

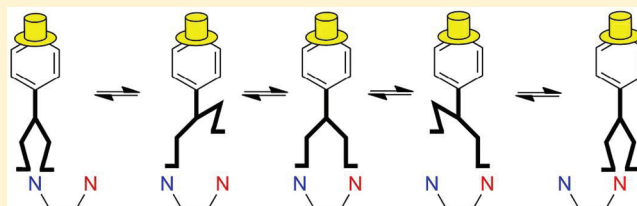
Merging Constitutional and Motional Covalent Dynamics in Reversible Imine Formation and Exchange Processes

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Supporting Information

ABSTRACT: The formation and exchange processes of imines of salicylaldehyde, pyridine-2-carboxaldehyde, and benzaldehyde have been studied, showing that the former has features of particular interest for dynamic covalent chemistry, displaying high efficiency and fast rates. The monoimines formed with aliphatic α,ω -diamines display an internal exchange process of self-transimination type, inducing a local motion of either “stepping-in-place” or “single-step” type by bond interchange, whose rate decreases rapidly with the distance of the terminal amino groups. Control of the speed of the process over a wide range may be achieved by substituents, solvent composition, and temperature. These monoimines also undergo intermolecular exchange, thus merging motional and constitutional covalent behavior within the same molecule. With polyamines, the monoimines formed execute internal motions that have been characterized by extensive one-dimensional, two-dimensional, and EXSY proton NMR studies. In particular, with linear polyamines, nondirectional displacement occurs by shifting of the aldehyde residue along the polyamine chain serving as molecular track. Imines thus behave as simple prototypes of systems displaying relative motions of molecular moieties, a subject of high current interest in the investigation of synthetic and biological molecular motors. The motional processes described are of dynamic covalent nature and take place without change in molecular constitution. They thus represent a category of dynamic covalent motions, resulting from reversible covalent bond formation and dissociation. They extend dynamic covalent chemistry into the area of molecular motions. A major further step will be to achieve control of directionality. The results reported here for imines open wide perspectives, together with other chemical groups, for the implementation of such features in multifunctional molecules toward the design of molecular devices presenting a complex combination of motional and constitutional dynamic behaviors.



1. INTRODUCTION

Dynamic covalent chemistry (DCC)^{1,2} rests on the implementation of reversible covalent reactions for the generation of dynamic covalent/combinatorial libraries (DCLs) of constituents from the reversibly connecting components. The elaboration of DCLs presents two major requirements: (1) high and (as much as possible) fast conversion of components into equilibrating library constituents; (2) fast component exchange and incorporation with concomitant reequilibration of constituents on addition of extraneous components to the equilibrating set. A third feature of much interest is the ability of a DCL to respond to external physical stimuli or chemical effectors, and thus to undergo adaptation.

Among the reversible covalent reactions one may consider the condensation of an amino group with a carbonyl functionality to form an imine/Schiff base is of special interest. It has been widely explored across the various types of C=N compounds (regular imines, hydrazones, acylhydrazones, oximes) as well as in terms of its physicochemical features.^{1–4}

Reversible imine formation processes have been implemented for the search of biologically active substances,⁵ for the generation of dynamic nanoarchitectures^{1,2,6} and for the development of dynamic materials,⁷ such as dynamic polymers

(dynamers).^{7b,c} It deserves particular attention in view of the ubiquity of the amino function in substances of interest in chemistry, biology,^{7c,d} and materials science.^{7a} As it proceeds with the liberation of water, its dynamic character depends on and may be controlled by the presence of water.

To further extend its scope in the realm of DCC, we undertook the exploration of the imine forming and exchange reactions of a number of aldehydes with typical amines. It led much further than simple molecular reactivity and recognition, uncovering some remarkable features involving both constitutional and motional covalent processes.

We herewith report specially attractive processes involving the imines of salicylaldehyde (SALAL),^{3b,8} adding novel facets to the chemistry of this extensively investigated molecule. They display remarkable formation and exchange features, of much interest for DCC,^{8d,e} and may act as an “imine clip”, whereby an internal hydrogen bond is established between imine nitrogen and the neighboring hydroxyl group. We have furthermore found that imines formed by SALAL with oligoamines (such as ethylene diamine, diethylene triamine,

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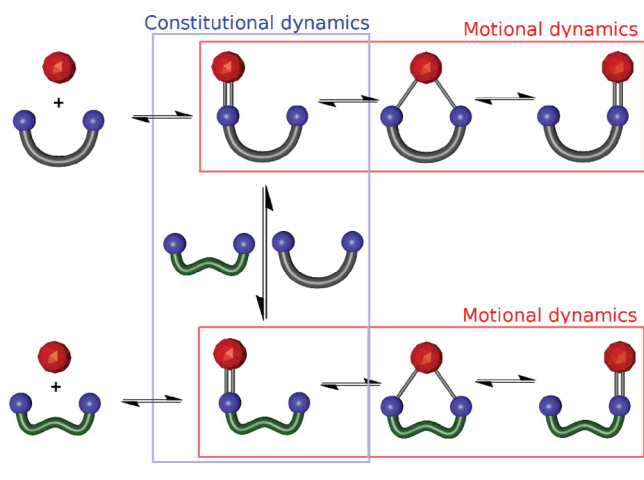
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etc.) display intramolecular nondirectional motional processes, involving transfer of the salicylidene group between amino groups by reversible covalent bond formation, that bear relation to the synthetic molecular “machines”⁹ and biological motor proteins¹⁰ areas, very actively investigated in recent times. We complement these results by a comparison with the behavior of pyridine-2-carboxaldehyde (PYRAL)^{11,12} and of benzaldehyde (BENZAL)¹³ as reference compounds. Imine formation by the related pyridoxal-5-phosphate has been extensively studied in the literature, in view of its importance as biological cofactor,^{8a,14} and the present data may also have implications for the related transamination reactions.

Group transfer through making and breaking of covalent bonds has been described for several functional groups, such as acyl or borinyl transfer.¹⁵ The dynamic behavior of imines is of special interest (see in particular ref 1c) in view of its widespread role in chemistry^{1,2} and biochemistry⁵ as well as in materials science.⁷

In more general terms, the results reported here represent a combination of constitutional and motional dynamic covalent processes (a feature envisaged earlier¹⁶) within the same system, as illustrated schematically in Scheme 1. They lead to

Scheme 1. Schematic Representation of the Merging of Constitutional and Motional Dynamic Covalent Processes, Involving: the Reversible Formation of Imines from a Carbonyl Compound (red object) and a Terminal Diamine (left), the Exchange of Diamines through Transamination (blue frame) and the Back and Forth Motion of the Carbonyl Moiety between the Terminal Amine Sites (red frames)



the notion of *Dynamic Covalent Motions* (DCMs), concerning motions that result from reversible covalent bond formation and dissociation within molecules, rather than by changes in noncovalent arrangements within supramolecular architectures. By extension, the processes uncovered also bear on the design of nanochemical devices of artificial as well as biological significance, whereby simple (ald)imine systems represent prototypes of entities that may undergo both intramolecular displacement motions and intermolecular exchange of their parts, thus enabling, in principle, adaptation by structural variation.

