Constitutional Dynamics

Generation of Dynamic Constitutional Diversity and Driven Evolution in Helical Molecular Strands under Lewis Acid Catalyzed Component Exchange**

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Constitutional dynamic chemistry (CDC)[1] rests on the implementation of dynamic features that act on the constitution of molecular[2] as well as supramolecular[3] entities

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through reversible covalent bonds and noncovalent interactions, respectively. Dynamic constitutional diversity is generated by exchange and recombination of components, as expressed in particular by the recently developed dynamic combinatorial chemistry.[4] CDC operates in the self-assembly[5] of well-defined molecular or supramolecular species which is driven by molecular information and recognition processes.

Control of the folding of molecular strands has been the subject of intense recent activity[6] in view of its significance in both chemistry and biology. In particular, the generation of helical species[6–8] may be enforced through the implementation of specific helicity codons based on nonbonded interactions in polyheterocyclic strands[7] or on hydrogen-bonding subunits.[8] The self-assembly of helical strands by formation of reversible hydrazone-type bonds between suitably designed hydrazino and carbonyl components[9,10] gives, in principle, access to dynamic libraries of molecular helices.

We report here a system that brings together the three major features mentioned above: constitutional dynamics, self-assembly, and control of helical folding.

The generation of dynamic constitutional diversity for both biological and materials science purposes depends on the availability of suitable chemical connections that are reversible in the desired conditions. The C=N unit, which is present in imines, hydrazones, and oximes, in principle offers highly attractive potentialities to CDC, provided that fast and efficient reversibility in organic solvents is achieved. Zinc(II) ions are known to catalyze transimination of Schiff bases[11] and have been found in our research group to accelerate component exchange in polyimine materials.[12] We now describe the efficient Lewis acid catalyzed exchange of hydrazones and apply the results to the generation of a constitutional dynamic library of helical strands incorporating hydrazone bonds that is capable of assembling, dissociating, and exchanging components. Moreover, we demonstrate that these libraries can undergo driven evolution in the presence of suitable metal ions to express [2×2] grid-type metal complexes preferentially from the mixture of helices. These processes are illustrated schematically in Figure 1.[13]

The condensation of pyrimidine-derived difunctional hydrazine and carbaldehyde building blocks leads to helicity-encoded oligomeric[9a] and polymeric[9b] molecular strands. These strands have been found to resist many attempts to perform component exchange,[9b] thus indicating their high stability even at elevated temperature and/or in the presence of acid. As a model system for the exploration of potential exchange catalysts, cross-over experiments between the dihydrazone compound **A** and the dihydrazine **B** in chloroform at 60 °C were performed first (Figure 2). Only 7 % of **A** was consumed after 48 h in these conditions without catalyst and slow degradation of constituents of the mixture had taken place. Extensive decomposition into unidentified compounds other than **C**–**E** occurred under acid catalysis (20 mol % CF_3CO_2H). In contrast, addition of 20 mol % $Zn(BF_4)_2 \cdot 8H_2O$ led to complete exchange with a half-life of 10 h, without observable degradation. The statistical distribution of the products at equilibrium indicates the nonspecific interaction of the Zn^{II} ions with the different compounds and the isoenergetic nature of the library.[4a] As in the case of

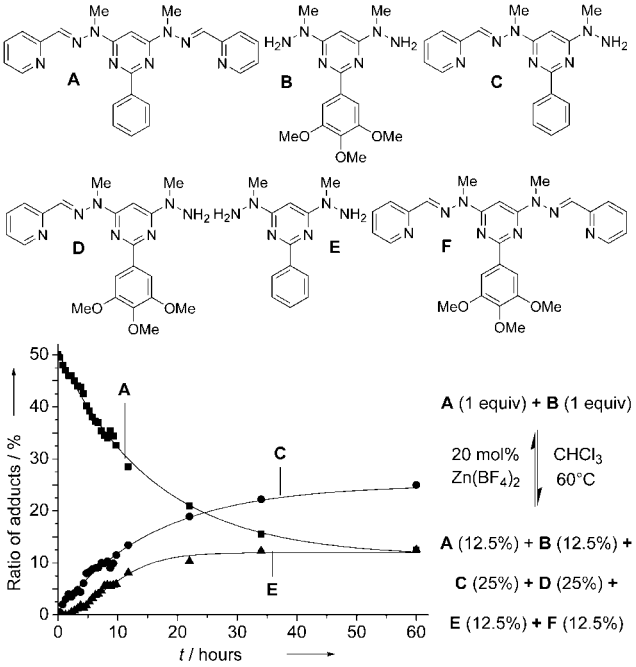


Figure 2. Evolution with time of the composition of a model hydrazone/hydrazine mixture **A** and **B** followed by ^{1}H NMR spectroscopy under Zn^{II} catalysis; $c(\mathbf{A}) = c(\mathbf{B}) = 50$ mM.[13]

