ M).
5) Finally, further increase in [H^+] results in an extended region of progressive but moderate decrease in *C* to about 50 % at 298 K and 40 % at 358 K for $[CF_3CO_2D] = 4.67\times10^{-1}$ M ; this region also corresponds to acidities higher than stoichiometry with respect to the amines.

The two cuts of the conversion surface at 308 K and at 358 K as a function of [H^+] clearly show these evolutions (Figure 2). Two other main trends are that whereas *C* increases with *T* at low [H^+], it decreases as *T* increases at higher [H^+] values once the valley has been reached

($[CF_3CO_2D] = 7.75 \times 10^{-2}$ M) and beyond. One also notes that in domain 5, deshielding of the imine proton signals and changes in fluorescence indicate that protonation of the imines takes place.

Temperature and protonic modulation of constituent expression in the 4/4 DCL (1–4, A–D): After examining reversibility and conversion, it remained to study the selectivity of the system in terms of relative amounts of imine products. It underlies the most significant feature of the DCL, the expression of its different imine constituents.[12] The hypersurface representing the expression space, defined by the relative abundance of the imines **A**–**D** multiplied by the conversion, as a function of the temperature and the acidity (CF_3CO_2D concentration), is represented in Figure 3.

It represents the expression of the individual imines by the system in specific (T, $[H^+]$) conditions. This three-dimensional diagram displays the complex behavior of the system and gives an overview of the expression domains obtained as a function of the two parameters. The main features of Figure 3 may be summarized as follows.

1) The predominant imine species display very marked constitutional variation over the whole hypersurface.
2) The three domains of high conversion (Figure 2) present markedly different expression. Whereas **C** and **A** predominate in the localized low $[H^+]$/high T region, **B** and then **A** predominate on the central ridge as T increases, and finally **A** and then **D** predominate over the whole T range at moderate and high $[H^+]$ respectively.
3) Because of the components constituting the imine products, that is, **A** (**1**,**3**), **B** (**1**,**4**), **C** (**2**,**3**), **D** (**2**,**4**), the expressions of the constitutionally unrelated pairs of products (no common component), that is, **A** and **D** on one hand and **B** and **C** on the other, are independent. However, the constitutionally related **A** and **C** interchange in the low $[H^+]$/high T region, and similarly **A** and **B** compete along the central ridge of high conversion. Furthermore,