2. RESULTS AND DISCUSSION

2.1. Salicylaldimine Formation and Exchange Processes. In order to promote high efficiency of formation, high

rates of formation, and high rates of exchange, a mixed aqueous–organic solvent, aqueous acetonitrile ($\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 7/3), was chosen, which in addition to ensuring a wide range of solubility also allowed the observation of novel dynamic features.

With the selection of *n*-propylamine as common amine partner, the reaction with the three aldehyde counterparts, SALAL, PYRAL, and BENZAL, was investigated under reversible conditions. Imine formation from aldehyde and *n*-propylamine (20 mM each) was directly observed by ^1H NMR in $\text{CD}_3\text{CN}/\text{D}_2\text{O}$ (7:3 v/v) solution (2 M triethanolamine buffer, $\text{pH} = 8.73 \pm 0.01$, uncorrected for deuterium isotope effect, throughout the measurements).

Although PYRAL reacted fastest, SALAL showed both high conversion and high formation rate (in agreement with the literature data),^{3b,8b} possibly involving a stabilizing “imine clip” effect by formation of a hydrogen bond between the imine nitrogen and the neighboring OH group. The presence of such a hydrogen bond has been extensively documented in numerous crystal structures.¹⁷

To further analyze the origin of the observed reactivity, kinetic experiments were performed on a series of substituted derivatives of SALAL. The calculated rate constants fitted very well a second-order kinetic model and correlated with the corresponding Hammett σ_p constants (see Supporting Information [SI], part 3). They increase with increasing electron-withdrawing character of the substituent in *para* position to the hydroxyl group. This result is in line with the role of hydrogen bonding on the reactivity of SALAL, described in literature, although direct comparison is difficult due to the different conditions used.^{8b,18}

Transamination (i.e., amine exchange) experiments were conducted by addition of isopentylamine to the equilibrated solution of the formation reaction (thus decreasing the initial concentration to 18.2 mM), and the process of formation of the new imine was again followed by ^1H NMR. Exchange was too fast for the imines formed by BENZAL and PYRAL with propylamine, and thus only results for SALAL were obtained. The kinetic data for both formation and exchange are given in Table 1. Interestingly, this imine exchange was found to follow

Table 1. Kinetic Data for Imine Formation with *n*-Propylamine (top) and for Amine Exchange of the Resulting Imine with *i*-Pentylamine (bottom)

aldehyde	k [$10^{-3} \text{ M}^{-1} \text{ s}^{-1}$]	conversion [%]	half-life [s] ^a	R^2
BENZAL	61.1 ± 0.9	20	818	0.88
SALAL	71.4 ± 0.4	77	700	0.99
PYRAL	202 ± 2	61	248	0.98
<i>n</i> -propylamine of	$k \cdot K$ [$\text{M}^{-1} \text{ s}^{-1}$]	conversion to <i>i</i> -pentylamine [%]	half-life [s] ^a	R^2
BENZAL	—	50	<20	—
SALAL	0.73 ± 0.02	50	76	0.97
PYRAL	—	50	<20	—

^aThe half-life indicated is calculated from the rate constant and initial concentration of 20 mM or 18.2 mM, respectively; study was performed in a mixture of $\text{CD}_3\text{CN}/\text{D}_2\text{O}$ (7:3 v/v) with triethanolamine buffer ($\text{pH} = 8.73$) with 20 mM starting concentration of reagents (aldehyde + *n*-propylamine) in 1:1 ratio and then followed by NMR. Exchange experiments were performed on samples equilibrated for 3 days, adding 1 equiv of *i*-pentylamine (decreasing initial concentration to 18.2 mM) and followed by NMR.

first-order kinetics at the pH used (8.73). Very extensive studies of carbonyl + amine reactions have been performed,^{3,8} indicating that formation or breakdown of the intermediate carbinolamine (hemiaminal) may be rate determining, depending on conditions, e.g., pH. The same holds for amine exchange involving an aminor intermediate.³ Explanation of the kinetic model is given in the SI, part 3.

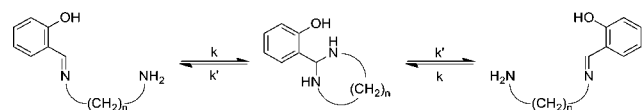
The rate of intermolecular amine exchange in the present case was found to be concentration dependent, as expected for an intermolecular process (Table 1.). Thus, dependence on concentration is a signature, and will be taken as such, of the intermolecular nature of a given process in the much more complex cases involving diamines and polyamines to be discussed below.

In fact, transimination can be performed as exchange of either the amine part (discussed above) or the aldehyde part. Thus, addition of 1 equiv of SALAL to the equilibrium mixture of PYRAL + *n*-propylamine (Table 1) leads to a reequilibration of the mixture giving 24% and 76% of the *n*-propylimines of PYRAL and SALAL, respectively. Similarly, when equilibrated mixtures of PYRAL + *i*-pentylamine and SALAL + *n*-propylamine are combined, reequilibration takes place again to give an equimolar mixture of *n*-propyl- and *i*-pentylimines of PYRAL (45%) and SALAL (55%).

Both experiments illustrate the constitutional exchange expected for exchanging aldehyde/amine systems.

2.2. Motional and Constitutional Dynamics in Salicylaldehydes of Aliphatic Diamines: Intramolecular Group Transfer and Intermolecular Component Exchange. (a) The amine exchange process on imines may occur either by hydrolysis followed by recondensation or by addition of the new amine to the imine double bond to give a gem-diamine/aminol intermediate. The latter may be facilitated by the “imine clip” effect and involves trivalent/tetravalent interchange at the carbon center, as reversible conversion between imine and aminol occurs. It follows that, if the amine groups undergoing exchange are linked, as in α,ω -aliphatic diamines, an intriguing situation presents itself, whereby *intramolecular self-exchange* takes place, with bonding fluctuation on imine–aminol–imine interconversion, via a cyclic aminol that may or may not be present in significant amount, depending on the relative stability of the two entities in the conditions used (Scheme 2). Such a process thus performs a motional-type displacement of two molecular moieties relative to one another.