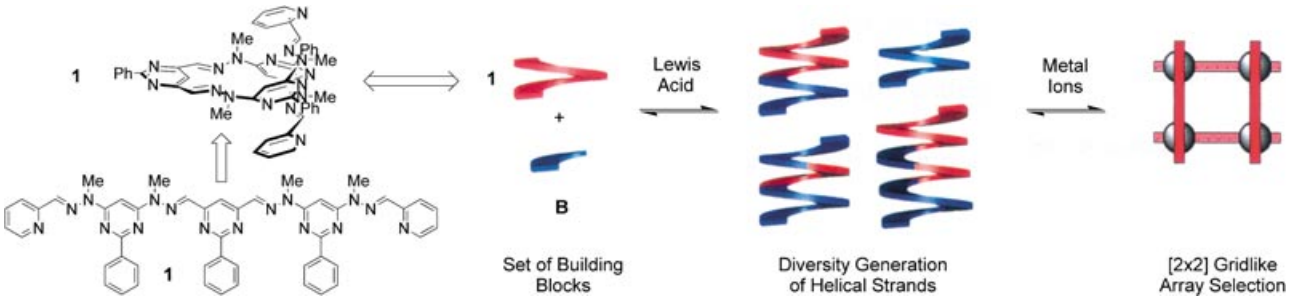


Figure 1. Schematic representation of the processes occurring in the present system. Left: Lewis acid catalyzed generation of dynamic constitutional diversity in helical molecular strands involving compounds **1** and **B** of Figure 3 (**1** is shown in both its extended and its preferred helical forms);[9,13] right: evolution of the dynamic library towards formation of a [2×2] grid driven by suitable metal ions.

imines,[11,12] the reaction proceeds through a transimination process; indeed, in similar conditions the pyrimidine 4,6-biscarboxaldehyde analogue of **B** and dihydrazone **A** did not show any detectable exchange after three days.

These promising results prompted us to explore the catalytic activity of other Lewis acids for the model exchange reaction depicted in Figure 3. The data indicated that the activity was directly correlated with the ionic radius of the trivalent metallic ions assayed, with scandium triflate being the most powerful Lewis acid catalyst for hydrazone scrambling. Moreover, utilization of scandium triflate in the exchange between compounds **A** and **B** (Figure 2) resulted in the half-reaction being reached after only 20 minutes, a 30-fold acceleration compared to the results obtained with $Zn(BF_4)_2{\cdot}8H_2O$.