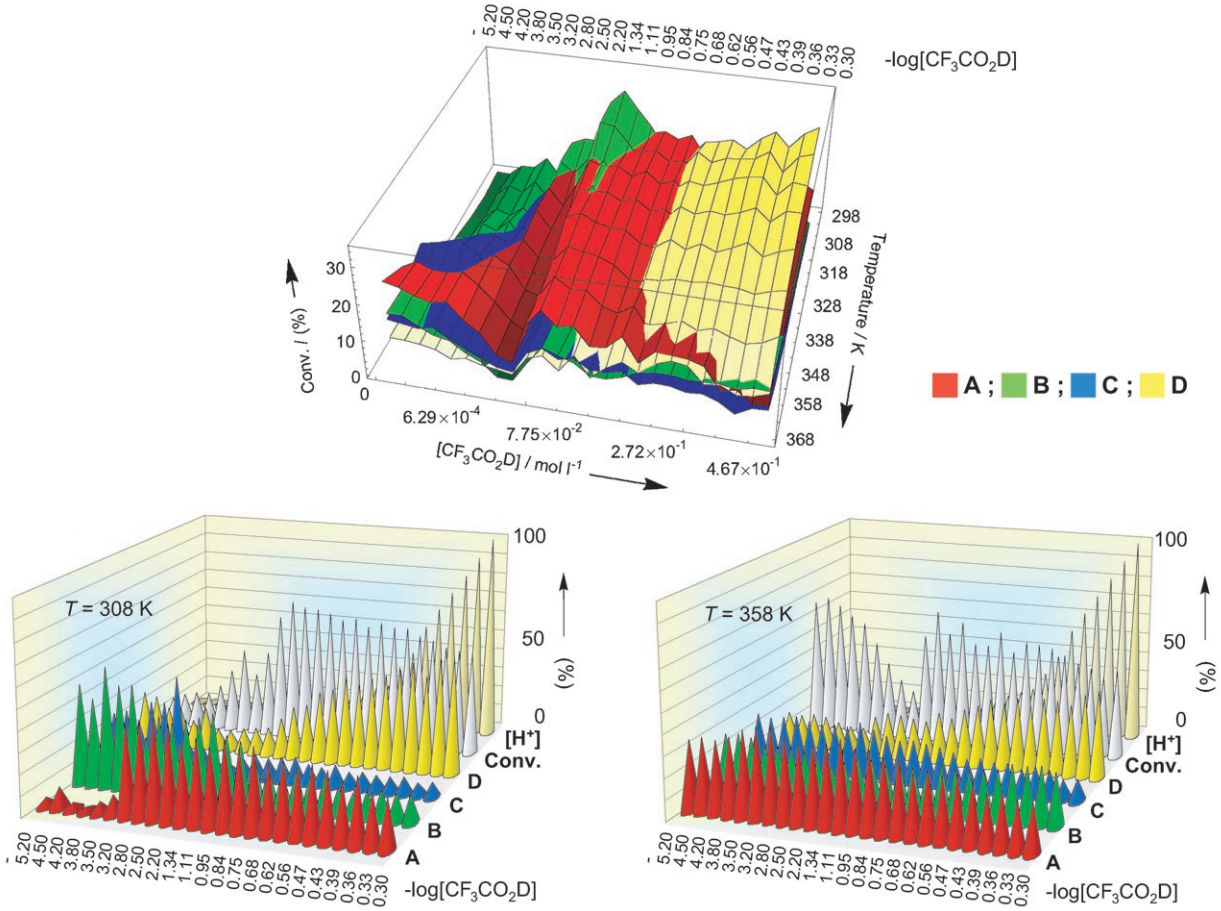


Figure 3. Top: Hypersurface for the expression of the four constituents **A**–**D** of the 4/4 DCL (**1**–**4**; **A**–**D**) as a function of temperature and CF_3CO_2D concentration.[12] Data were recorded after 12 h equilibration. Red surface: compound **A** and its protonated form $\mathbf{AH^+}$; green surface: **B** and $\mathbf{BH^+}$; blue surface: **C** and $\mathbf{CH^+}$; yellow surface: **D** and $\mathbf{DH^+}$. Bottom: Distributions of imines **A**–**D** at two temperatures as a function of acidity $[H^+]$. The following concentrations of CF_3CO_2D were used: $c = 0$; 6.29×10^{-6}; 3.10×10^{-5}; 6.29×10^{-5}; 1.57×10^{-4}; 3.14×10^{-4}; 6.29×10^{-4}; 1.57×10^{-3}; 3.15×10^{-3}; 6.29×10^{-3}; 4.50×10^{-2}; 7.75×10^{-2}; 1.10×10^{-1}; 1.42×10^{-1}; 1.75×10^{-1}; 2.07×10^{-1}; 2.39×10^{-1}; 2.72×10^{-1}; 3.00×10^{-1}; 3.37×10^{-1}; 3.69×10^{-1}; 4.02×10^{-1}; 4.34×10^{-1}; 4.67×10^{-1}; 4.99×10^{-1} M.

A and **D** share the extended high conversion domain and therefore **B** and **C** are depressed in this region. However, such competition is not exclusive, as higher expression may also incorporate higher conversion, that is, higher formation from the pool of unreacted compounds.

Protonic modulation of the composition of the 3/2 DCL (1, 3, 5, A, E): Considering the highly complex behavior of the above system of four starting components and four resulting constituents, we also investigated a simpler system that might reveal some directing features of the processes involved.