Scheme 2. Mechanism of the Intramolecular Exchange Process Displayed by the Monoimines formed by SALAL with Aliphatic Diamines $H_2N-(CH_2)_n-NH_2$



Indeed, the reactions of the aldehydes with the simple aliphatic diamines $H_2N-(CH_2)_n-NH_2$ (Figure 1) turned out to follow such a scheme. When SALAL, BENZAL, and PYRAL were mixed with a diamine in chloroform, a mixture of monoimine and bis-imine was obtained, and sharp 1H NMR signals were observed, as one would expect¹⁹ (see SI, Figures SI-04-1 and SI-04-2). However, the situation was very different when the same reactions were run in CD_3CN/D_2O (7:3 v/v).

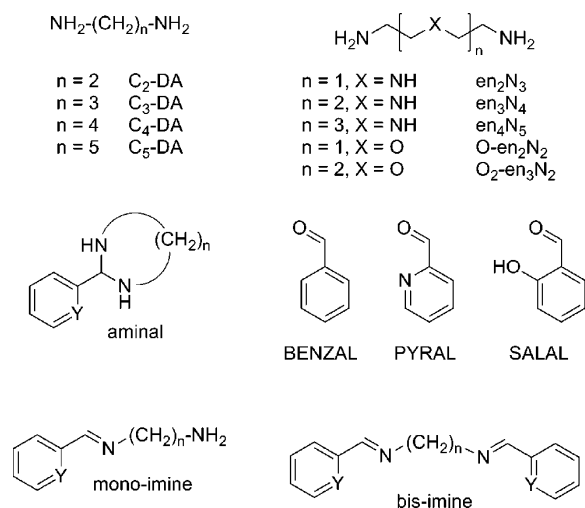


Figure 1. Oligoamines and aldehydes used in this study and their condensation products with an aldehyde: aminol, monoimine, and bis-imine.

A 1/1 mixture of SALAL and C_2 -DA displayed very broad 1H NMR signals for the CH_2 groups and broadened signals for the imine protons, whereas the signals of the aromatic protons were sharp. Signal integration showed that these bands belonged to the monoimine (~55% based on aldehyde). The bis-imine (~45% based on aldehyde) was also formed but presented the expected sharp peaks, while the aminol of SALAL is not observed if the imine can be formed, as documented in the literature.²⁰ Moreover, no signal was observed for a $-CH(O)-(N)$ proton corresponding to the hemiaminal that would form by addition of a water molecule to the imine (expected around 5–5.5 ppm). The presence of the very broad peaks at a chemical shift between those expected for CH_2 protons next to the $C=N$ group and next to an NH_2 group was interpreted as indicating the operation of a kinetic process in the monoimine, whereby the two CH_2 groups exchange at a rate compatible with the NMR time scale.

Variable-temperature (VT) 1H NMR measurements showed a coalescence of the two broad signals at a temperature of about 37 °C (Figure 2). The corresponding rate was found to be independent of the concentration and of the ratio between SALAL and C_2 -DA, indicating that the process was *intramolecular*. Thus, NMR line-shape analysis was performed in the temperature range of 10–75 °C (steps of 5 °C) at three different concentrations (4, 20, and 100 mM) and three different ratios (2:1, 1:1 and 1:2) of reagents. In all cases, the same coalescence temperature of 37 ± 1 °C was observed, which clearly confirmed that the process was of intramolecular nature, independent of concentration as expected for such a unimolecular reaction at equilibrium. Furthermore, line-shape analysis (see SI, Figure SI-05-1) gave very consistent rate data suitable for fitting the Eyring equation to obtain the activation enthalpy $\Delta H = 9.3$ kcal mol⁻¹ and entropy $\Delta S = -15.8$ cal mol⁻¹ K⁻¹. The rate of exchange was also examined for the effect of pH. The coalescence temperature of the two methylene signals of the monoimine was found to be independent of pH in the range 9.3–12.0; below pH 9 only very small amounts of monoimine were formed and for pH above 12 the acetonitrile/water mixture tended to phase separate. For all following results, the pH of the mixture was adjusted to 10.7 ± 0.1 by DCl or NaOD.

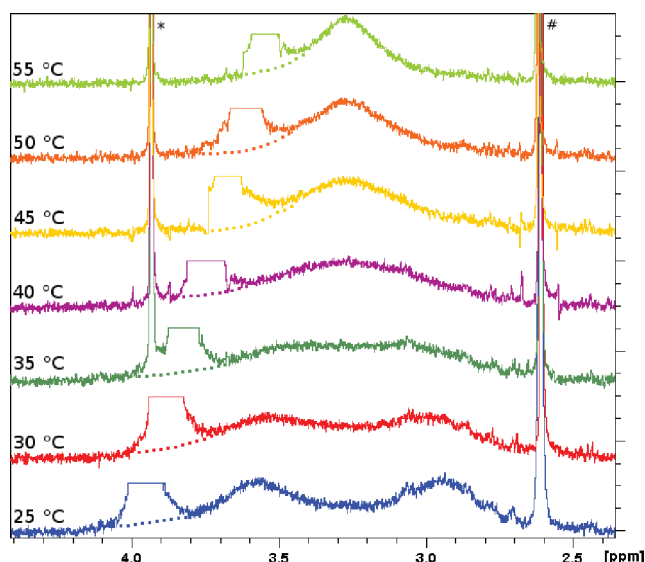


Figure 2. Variable-temperature 400 MHz ^1H NMR of the $\text{CH}_2\text{--CH}_2$ signals of *N*-salicylidene-1,2-diaminoethane, the monoimine of SALAL with $\text{C}_2\text{-DA}$, in the temperature range 25–55 $^\circ\text{C}$ from bottom to top (steps of 5 $^\circ\text{C}$) in $\text{CD}_3\text{CN}/\text{D}_2\text{O}$ (7:3 v/v). The sharp signal at 2.6 ppm (#) is free $\text{C}_2\text{-DA}$, the singlet at 3.95 ppm (*) is the signal of the methylene groups of the bis-imine. The water signal moving with temperature in the 3.5–4.0 ppm region has been truncated for clarity.

Intermolecular exchange with the free diamine present in solution was also observed but could not be quantified because of the breadth of the corresponding signal in the monoimine with which exchange is taking place.