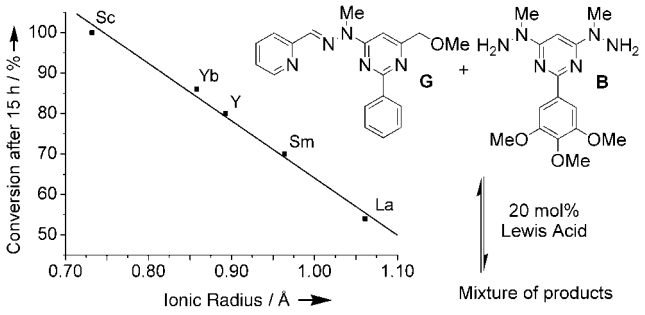
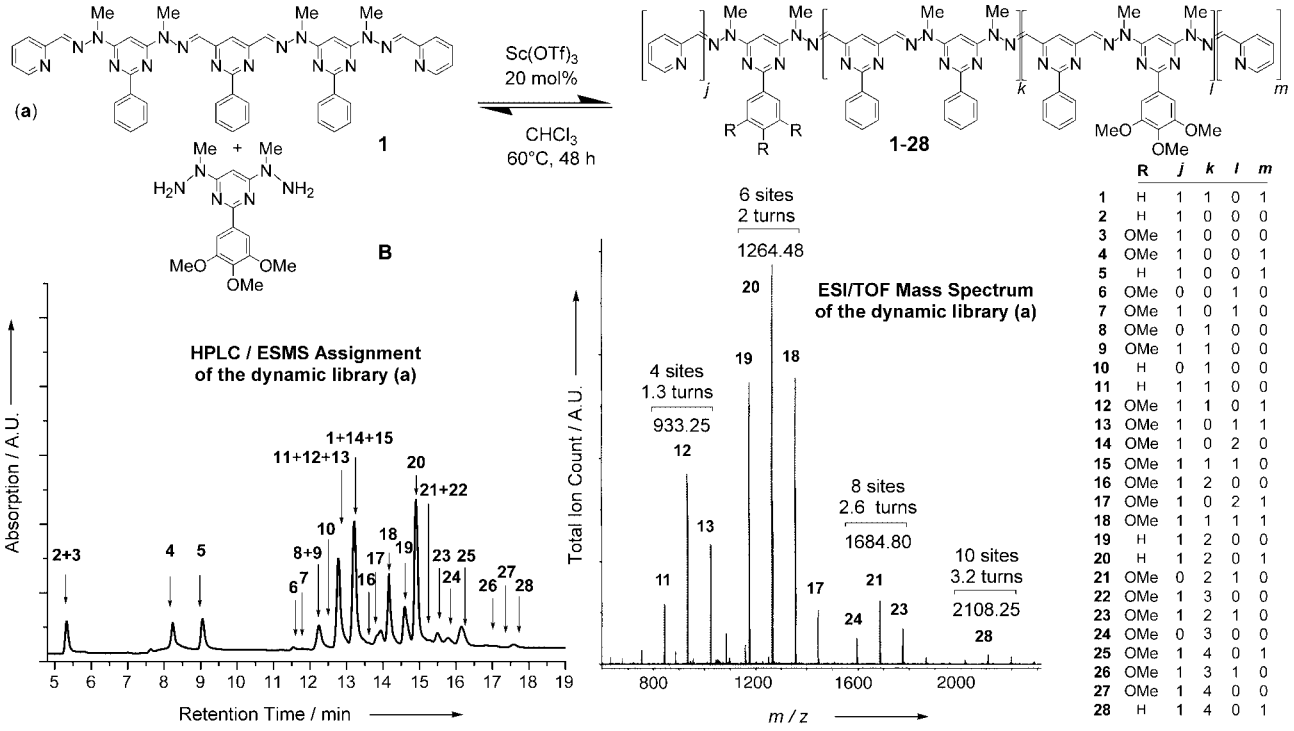


Figure 3. Comparative catalytic activity of different trivalent Lewis acids $M(OTf)_3$ for the exchange of hydrazones (right) as a function of ionic radius (left); $c(\mathbf{B}) = c(\mathbf{G}) = 5$ mM at 60 °C in $CDCl_3$. The conversion is measured by following, through integration of the ^1H NMR signal, the decrease of compound **G** over 15 h, which was the time required for reaching equilibrium in the case of the most active catalyst, $Sc(OTf)_3$. In the same conditions, the conversions for the uncatalyzed and for the $Zn(OTf)_2$- or $Zn(BF_4)_2$-catalyzed reactions were 1% and 30%, respectively.[13]

To test the efficiency and generality of the system we turned to compound **1**,[9a] a one-turn helical strand containing four hydrazone groups, which was expected to be much more reluctant to undergo component exchange (Figure 4, equilibrium (**a**)) than the shorter related structures (**A**, **C**, **D**, **F**, Figure 2), as a consequence of its folding and the resulting lower accessibility of its hydrazone sites. Compound **1** nevertheless underwent exchange of its two bishydrazine components with compound **B** in 48 h when mixed in a stoichiometric ratio in the presence of 20 mol% (namely, 5 mol% per hydrazone site of **1**) $Sc(OTf)_3$ in chloroform at 60 °C. The equilibrium was reached after about 48 h as indicated by NMR spectroscopy and mass spectrometry. Extensive exchange had taken place after 48 h even with only 4% catalyst (that is, 1% per site), although the reaction was much slower. The constituents of the mixture could be separated and identified by HPLC/ESMS. The data analysis demonstrated that full recombination between **1** and **B** had taken place, with the generation of the set of compounds **1**–**28** containing expanded helices with up to ten hydrazone sites (more than three helical turns).[9] Moreover, all the possible cross-combinations with phenyl and/or methoxyphenyl moieties were generated for each size of helical strand, thus highlighting the efficiency of the reorganization process. In