To highlight the effect of amine basicity,[15] we studied a three-component set involving two amines of markedly different basicities, the aromatic **1** and the aliphatic cyclopentylamine (**5**), which form the imines **A** and **E** with aldehyde **3** (Scheme 2). Figure 4 illustrates the variation in conversion and composition of the CDL at 298 K as a function of CF_3CO_2D concentration.

The effect of acidity on the system has been determined by analysis of the proton NMR spectra as illustrated in Figure 4, which also shows a graphical presentation of the results. It is clearly seen that whereas imine **E**, formed from the more basic aliphatic amine **5**, predominates with high conversion at low $[H^+]$, increasing the acidity leads to a strong decrease and finally disappearance of **E**, shifting the library towards the expression of imine **A**.

This evolution may be attributed to the preferential protonation of **5**, which displaces it from the imine **E**, thus allowing the formation of the imine **A** of the appreciably less basic aromatic amine **1**. On further increase of the acidity, **A** also decreases as **1** is eventually protonated.

This shift from imine of an aliphatic amine **E** towards imine of an aromatic amine **A** on protonation of the corresponding amines is reminiscent of a similar effect caused by coordination of zinc ions to related amines.[10b]

To further analyze the behavior of the system, the formation of imine **A** was also studied separately as a function of acidity at room temperature, yielding a bell-shaped curve (Figure 5).

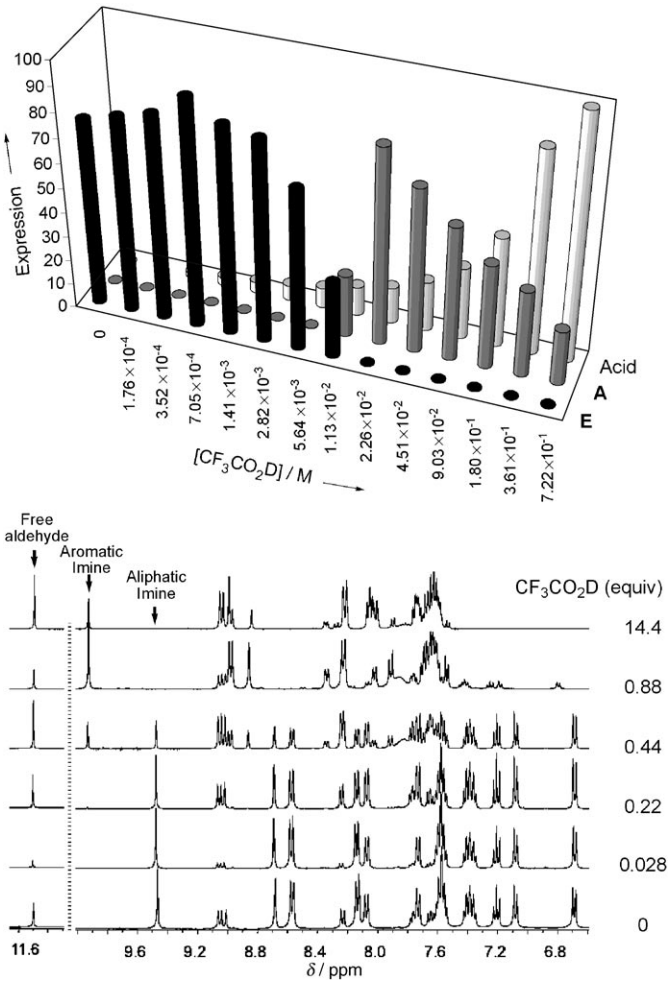


Figure 4. 3/2 DCL (**1**, **3**, **5**; **A**, **E**). Top: Expression of constituents **A** and **E** as a function of $[H^+]$. Bottom: 400 MHz proton NMR spectra as a function of added acid CF_3 COOD.

