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Transfer of structural units through imine exchanges, in solution or without solvent: successive transiminations, stimuli (pH)-modulated covalent switches, and mathematical models

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Transfer of structural units through covalent constitutional (non mechanical) switches based on (bis-)imine/amine exchanges (transiminations), can reversibly be modulated by external stimuli, namely by pH changes through alternate additions of acid and base. This is illustrated in this work, in solution, by means of mono- and dialdehydes derived from pyridine. For example, in the case of a dialdehyde Ald, its reaction with an aromatic amine Am1, produces a first bis-imine Im1. Reaction of bis-imine Im1 with an aliphatic amine Am2 produces the aliphatic bis-imine Im2. Addition of acid regenerates the first bis-imine Im1. Subsequent addition of base produces again the second bis-imine Im2. The aromatic amines Am1 used in this work are aniline-based ones, while the aliphatic ones Am2 are primary alkylamines. Trifluoroacetic acid (TFA) and triethylamine (TEA) are used as pH-triggers (external stimuli) in solution. No metal ions are needed to perform the exchanges. In several cases, an excess of aromatic amine Am1, and further, correlatively, an excess of amine Am2 were used to increase the yields. It is also shown that it is possible to invert the steps and to start with aliphatic amine Am2, to continue with aromatic amine Am1 and acid, then, after appropriate adjustments, with base. (Bis-, tris-)imine/(di)aldehyde exchanges in solution were investigated as well. In addition, in a green chemistry approach, under solvent-free conditions, were performed formation of imines, (bis-)imine/amine exchanges and (bis-)imine/(di)aldehyde exchanges, as well as multistep sequences of successive transiminations. In the solvent-free imine/aldehyde-type sequence of successive exchanges, a monoimine is converted into a tris-imine, the tris-imine, into a bis-imine, which finally generates a new monoimine. In the solvent-free imine/amine-type sequence of transiminations, three monoimines derived from the same aldehyde, are successively generated. The experimental work is complemented with an equilibrium-constants-based, mathematical treatment of exchanges between amines and dialdehyde-based bis-imines at equilibrium, in solution: calculation of the composition at equilibrium, modeling of the pH-adaptive behavior of small dynamic libraries

of imines, as well as water-dependent distribution curves. Under particular conditions, a simplified mathematical approach to exchanges (transiminations) can be used, where equilibriums involving di- or monoaldehydes do not appear directly.

KEYWORDS

imines, transimination, dynamic chemistry, pH, solvent-free reaction, acid-base stimuli, mathematical models, exchange

1 Introduction

The structural tuning of chemical species can be performed at covalent and/or supramolecular level, when the concerned bonds are made enough dynamic. It may appear that one or more of the constitutive units of a given molecule can play a structural and/or a functional role in other species and it would be advantageous to transfer it from the first to the second molecule (Figure 1). Such displacement processes can be made possible in the framework of dynamic covalent chemistry (DCC) (Corbett et al., 2006; Lehn, 2007; Rowan et al., 2002), where imines are of much interest (Belowich and Stoddart, 2012; Zentner et al., 2019; You, 2023). In the area of biological catalysts, transiminations take place in reactions catalyzed by pyridoxal phosphate-dependent enzymes (John, 1995; Soniya et al., 2019). Imine exchanges may occur in drug release processes, as well (Dizdarevic et al., 2019).

1.1 Di- and oligoaldehydes in dynamic chemistry

Molecules bearing two or more functional groups, like di- and oligoaldehydes and di- and oligoamines, are good candidates for generation of imine-based complex structures. Constitutional exchanges based on imines derived from dialdehydes may be needed and implemented in cases such as the passage from a macrocycle to a cage-like structure (Figure 2A; Yang and Lehn,

2020), the replacement of a co-monomer in a given polymer (Figure 2B) (Skene and Lehn, 2004) or the transfer of a monoamine between helicates based on bis-imine ligands (Figure 2C) (Schultz and Nitschke, 2006). In the area of dynamic imine chemistry, dialdehyde-based building blocks can act as structural units of dynamic polyimine macrobicyclic cryptands (Kolodziejcki et al., 2019), of imine-linked covalent organic frameworks (Wang et al., 2023), of cages (Schick et al., 2020), of recyclable polymers (Deng et al., 2022) or of polymeric architectures from imine-based covalent adaptable networks (Schoustra et al., 2021). They can also be exchanged between imine-based open circular helicates or between closed-loop pentafoil knots (Ayme et al., 2019). Moreover, recently, in the domain of oligoaldehydes, an imine cage derived from a trialdehyde was transformed, through transimination, into a covalent organic framework film (Giri et al., 2023).

1.2 General motivation for alternate transiminations

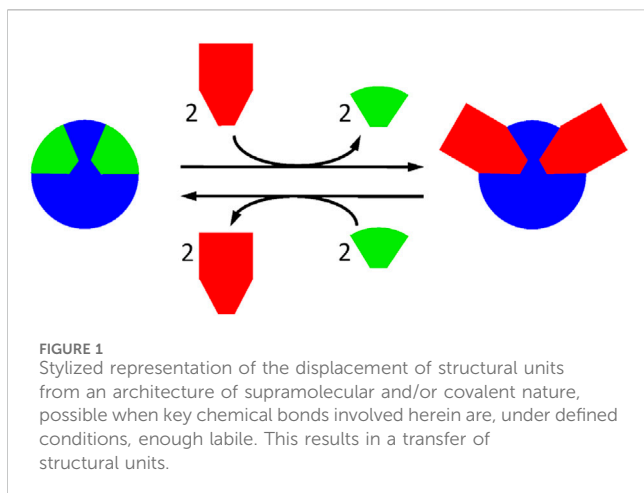
The study of such dynamic processes can be motivated by, for example.