	R	*j*	*k*	*l*	*m*
1	H	1	1	0	1
2	H	1	0	0	0
3	OMe	1	0	0	0
4	OMe	1	0	0	1
5	H	1	0	0	1
6	OMe	0	0	1	0
7	OMe	1	0	1	0
8	OMe	0	1	0	0
9	OMe	1	1	0	0
10	H	0	1	0	0
11	H	1	1	0	0
12	OMe	1	1	0	1
13	OMe	1	0	1	1
14	OMe	1	0	2	0
15	OMe	1	1	1	0
16	OMe	1	2	0	0
17	OMe	1	0	2	1
18	OMe	1	1	1	1
19	H	1	2	0	0
20	H	1	2	0	1
21	OMe	0	2	1	0
22	OMe	1	3	0	0
23	OMe	1	2	1	0
24	OMe	0	3	0	0
25	OMe	1	4	0	1
26	OMe	1	3	1	0
27	OMe	1	4	0	0
28	H	1	4	0	1

Figure 4. Generation of a highly diverse recombination library of helicity-encoded molecular strands from the one-turn/four-sites helical compound **1** ($c = 50$ mM) and the dihydrazine **B** ($c = 50$ mM) using $Sc(OTf)_3$ (20 mol%) as a catalyst in $CDCl_3$ at 60 °C; 28 constituents were identified by LC/MS (bottom left) and direct introduction ESI/TOF (bottom center) mass spectrometry, as indicated (bottom right).[13]

the same conditions but under acid catalysis (20 mol% CF_3CO_2H) less than 5% of **1** was converted into compounds **11** and **3**; degradation of the dihydrazine **B** had also started (as shown by NMR analysis and LC/MS).[14]

Finally, the dynamic library of helical structures under equilibrating conditions was treated with $Zn(OTf)_2$ (1 equiv with respect to the inital amount of compound **1**), which is known to self-assemble with two-site ligands such as **5**, to yield $[2\times2]$ grid-type complexes in acetonitrile (Figure 5, equilibrium (**b**)).[15] The formation of $[Zn_4\mathbf{5}_4]$ as the major tetranuclear grid together with the $[Zn_4\mathbf{5}_3\mathbf{4}]$ and $[Zn_4\mathbf{5}_2\mathbf{4}_2]$ analogues was observed by ESI/TOF mass spectroscopy using direct injection. The HPLC trace (**b**) (displaying the ligands resulting from dissociation of the complexes on the column) and the ESMS data indicated a marked increase in the amount of **5**, which forms the $[2\times2]$ grid structure, accompanied by a decrease in the larger helical species compared to the initial equilibrium (**a**). Moreover, Zn^{II} ions favored formation of **5** over **4**, which contains a more bulky central group that hinders the formation of the homoleptic grid complex $[Zn_4\mathbf{4}_4]$. These observations indicate that addition of Zn^{II} ions had driven the evolution of the dynamic set towards the expression of the ligand **5** under the pressure of the formation of the (less bulky) grid-type complex by dissociation and recombination of the subunits of the helical strands. The evolution was also found to depend on the concentration of Zn^{II} ions, as was demonstrated by using three equivalents of its triflate salt (Figure 5, equilibrium (**c**)). The HPLC trace and direct introduction ESI/TOF mass spectroscopy showed that, in addition to an increase of **5** (and of **4** to a lesser extent), the main effect observed when three equivalents of $Zn(OTf)_2$ were added to the mixture was the formation of mononuclear $[Zn\mathbf{2}_2]$, $[Zn(\mathbf{2})(\mathbf{3})]$, and $[Zn\mathbf{3}_2]$ complexes, thus leading to a huge amplification of the single site ligands **2** and **3** in the library compared to the equilibria (**a**) and (**b**). This observation may be explained as resulting from the adaptation of the system to generate the ligands providing the sites required for most complete zinc coordination.

The data reported here demonstrate the ability of Sc^{III} ions to efficiently catalyze the exchange of the components of hydrazones (and, by extension, of any C=N functionality) in organic medium and to establish a library of equilibrating entities, a feature of crucial importance for CDC. The method provides a general and efficient procedure for establishing dynamic behavior in sets of discrete molecules (in particular bioactive ones) and in materials (such as polymers). It also allowed the generation of a highly diverse dynamic combinatorial library of oligomeric helical strands from two constituents undergoing assembly, dissociation, and exchange processes. Addition of Zn^{II} ions subsequently shifted this library towards the selective amplification of specific ligand constituents, driven by the formation of $[2\times2]$ gridlike complexes (Figure 1). From a broader perspective, the results described illustrate the ability of constitutional dynamic systems to respond to environmental parameters and to perform effector-driven evolution toward the fittest con-