$$R{-}NH_2 + R'\text{-}CHO \rightleftharpoons R{-}NH{-}CHOH{-}R' \quad (1)$$

Elimination of water from the hemiaminal intermediate [Eq. (2)]

Discussion

The expression of the imine constituents of a DCL may be expected to result from a superposition of acidity and protonation of the different species on one hand and of the temperature on the other hand, on the two steps of the overall imine formation process:[15]

Addition of the amine to the carbonyl group [Eq. (1)]

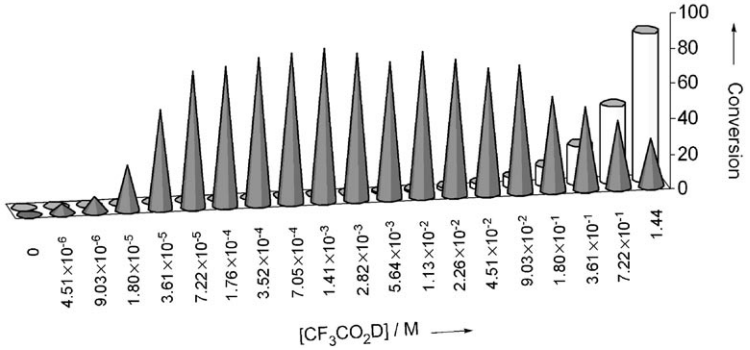


Figure 5. Bell-shaped curve for the formation of imine **A** from amine **1** and aldehyde **3** as a function of acid concentration $[H^+]$ at 298 K.

$$R{-}NH{-}CHOH{-}R' \rightleftharpoons R{-}N{=}CH{-}R' + H_2O \qquad (2)$$

One may attempt to rationalize the behavior of the systems in terms of the effects of T and $[H^+]$ on these two steps; however, note that in addition, transimination by direct reaction of an amine with an imine may occur, as in the case of scandium(III)-catalyzed exchange of the amine component of imines.[16]

Considering first the simplest case (**1**, **3**, **A**), the bell-shaped curve, for the formation of the single imine **A** (Figure 5) may be considered to result from the effect of acidity on the equilibria in Equations (1) and (2): decrease in conversion being due to decreased water elimination at low $[H^+]$ [Eq. (2)], and to increased amine protonation at high $[H^+]$ [Eq. (1)], following the general scheme for the effect of acidity on imine formation.[15]

In the competitive formation of imines **A** and **E** in the (**1**, **3**, **5**; **A**, **E**) 3/2 DCL, the expression of **A** and **E** is clearly determined by the very different basicities of the amines **1** and **5**.

Coming to the behavior of the more complex 4/4 DCL (**1**–**4**; **A**–**D**), the following remarks may be made.

1) At low $[H^+]$ (left of the central ridge, Figure 2), the limiting step is water elimination[17] and increasing T increases imine formation.
2) At higher $[H^+]$, up the ridge and above, acid catalysis and temperature effects on either or both steps increase imine formation, reaching maxima of conversion.
3) At the highest acidities studied, conversion to imines decreases due to protonation of the amines, driving the equilibria towards the starting components. The analysis of the behavior of the system is further complicated by the fact that the imine products are also protonated, at the higher acidities.

The complex hypersurface representing the constituent expression (Figure 3) results from the interpenetration of the formation surfaces of the four imines **A**–**D**. A cross section around room temperature as a function of acidity contains the bell-shaped curves for the four imines **A**–**D**, yielding the variation of the distributions of **A**–**D** with acidity $[H^+]$ (Figure 6).

The connectivities between the four imines **A**–**D** may be represented in a square graph (Scheme 3): constituents directly related through one of their components share an edge and may be considered as antagonists (increasing one, decreases the others), whereas constituents with no common component are located on the diagonals and behave as agonists (increasing one, increases the other).

Conclusion

The aim of the present study was to describe the complex behavior displayed by the constitutional recomposition of a dynamic library under the effect of two parameters, acidity and temperature.