The mechanism of intramolecular exchange between the two methylene groups =N--CH_2 and $\text{H}_2\text{N--CH}_2$ in the monoimine requires going through a cyclic aminal form as shown in Scheme 2 for the case of SALAL and $\text{C}_2\text{-DA}$. Such a process represents an intramolecular molecular motion involving the continuous exchange of the salicylidene group between the two ends of the $\text{C}_2\text{-DA}$ molecule in a binary rhythm of either “stepping-in-place” or “single-step” type.

SALAL strongly prefers the monoimine state,¹⁹ and the presence of aminal was only detected by two-dimensional (2D) ^1H NMR NOESY studies via cross-peaks between imine and aminal protons, although the aminal proton is hardly visible in the 1D ^1H NMR spectrum. The corresponding NOESY spectrum is shown in Figure 3 as a typical illustration.

(b) In order to investigate the possibility of exchange between more distant terminal amino groups, similar line shape analysis and/or ^1H NMR EXSY studies (see SI, part 8) were conducted with the longer aliphatic diamines $\text{H}_2\text{N--(CH}_2)_n\text{--NH}_2$, $\text{C}_3\text{-DA}$, putrescine ($\text{C}_4\text{-DA}$, $n = 4$), and cadaverine ($\text{C}_5\text{-DA}$, $n = 5$). The independence of the rate of exchange of the two N--CH_2 groups from concentration was taken as diagnostic of the intramolecular nature of the process. The rates of end-to-end exchange decreased rapidly on chain lengthening, as may be expected (Table 2), going from 365 Hz for $\text{C}_2\text{-DA}$ down to 10 Hz for $n = 4$ in $\text{C}_4\text{-DA}$ and to not observable for $n = 5$, as the intermolecular exchange becomes faster than the intramolecular one (see also c below).

The intramolecular process was similarly observed with PYRAL and BENZAL, but at widely different rates (Table 2). With $\text{C}_2\text{-DA}$ and $\text{C}_3\text{-DA}$, PYRAL forms stable cyclic aminals which predominate over the imines in solution. Nevertheless, dynamic equilibrium between the ring and chain forms takes

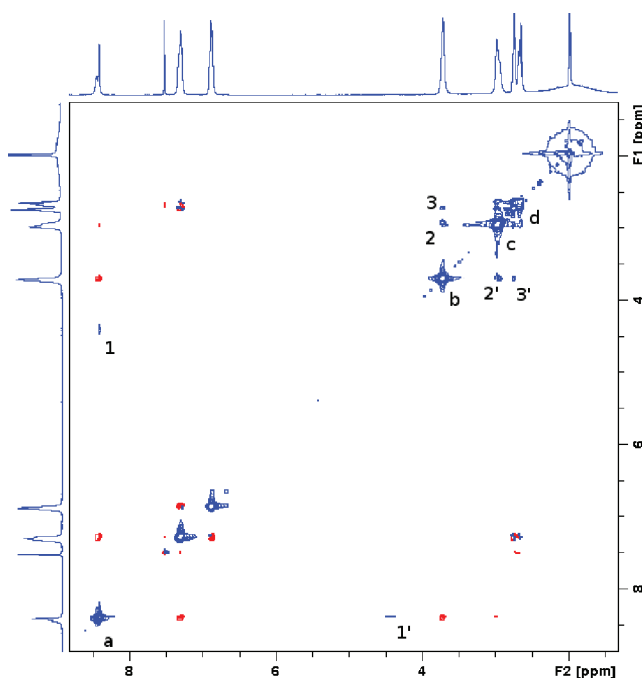


Figure 3. Two dimensional covariant NOESY spectrum of SALAL with en_2N_3 in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (1:1 v/v) at 50 mM concentration of both reagents in 1:1 ratio. Diagonal signal assignment: a is methine signal of imine and bis-imine, b is $\text{=N--CH}_2\text{--}$ group of the imines, c is $\text{--CH}_2\text{--NH}_2$ of the imines, d contain signals of unreacted en_2N_3 . Cross-peak assignment: 1 is imine-to-aminal exchange cross-peak, 2 is intramolecular imine exchange cross-peak, 3 is intermolecular exchange cross-peak. Diagonally symmetrical peaks are labeled with prime.

Table 2. Inter- and Intramolecular Exchange Rates for End-to-End Transfer (see Scheme 2) in Monoimines of Aldehydes and Aliphatic Diamines [Hz] in 1:1 Ratio at 25 $^\circ\text{C}$ in $\text{CD}_3\text{CN}/\text{D}_2\text{O}$ (7:3 v/v) and 20 mM Concentration

$\text{H}_2\text{N--(CH}_2)_n\text{--NH}_2$	$n =$			
	2	3	4	5
SALAL				
intra	365	187	10	— ^b
inter	— ^a	0.22	— ^a	0.32
PYRAL				
intra	0.17	0.5	1.4	0.60
aminal opening r'	0.44	1	— ^c	— ^c
aminal closing r	1.35	74		

^aExchange observed, but broad signal shapes or low intensities prevent quantification. ^bExchange not observed. ^cNo aminal signals observed in the spectrum; therefore, value can not be calculated.

place and can be quantified. To make the rates of such exchanges comparable with other end-to-end exchanges, they were calculated according to Scheme 2 from the residence times $1/r$ and $1/r'$ of the protons in the two sites, as $[2(1/r + 1/r')]^{-1}$ where r is rate of ring closing and r' is rate of ring opening, as determined by EXSY NMR. Since the cyclic intermediate is symmetrical, the chance of opening on each nitrogen site is the same, giving 50% probability to go back and 50% probability to perform end-to-end exchange. For $\text{C}_4\text{-DA}$ and $\text{C}_5\text{-DA}$ no aminals are observed.

PYRAL showed much slower intramolecular exchange than SALAL as well as the presence of both the monoimine and the

aminal in a ratio of about 1:2.7 for C_2 -DA. With C_2 -DA or C_3 -DA, the intermediate aminal is the major species present in the solution,²⁰ in clear contrast to salicylaldehyde, where aminal is not seen. On the other hand, this observation supports the existence of cyclic aminal as intermediate of intramolecular exchange, even when it is not detected. The formation of intermediate geminal diamines has been studied in detail for pyridoxal-5-phosphate.^{14b,d}

Similarly to PYRAL, BENZAL also gave a mixture of imine and cyclic aminal, but here the imine was the major product, in agreement with published results.²⁰ The signal shape in this case disqualifies EXSY for evaluation of the exchange rates, and the coexistence of both imine and aminal prevents the end-to-end exchange rate determination by line-shape analysis, allowing only a rough estimation of ~ 15 Hz. However, VT-NMR in the range 25–75 °C again showed signal broadening but coalescence could not be reached (see Figures SI-04-11 and SI-04-12 in SI). Thus, the phenomenon is general and lends itself to a variety of far-reaching extensions (see below).