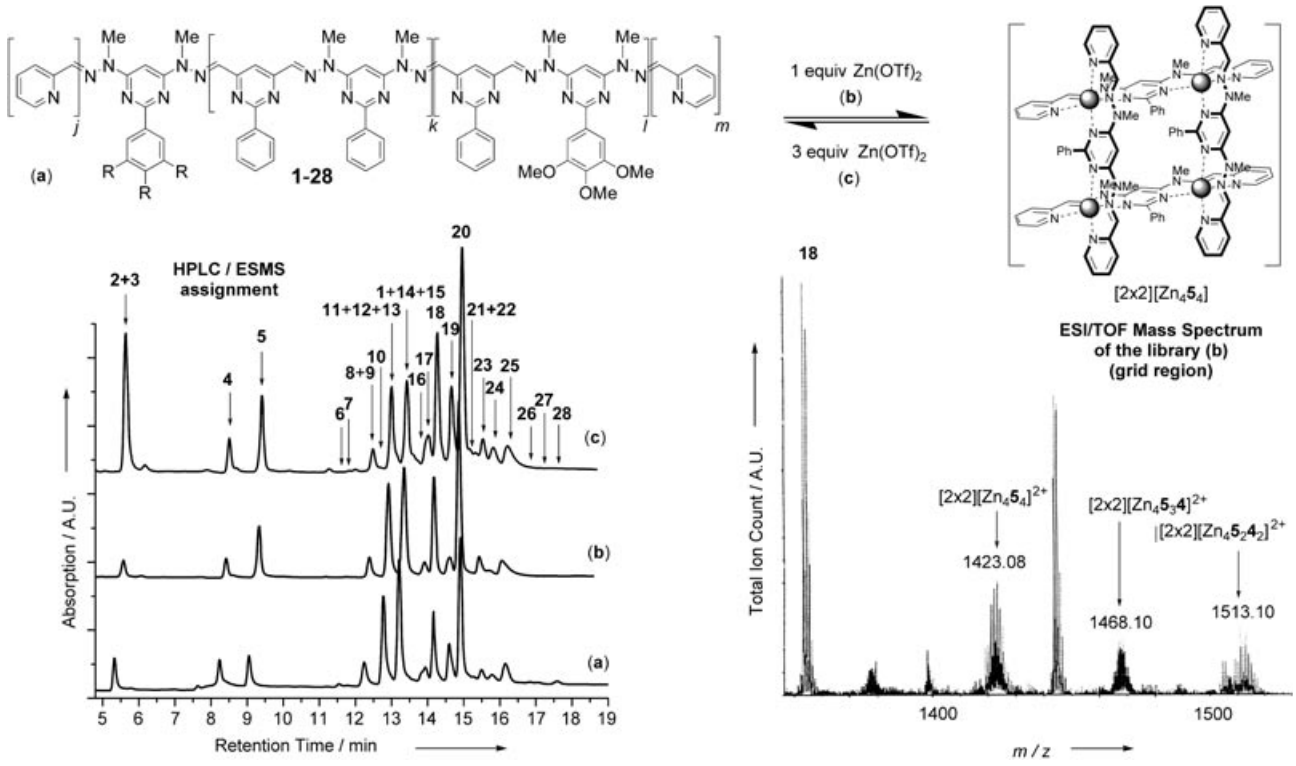


Figure 5. Driven evolution of the dynamic library (**a**) towards the generation of the $[2\times2]$ grid complex $[Zn_4\mathbf{5}_4]$ (bottom left: HPLC traces; bottom right: ESMS direct injection) by addition of 1 (**b**) or 3 (**c**) equivalents of $Zn(OTf)_2$ (CD_3CN; 60°C; 24 h) to the library (**a**), preequilibrated as in Figure 4 (20 mol% $Sc(OTf)_3$; $CDCl_3$; 60°C; 48 h), and then evaporated and redissolved in CD_3CN; the equilibrium was not significantly affected by the change in solvent. The identification of compounds **1**–**28** is given in Figure 4. Compounds **4** and **5** are identical to **F** and **A**, respectively.[13]

stituent, an essential feature characterizing the adaptive and evolutive nature of CDC under the pressure of external factors.

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[14] In all our attempts involving crossover reactions, the use of the metallic salts $Zn(BF_4)_2 \cdot 8H_2O$ or $Sc(OTf)_3$ avoided the degradation of the library constituents, whereas uncatalyzed and, to a larger extent, proton-catalyzed reactions always underwent extensive side reactions.
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