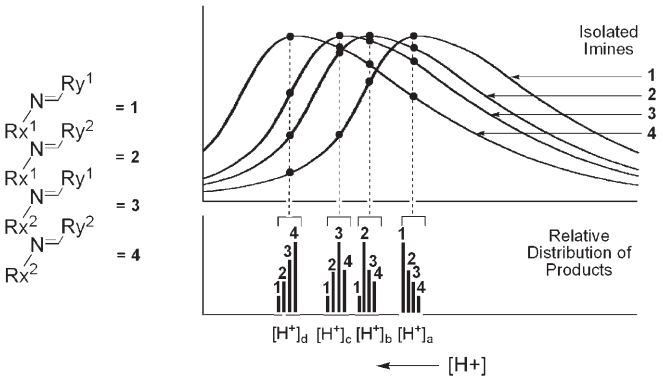
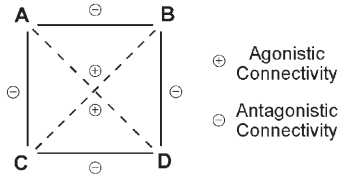


Figure 6. Cross section of the hypersurface of Figure 3 showing the bell-shaped curves and the distribution of the constituent imines **A**–**E** as a function of $[H^+]$ at 298 K.



Scheme 3. Representation of the connectivities between the constituents **A**–**D** of the 4/4 DCL. Antagonists are connected by edges and agonists by the diagonals (see text).

The complexity of the effects does not allow a detailed quantitative explanation in terms of structure and mechanism.[15] However, the results illustrate the response of such a dynamic system to a physical (T) stimulus and a chemical effector ($[H^+]$), thus demonstrating the adaptive behavior of the system under the pressure of external factors. They also point to the possibility of modulating a given functional property (optical, electronic, ionic) by constitutional recomposition induced by a specific trigger.[17] Such features are of great interest for the development of stimuli-responsive, functional dynamic materials.[7]

Experimental Section

General aspects: All reagents and solvents were purchased at the highest commercial quality and used without further purification unless otherwise noted. Yields refer to purified spectroscopically (^{1}H NMR) homogeneous materials. ^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrometer. The spectra were internally referenced to the residual proton solvent signal. In the ^{1}H NMR assignments, the chemical shifts are given in ppm. The coupling constants J are listed in Hz. The following notation is used for the ^{1}H NMR spectral splitting patterns: singlet (s), doublet (d), triplet (t), multiplet (m), broad (br). The temperatures that are given for the kinetic and thermodynamic data were directly measured and regulated in the NMR probe using a thermocouple. Electrospray (ESI and ESI-TOF) studies were performed on a Bruker Micro TOF mass spectrometer (sample solutions were introduced into the mass spectrometer source with a syringe pump with a flow rate of 160 $\mu L\,min^{-1}$). Melting points (m.p.) were recorded on a Kofler Heizblock and on a Büchi Melting Point B-540 apparatus and are uncorrected. Microanalyses

were performed by the Service de Microanalyse, Institut de Chimie, Université Louis Pasteur.

General procedures for the synthesis of isolated imines: Equimolar amounts of amine and aldehyde were solubilized or suspended in ethanol at a concentration of 0.1 M and the reaction mixtures were refluxed overnight under vigorous stirring. The solutions were then either evaporated to dryness and the crude residues were purified by flash chromatography or, after cooling of the solutions to 0 °C, the precipitates formed from the reaction mixture were filtered and washed with cold ethanol and the compounds crystallized or precipitated from AcOEt/hexane mixtures.

General procedure for crossover experiments and determination of thermodynamic and kinetic data: A typical protocol is realized by the preparation in a NMR tube of a fresh solution of the compounds to exchange in [D_6]DMSO (0.6 mL, 5.12×10^{-2} M in each amine and aldehyde) at a given concentration of CF_3CO_2D. The NMR tubes were topped with teflon caps to keep a constant concentration and to avoid water evaporation upon heating. The mixtures were equilibrated for 12 h at a given temperature and ^{1}H NMR spectra were recorded at the same temperature by direct heating inside the NMR probe.