(c) *Intermolecular constitutional exchange* may occur by reaction of free diamine with monoimine and compete with the intramolecular process. It can be observed by 2D-NMR spectra where cross-peaks indicate exchange between free diamine and monoimine giving the very same imine and free diamine. Indeed, cross-peaks in the 1H NMR NOESY spectrum of SALAL with C_3 -DA in $CD_3CN:D_2O$ (7:3 v/v) were indicative of an intermolecular exchange (see Scheme SI-07-1 in SI). The intermolecular nature of the process was confirmed by the concentration dependence of the exchange rate, which was much slower than the intramolecular process (Table 2). EXSY 1H NMR²¹ studies offer a powerful access to both the intermolecular and the intramolecular exchange rates (see SI, part 8). The data for SALAL and C_5 -DA gave a good fit for first order kinetics.

Furthermore, due to formation of bis-imine, another intermolecular process can be observed where two monoimines react to give the bis-imine and free diamine. The rates of intermolecular exchange can be evaluated by EXSY (SI, parts 7 and 8) and, unlike the intramolecular process, they are concentration dependent (following first order kinetic, vide supra). The rates of the intra- and intermolecular exchange processes are given in Table 2.

(d) It was shown above (Table 2) that imines formed by SALAL with diamines present two dynamic features: *intramolecular motion* and *intermolecular exchange*. When only one diamine is present in the solution, the intermolecular exchange results in the same composition of the mixture as before the reaction in a degenerate process. However, when there are two or more different diamines present, the imine can react with either of these amines, thus undergoing constitutional change by transimination. In the simple case where SALAL was mixed with 1 equivalent of both C_2 -DA and C_3 -DA (each component at 20 mM concentration in CD_3CN/D_2O 7:3 v/v), the 1H NMR spectrum showed the intramolecular motions in both monoimines (although the signals of the C_2 -DA and C_3 -DA monoimines are very close and very broad and therefore cannot be separated), while 2D-EXSY experiments revealed incorporation of both diamines into the monoimines with rates of intermolecular exchange similar to those obtained with only one diamine at the same concentration (0.45 ± 0.05 for C_2 -DA and 0.34 ± 0.01 Hz for C_3 -DA).

In the same manner, addition of 5-chloro-SALAL to an equilibrated mixture of 5-hydroxy-SALAL and C_2 -DA (1 equiv

each) gave an 1H NMR spectrum containing the $CH=N$ proton signals of the mono- and bis-imines formed, together with broad signals for the CH_2-CH_2 protons, resulting from the superposition of the corresponding signals of each monoimine (see Figure 4, below and Figure SI-07-4 in SI).

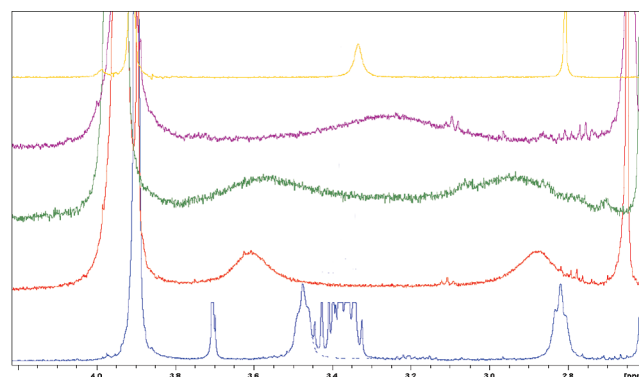


Figure 4. Modulating the internal motion speed by introducing substituents on salicylaldehyde core. The 400 MHz 1H NMR spectra of the methylene signals of the monoimines of C_2 -DA with substituted derivatives of SALAL; from bottom to top: 4-diethylamino-, 5-hydroxy-, no substitution, 5-chloro-, and 5-nitro-salicylaldehyde. In the bottom spectrum, the signals left of the water signal (at 3.9 ppm) are those of the methylene groups of the bis-imine, the methylene group next to the monoimine nitrogen, the methylenes of the ethyl groups, the methylene group next to the amino nitrogen of the monoimine, the methylene groups of the free C_2 -DA. Note: the peaks of the ethyl groups of 4-diethylaminosalicylaldehyde have been truncated for clarity, and the underlying methylene signal (dotted line) has been reconstituted by deconvolution.

These data indicate again the occurrence of equilibration and constitutional dynamics by intermolecular exchange of both the amino and the salicyldehyde groups.

e) Taken together, the data above indicate that monoimines of α,ω -diamines undergo both internal and intermolecular exchanges of components, thus merging motional and constitutional dynamics. The internal process amounts to a *stepping-in-place* when the initial imine is regenerated backward from the intermediate aminal and to taking a *single step* forward when the salicylidene group goes over to the other nitrogen site (Scheme 2).

2.3. Controlling the Speed of Intramolecular Group Transfer. As the intramolecular group transfer process described above is of motional type (see also below), it is of much interest to be able to modulate its speed. There are several ways to achieve such a control.

2.3.1. Introduction of Substituents. The aromatic core of salicylaldehyde allows for a wide range of substitution in up to four positions. Introducing various substituents from electron-withdrawing to electron-donating, both the electrophilicity of the carbonyl (or imine) and the acidity of the OH group are modified. These two factors markedly influence the rate of the internal motion of C_2 -DA as can be seen in Figure 4, showing the signals of the two CH_2 groups of the monoimine. The spectrum of the monoimine of C_2 -DA with the most electron-donating 4-diethylamino group substituted SALAL shows two well separated signals with visible triplet structure of the signals. The less electron-donating 5-hydroxy group gives two well separated but broad signals, similar to SALAL itself. The electron-withdrawing 5-chloro derivative presents only one

broad signal for both CH₂ groups with a coalescence temperature around 12 °C. The most electron-withdrawing substituent, 5-nitrosalicylaldehyde, displays only one relatively sharp signal for both CH₂ groups. The composition of the mixtures (monoimine, bis-imine, free aldehyde) is given in the SI for the five cases studied (SI, Table SI-05-3).

VT-¹H-NMR experiments were performed for four derivatives (4-diethylamino, 5-chloro, 5-hydroxy, and 5-nitro) of SALAL and the spectra were evaluated by line-shape analysis to obtain the rates of motion. These rates were then also fitted by the Eyring equation, and activation parameters were calculated. The values obtained are given in SI, Table SI-05-3.