Azulene-1-carbaldehyde (4): The product was synthesized using the method described by Hansen et al.[20] ^{1}H NMR ([D_6]DMSO): $\delta=7.47$ (d, $^3J=4.1$ Hz, 1H), 7.68–7.80 (m, 2H), 8.00 (t, $^3J=9.9$ Hz, 1H), 8.36 (d, $^3J=4.1$ Hz, 1H), 8.72 (d, $^3J=9.9$ Hz, 1H), 9.52 (d, $^3J=9.6$ Hz, 1H), 10.37 ppm (s, 1H)); ^{13}C NMR ([D_6]DMSO): $\delta=119.65$, 126.00, 129.35, 130.05, 137.25, 140.25, 140.45, 141.15, 141.30, 145.85, 186.65 ppm; MS (electrospray): *m*/*z* (%): 157.1 (100) $[M+H]^+$; HRMS: calcd 157.0648; found: 157.0648.

(*E*)-*N*-(Anthracen-10-ylmethylene)naphthalen-1-amine (A): The product was synthesized by using the general method and obtained as a bright yellow powder (yield 85%). M.p. 151–152 °C; elemental analysis calcd (%) for $C_{20}H_{19}N$: C 90.60, H 5.17; N 4.23; found: C 90.23, H 5.23, N 4.05; ^{1}H NMR ($CDCl_3$): $\delta=7.32$ (d, $^3J=7.3$ Hz, 1H), 7.55–7.66 (m, 8H), 7.85 (d, $^3J=7.8$ Hz, 1H), 7.95 (d, $^3J=8.8$ Hz, 1H), 8.12 (d, $^3J=8.3$ Hz, 2H), 8.47 (d, $^3J=7.3$ Hz, 1H), 8.65 (s, 1H), 8.97 (d, $^3J=8.8$ Hz, 2H), 9.86 ppm (s, 1H); ^{1}H NMR ([D_6]DMSO): $\delta=7.50$–7.77 (m, 7H), 7.90 (d, $^3J=8.2$ Hz, 1H), 7.99–8.04 (m, 1H), 8.21 (m, 2H), 8.31 (m, 1H), 8.86 (s, 1H), 8.97 (d, $^3J=8.2$ Hz, 2H), 9.93 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta=112.95$, 124.25, 124.85, 125.45, 126.00, 126.15, 126.20, 126.50, 127.15, 127.40, 127.70, 128.80, 129.10, 130.90, 131.00, 131.35, 134.05, 150.30, 159.95 ppm; MS (electrospray): *m*/*z* (%): 332.1 (100) $[M+H]^+$.

(*E*)-*N*-(Azulen-1-ylmethylene)naphthalen-1-amine (B): The product was synthesized by using the general method and obtained as a brown-purple oil (yield 72%). ^{1}H NMR ([D_6]DMSO): $\delta=7.31$ (d, $^3J=6.8$ Hz, 1H), 7.48–7.63 (m, 6H), 7.78 (d, $^3J=8.2$ Hz, 1H), 7.91–7.96 (m, 2H), 8.44–8.46 (m, 1H), 8.52 (d, $^3J=4.1$ Hz, 1H), 8.62 (d, $^3J=9.2$ Hz, 1H), 9.22 (s, 1H), 9.62 ppm (d, $^3J=9.6$ Hz, 1H); ^{13}C NMR ([D_6]DMSO$_{d6}$): $\delta=107.85$, 113.20, 119.70, 124.05, 124.20, 125.20, 125.85, 126.05, 126.75, 126.95, 127.25, 127.40, 128.05, 134.10, 136.90, 139.05, 139.30, 140.35, 144.90, 150.25, 155.85 ppm; MS (electrospray): *m*/*z* (%): 282.1 (100) $[M+H]^+$; HRMS: calcd 282.1277; found: 282.1299.