The range of motion speeds (see Table 3) is remarkably wide: while substitution by a slightly electron-donating 5-

Table 3. Rates of Internal Exchange Motion in the Monoimines of C₂-DA with Substituted Derivatives of SALAL, at 25 °C in CD₃CN/D₂O (7:3 v/v, pH maintained at 10.7 ± 0.1)

substituent on SALAL	4-Et ₂ N	4-OH	5-OH	H	5-Cl	5-NO ₂
motion rate [Hz]	20	108	148	365	1040	~17 000

hydroxy group lowers the rate to approximately half of that of unsubstituted SALAL, the strong electron-donor 4-diethylamino group drops the rate to as low as 5% of its original value. A 4-hydroxy substitution has an effect very similar to that of a 5-hydroxy group, although the activation enthalpy is close to that of the 4-diethylamino group, differing mostly in activation entropy (see SI, Table SI-05-3). Introducing electron-withdrawing groups has an even larger effect: the weakly electron-accepting 5-chlorosalicylaldehyde increases the motion rate 3 times compared to SALAL. The strongest electron-acceptor, the 5-nitro group, shoots the motion rate up into the range of ~17 kHz, a 50-fold increase in speed, thus covering a range of 3 orders of magnitude!

2.3.2. Solvent Composition. The rate of intramolecular exchange in the SALAL-C₂-DA monoimine is also very dependent on the composition of the solvent. Gradually changing the CD₃CN/D₂O solvent composition from 5:5 to 6:4, 7:3, 8:2, and 9:1, the coalescence temperature of the CH₂ ¹H NMR signals increased from 29 °C to 32, 37, 46, and 80 °C, respectively, corresponding to rates of internal motion at 25 °C from 552, to 442, 365, 226, and 158 Hz, respectively. In pure d₃-acetonitrile the rate of intramolecular exchange is only 7 Hz at 25 °C, and obviously coalescence cannot be reached since the boiling point of acetonitrile is 82 °C. The exchange rates have been determined by line-shape analysis over a range of temperatures of about 50 °C and used to calculate the Eyring activation parameters (see SI, part 8). It is thus possible to modulate the rate of the process by changing the nature or the composition of the solvent in a much more delicate way compared to core substitution.

(c) Finally, temperature variation allows for a very gradual modification of exchange rates.

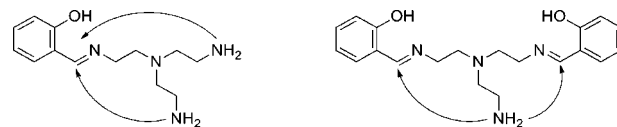
In total, the speed of internal group displacement motion may be modulated easily in three different ways: coarse adjustment by introduction of substituents on the SALAL core, more gentle adjustment by changing the solvent composition, and fine-tuning by temperature. Of course, other factors may affect the speed of this process, such as pH (see SI, part 4), addition of a chemical effector, etc. By a combination of these

different effects, one may expect to be able to cover a range of rates even much larger than the 4 orders of magnitude achieved here.

2.4. From Stepping-in-Place to Taking Steps. The intramolecular exchange process described above for simple aliphatic α,ω-diamine molecules (Scheme 2) becomes particularly attractive when one considers its extension to more complex polyamino molecules.

(a) In the case of the branched trisamine compound **tren** (tris(2-aminoethyl)amine), EXSY studies enable insight into the behavior of the reaction mixture it generates with SALAL (1:1 ratio, 20 mM) in CD₃CN/D₂O (7:3 v/v), where three different imines are observed: monoimine (59%), bis-imine (28%), and trisimine (10%) and 3% of aldehyde remains unreacted. Cross-peaks in the NOESY spectrum revealed multiple exchange processes involving specific signals. The data from the azomethine signals indicate that the imines are interchanging intermolecularly between themselves rather than reacting with the small amount of available aldehyde. In the aliphatic region, the spectrum is much more complicated. Nevertheless, the same exchange pattern as described for the azomethine protons can be observed here as well. Furthermore, exchange cross-peaks of =N-CH₂- protons with H₂N-CH₂- protons are clearly visible. Among all the exchange processes, two concentration-independent ones, clearly assignable to monoimine and bis-imine intramolecular interchanges (Scheme 3), could be evaluated with rates of 3.84 ± 0.16 and 1.13 ± 0.18 Hz, respectively.

Scheme 3. Intramolecular Exchange Processes in the Mono- and bis-imine Formed by SALAL with the Triamine Tren

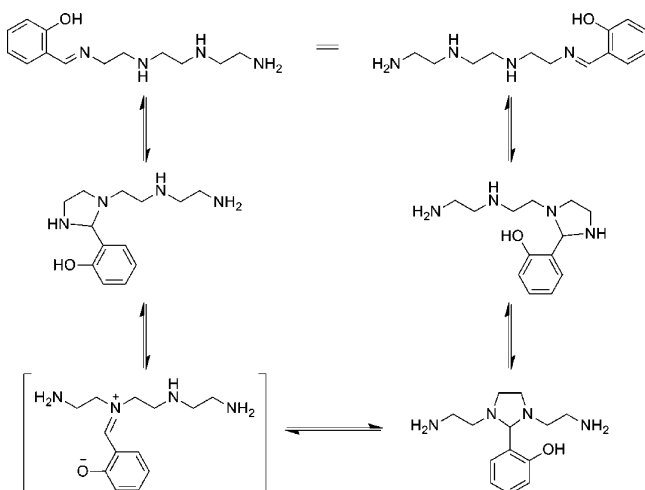


(b) A second category of polyamines consists of linear polyamines. The behavior observed above for monoimines of diamines suggests an especially intriguing extension into the area of motional dynamics involving relative displacements of two linked molecules. The end-to-end transfer of an aldehyde residue on a diamine unit, together with the formation of an intermediate aminal, leads to envision systems where the aldehyde moiety would effect a back-and-forth, nondirectional “walk” along a polyamine chain such as diethylenetriamine (en₂N₃) and its longer analogues, triethylenetetraamine (en₃N₄) and tetraethylenepentamine (en₄N₅), as well as the biogenic amines spermine and spermidine, which contain amino sites separated by two, three, or four methylene groups (Figure 1).