(*E*)-*N*-(Anthracen-10-ylmethylene)anthracen-2-amine (C): The product was synthesized by using the general method and obtained as a green powder (yield 88%). M.p. 231–232 °C; ^{1}H NMR ([D_6]DMSO): $\delta=7.55$–7.56 (m, 2H), 7.62–7.72 (m, 4H), 7.84 (d, $^3J=8.6$ Hz, 1H), 8.13 (l, 3H), 8.22–8.27 (m, 3H), 8.68 (d, $^3J=9.2$ Hz, 2H), 8.86 (s, 1H), 8.99 (d, $^3J=8.2$ Hz, 2H), 10.03 ppm (s, 1H); ^{13}C NMR ([D_6]DMSO): $\delta=118.00$, 122.60, 125.50, 125.95, 126.15, 126.30, 126.60, 126.70, 127.40, 128.00, 128.35, 128.65, 129.50, 129.85, 130.55, 130.65, 131.25, 131.35, 131.50, 132.15, 132.35, 149.60, 160.45 ppm; MS (electrospray): *m*/*z* (%): 382.2 (100) $[M+H]^+$; HRMS: calcd 382.1590; found: 382.1614.

(*E*)-*N*-(Azulen-1-ylmethylene)anthracen-2-amine (D): The product was synthesized by using the general method and obtained as a brown-purple powder (yield 80%). M.p. 124–126 °C; ^{1}H NMR ([D_6]DMSO): $\delta=7.48$–7.59 (m, 6H), 7.62–7.76 (m, 2H), 8.05–8.10 (m, 1H), 8.15 (d, $^3J=8.9$ Hz, 1H), 8.57 (d, $^3J=7.8$ Hz, 2H), 8.74 (d, $^3J=9.6$ Hz, 1H), 9.38 (s, 2H), 9.57 ppm (d, $^3J=9.9$ Hz, 1H); ^{13}C NMR ([D_6]DMSO): $\delta=117.30$, 119.65, 119.85, 122.90, 125.60, 125.85, 126.00, 126.15, 126.40, 127.20, 128.25, 128.60, 129.40, 129.60, 130.05, 130.25, 131.15, 132.10, 132.65, 136.85, 137.25, 138.75, 139.00, 144.95, 155.41 ppm; MS (electrospray): *m*/*z* (%): 332.1 (100) $[M+H]^+$; HRMS: calcd 332.1438; found: 382.1460.

(*E*)-*N*-(Anthracen-10-ylmethylene)cyclopentylamine (E): The product was synthesized by using the general method and obtained as a yellow, fluffy powder (yield 92%). M.p. 95–96 °C; elemental analysis calcd (%) for $C_{20}H_{19}N$: C 87.87, H 7.01, N 5.12; found: C 87.28, H 7.07, N 5.18; ^{1}H NMR ($CDCl_3$): $\delta=1.80$ (l, 2H), 2.00 (l, 4H), 2.13 (l, 2H), 4.15 (qt, $^3J=5.9$ Hz, 1H), 7.53 (m, 4H), 8.05 (d, $^3J=8.3$ Hz, 2H), 8.49 (d, $^3J=8.3$ Hz, 2H), 8.50 (s, 1H), 9.43 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta=24.95$, 34.90, 73.35, 124.85, 125.20, 126.45, 128.70, 128.85, 129.90, 131.35, 157.55, 162.00 ppm; MS (electrospray): *m*/*z* (%): 274.15 (100) $[M+H]^+$.

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[13] Another complementary experiment performed at $[CF_3CO_2D] = 2.72\times10^{-1}$ M, involved a sequence of four heating (358 K, 24 h)/cooling (298 K, 24 h) cycles and showed no changes in the distribution of products for the same temperature.

[14] The system was heated up to 428 K, but above 368 K, unassigned supplementary signals were observed, so that the study was limited to the 298–368 K range.

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