Such processes, where a given molecule moves along another one, are of great interest as nanomechanical molecular devices both in biology and in nanoscience,^{7,22} two areas of high current activity. There are numerous cases of motor proteins (of the dyenin, myosin, and kinesin types) performing displacements along another protein acting as molecular track (e.g., actin or tubulin) in cells.¹⁰ The design of synthetic systems effecting analogous molecular motions has also attracted much attention.²² The present case would represent a very simple implementation of such a behavior. One may further note that, whereas in the biological systems the attachment of the molecules and the walking process involve

formation and rupture of supramolecular interactions, in the present case, *the motion is enabled by dynamic covalent bond forming and breaking*. Furthermore, whereas two mechanisms of displacement have been envisaged for the biological motions (hand-over-hand and inchworm),^{22,23} the mechanism of the motional process envisioned here (Scheme 4) would be of the

Scheme 4. Mechanism of the Dynamic Intramolecular Inchworm-Type Motion of a Salicylidene Residue along an Oligoamine Chain



inchworm type and be processive,^{22a} as the two moieties remain attached along the way. Nevertheless, detachment can occur by intermolecular reaction with an external partner (such as a solvent molecule or an amine group) at the terminal imine or an intermediate immonium state.

When 2D-EXSY ¹H NMR measurements were performed on the reaction of SALAL with en₂N₃ or en₃N₄, cross-peaks indicated that intramolecular exchange was taking place between the two ends of the polyamine moiety. In the case of en₄N₅ it could not be observed, as it is probably so slow that it is hidden under faster intermolecular exchange. The data from these EXSY experiments are given in Table 4. The

Table 4. Intramolecular and Intermolecular Exchange Rates for SALAL and Linear Polyamines

polyamine	en ₂ N ₃	en ₃ N ₄	en ₄ N ₅
intramolecular rate [Hz]	0.60 ± 0.05	0.28 ± 0.03	— ^b
intermolecular rate [Hz] ^a	— ^b	— ^b	0.40 ± 0.04

^aRate of first-order intermolecular exchange given at 20 mM concentration of both reagents. ^bNot observed.

intermolecular exchange rate for 20 mM solutions of both components in CD₃CN/D₂O (7:3 v/v) fits again very well with first-order kinetics. The intermolecular exchange process would correspond to the falling-off in biological motor systems.^{10,22}

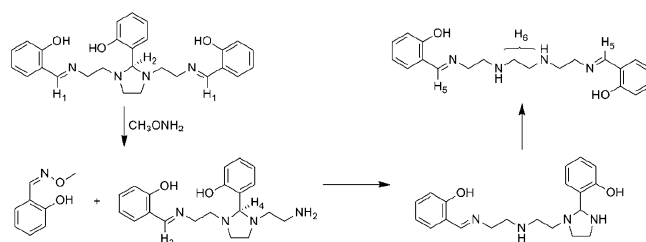
In fact, the mere existence of intramolecular exchange is not sufficient proof that the aldehyde residue is really moving along the polyamine strand. Indeed, a long chain might adopt a conformation which would allow a direct “jump”-type, end-to-end transfer of the aldehyde unit from one terminal nitrogen to the second terminal free NH₂, even though the results obtained with cadaverine, C₅-DA, indicate that such a distant jump is not very likely to happen. The strong preference for imine formation over amina in the case of SALAL is here very

beneficial, because it makes the spectra much easier to decipher compared to PYRAL, which forms multiple amina and mixed imine-aminals, leading to a complex ¹H NMR spectrum, very difficult to unravel and impossible to quantify. On the other hand, when salicylidenepropylamine is treated with N,N'-dimethylethylenediamine in CDCl₃ the amina is obtained with K = 1.4, as the imine cannot form.

To investigate whether the aldehyde moiety is indeed “walking” along the polyamine track molecule, the oxa-analogue of en₃N₄, where the two internal nitrogens are replaced by oxygens, O₂-en₃N₂, was studied. The absence of the secondary amines on the track prevents formation of amina and iminium states and, indeed, prevents intramolecular exchange as the observed process was found to be concentration dependent, indicating intermolecular exchange, with first-order kinetics. The exchange rate values were 0.30 ± 0.02 and 0.17 ± 0.02 Hz for 20 and 8 mM solutions, respectively. The case of O-en₂N₂ is discussed in SI, part 10.

To further support the “walking” mechanism, the derivative of en₃N₄ with two SALAL moieties attached as imines and a third one forming a central amina (bis-imine-aminal), Sal₃en₃N₄, was synthesized²⁴ and treated with methoxyamine, expecting that it would first react with the imine double bond and thus release one of the terminal NH₂ groups. As SALAL prefers to form a terminal imine, the group of the central amina should thereafter move from the central position toward the end of the en₃N₄ molecule, through a lateral amina to the terminal nitrogen site, to give a bisimine (Scheme 5). Reacting

Scheme 5. Representation of the Reaction of Sal₃en₃N₄ with Methoxyamine, Removing One Terminal Salicylidene Residue (left) and Performing Intramolecular Steps (bottom) Shifting the Central Salicylidene Group to the Terminal Site (right)^a



^aThe signal assignment refers to the kinetic experiment in Figure 5.

Sal₃en₃N₄ with one equivalent of methoxyamine (free base) in CDCl₃ at 25 °C gradually gave rise to the signals of monoimine-aminal. A steady-state concentration was reached, and no further increase in concentration was observed as this monoimine-aminal subsequently transformed into the α,ω-bisimine of en₃N₄. The corresponding kinetic profile is shown in Figure 5. Because the reaction was run in CDCl₃ with no free SALAL present, an intermolecular mechanism can be excluded, thus confirming the linear displacement process (see Scheme 5 and Figure 5, details in SI, part 9). Further evidence in favor of the motion of the SALAL moiety along the en₃N₄ chain is provided by the observation that N₁,N₄,N₄-tris(o-hydroxyphenylmethyl) triethylenetetramine is formed as a minor product in the borohydride reduction of Sal₃en₃N₄. The presence of a terminal amine bearing two aldehyde residues may be explained as resulting from the shift of the aldehyde residue of the central

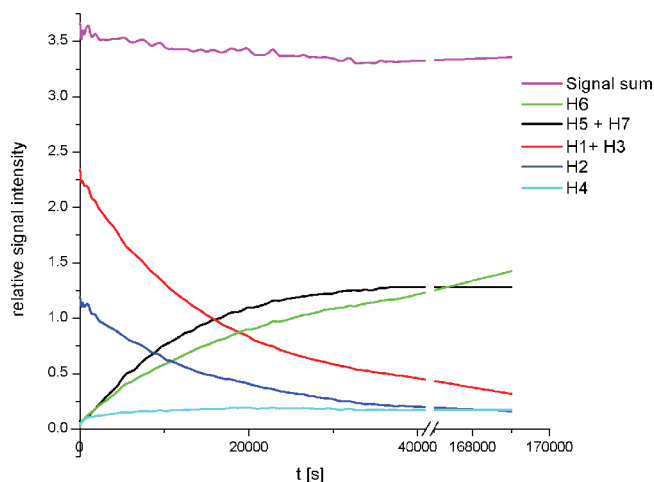


Figure 5. Kinetic data for the reaction of $\text{Sal}_3\text{en}_3\text{N}_4$ with methoxyamine. Signals are assigned in Scheme 5: signal H_7 corresponds to the monoimine of SALAL and en_3N_4 which is formed due to relatively slow reaction between $\text{Sal}_3\text{en}_3\text{N}_4$ and methoxyamine. “Signal sum” represents the sum of the signals of amins, imines, and oxime (described in Scheme 5), integrated with respect to an internal standard of *n*-butanol. For full NMR traces see SI, part 9.

aminal over to the terminal nitrogen site through an intermediate iminium state.^{24b}

The existence of such an iminium species cannot be confirmed by NMR experiments due to its short half-life under the conditions used. However, one might be able to trap it by participation of a neighboring nucleophilic group. To this end, sodium 2-formylbenzoate was reacted with one equivalent of en_2N_3 in $\text{CD}_3\text{CN}/\text{D}_2\text{O}$ (7:3 v/v) and compared to the reaction with propylamine and $\text{C}_2\text{-DA}$ (see SI, part 6 for experimental details).²⁵ While propylamine and $\text{C}_2\text{-DA}$ give only imine, a new peak appeared at 5.12 ppm in the reaction with en_2N_3 (Figure 6). By extensive multidimensional NMR characterization (see SI, part 6), it was assigned to the O–CH–N proton of the amino-lactone generated by internal addition of the carboxylate to the iminium expected to form as a transient species in the displacement process. This observation points to the possibility of trapping the iminium species occurring as intermediates along a polyamine chain and to

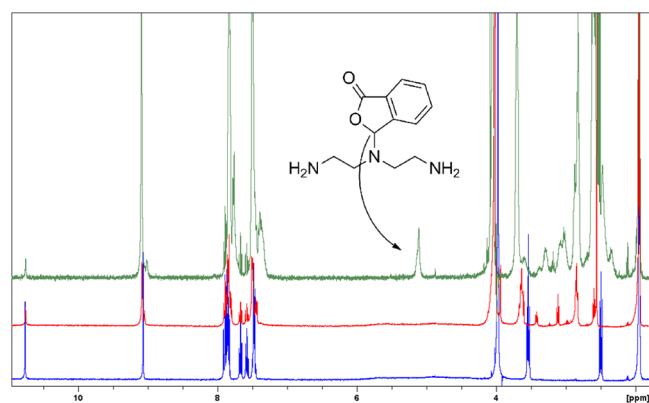


Figure 6. Comparison of the ^1H NMR spectra of sodium 2-formylbenzoate reacted with propylamine (blue), $\text{C}_2\text{-DA}$ (red), and en_2N_3 (green). The signal of the O–CH–N proton of the aminolactone formed is indicated. Full NMR characterization is given in SI, part 6.

observe the consecutive steps in the displacement process along the molecular track.²⁶

3. CONCLUSION

The results described herein on processes occurring in amine–aldehyde systems lead to a number of conclusions.

- (1) The remarkable reactivity features of salicylaldehyde toward amines to form imines with high formation efficiency and high exchange rates, make this carbonyl compound highly suited for applications in dynamic covalent chemistry.
- (2) A *stepping-in-place* or a *single-step* motion by internal degenerate exchange occurs in monoimines formed by aliphatic α,ω -diamines with salicylaldehyde, pyridine-2-carboxaldehyde, and benzaldehyde itself, depending on whether the aldehyde-derived group remains on the same nitrogen or moves to the other one.
- (3) *Speed control* of the internal motion by varying specific parameters (substituents, medium composition, temperature, etc.) may be achieved, up to high rates of motion. This property, studied here for diamines, should also apply to polyamines (see point 4) and represents a particularly sought after feature of molecular motors.²⁷
- (4) The behavior displayed by imines, described herein, allows for *intramolecular linear displacement* of a molecular group along another one, by nondirectional shift of the aldehyde residue along linear polyamines serving as molecular tracks. It represents a simple, prototypical implementation of intramolecular processes of motional-type, an area of high current interest in biological as well as synthetic systems.^{9,10,22,27} A major challenge is to introduce directionality, as has been realized in other instances.^{22,27}
- (5) The intramolecular displacement processes described involve a *valency increase* at the connecting and moving center. This feature may be implemented in a number of other cases involving different centers in various functional groups.¹⁵
- (6) (a) Within the general framework of constitutional dynamic chemistry,²⁸ the present group displacement processes are of *dynamic covalent* nature. They implement the reversible formation of covalent bonds without constitutional change, thus preserving constitution while generating molecular motion. They are thus covalently dynamic but constitutionally static, and extend dynamic covalent chemistry into the area of molecular motions. (b) Within the framework of molecular motional devices, the processes described here represent a category of *Dynamic Covalent Motions*, resulting from reversible covalent bond formation and dissociation. The extensively studied motional processes in rotaxanes, catenanes, and related entities are of a dynamic noncovalent nature, occurring at the supramolecular level and involving displacements induced by changes in noncovalent interactions. On the other hand, motions may be generated by conformational or configurational changes.^{16,27,29}
- (7) The coexistence of intramolecular group transfer and intermolecular group exchange in the processes displayed by imines represents the *merging of motional and constitutional dynamics* within the same system.

Looking ahead, the results reported above suggest numerous extensions in the area of constitutional dynamic covalent processes, such as group transfer between sites in branched polyamines, pattern formation on reversible multiple attachment to polyfunctional amines, oriented motions along a track seeking the thermodynamically most stable patterns or kinetically the most easily accessible ones, exploiting internal self-catalysis, operating fluxional degenerate exchange through continuous bond breaking–bond making processes (that present analogies to the epitomic molecule bullvalene³⁰) in multifunctional carbonyl as well as amine molecules. The processes described here, together with their molecular motor-type features³¹ make imines a class of compounds presenting a particularly rich and wide palette of structural, conformational, and configurational features,^{31b} as well as of constitutional and motional dynamic behaviors.

■ ASSOCIATED CONTENT

■ Supporting Information

All experimental details, NMR spectra, and calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED IN PROOF

An article on a related subject was just published.³²