- The wish to explore new dynamic covalent assemblies and/or to solve synthetic problems with help of the DCC;
- The wish to design and synthesize versatile chemical systems with alternate properties and functions, associated to structures which can alternately be generated in the same pot;
- The saving of starting materials and reagents in a green chemistry approach or due to their limited availability (difficult to synthesize or to recover, expensive). Indeed, in the case of stimuli-triggered switches, the reagents and products of transimination can be reused in a certain number of cycles, without isolation and loss;
- The saving of solvents, the sequence of reactions being done in the same pot or, when possible, under solvent-free conditions;
- The development of methods (e.g. separation, purification) or (nano)materials based on exchanges between amines and imines (Diez-Castellnou et al., 2021) derived from immobilized (Krishnamoorthy and Grubbs, 2020) aldehydes.

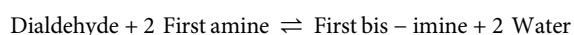
1.3 Exchanges involving dialdehyde-based bis-imines

In the typical and illustrative example of dialdehyde-based bis-imines (which are investigated in the main part of this work), for

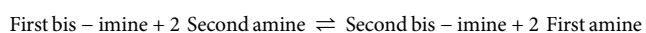




transiminations through reaction with primary monoamines, a first (or initial) bis-imine should form from the corresponding dialdehyde and a first amine, according to the reaction



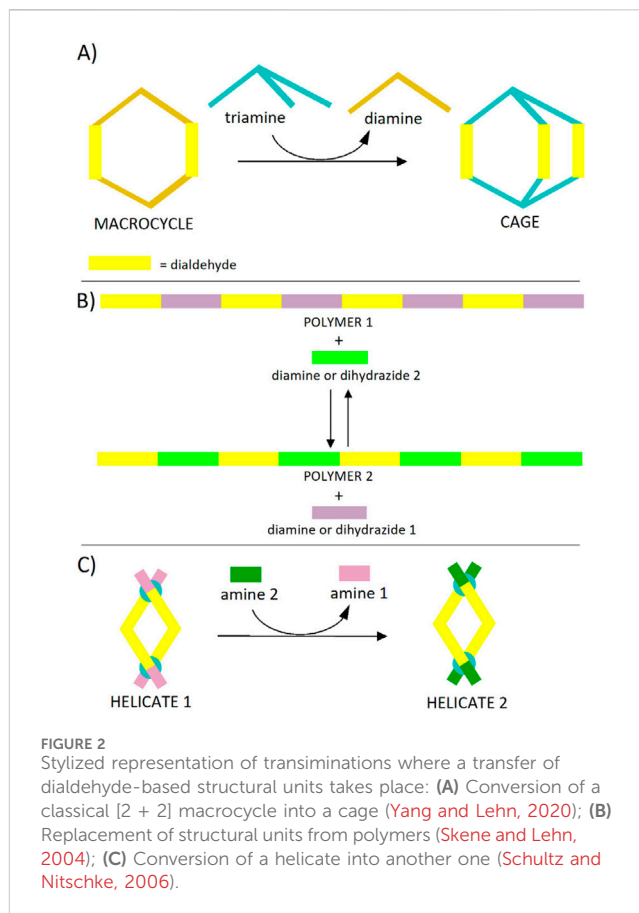
This first bis-imine reacts with a second amine that replaces the first amine. In this way is produced, through transimination (for transiminations, see: [Ciaccia et al., 2013](#); [Ciaccia et al., 2014](#); [Madedec et al., 1997](#); [Vitaku and Dichtel, 2017](#); [Wang et al., 2019](#); [Ye et al., 2012](#)), the second bis-imine:



An important question related to these processes, is if there are some general conditions that could ensure a good yield of transimination reactions. Another point is whether there is a quite fast and simple means that can reverse this situation at equilibrium (thus leading to the formation of the first imine) and that could be generalized and applied without isolation of the products. And once this equilibrium is reversed, one may wish to find a quite conveniently to implement means to go back again and to regenerate the second imine.

1.4 pH-modulated, imine-involving exchanges

It was shown that selection in libraries of imines can be modulated through pH changes ([Giuseppone and Lehn, 2006](#)). An aliphatic diamine incorporated into the bis-imine ligand of a Cu(I) mononuclear complex, was displaced on treatment of the complex with an aromatic diamine dihydrochloride ([Schultz and Nitschke, 2005](#)). Sulfanilic acid produced, by protonation and transimination, displacement of aliphatic amines from bis-imines acting as ligands in Cu(I) dinuclear helicates ([Nitschke et al., 2004](#)). We have previously shown ([Stadler, 2013](#)) that the selectivity of Schiff base formation in mixtures of 1 equiv. of aromatic amine and 1 equiv. of aliphatic amine upon reaction with 1 equiv. of aldehyde, can significantly be modulated between the absence and the presence of 1 equiv. of acid. Indeed,



in the absence of acid, mainly forms the aliphatic imine, while in its presence, the main product is the aromatic one. Similarly, gold nanoparticles bearing immobilized aldehydes react, in the presence of equal amounts of aliphatic and aromatic amine, preferentially with the aliphatic amine, while in the presence of acid, the preference is reversed; it is reestablished on addition of base ([Diez-Castellnou et al., 2021](#)).

Such processes of reorganization of the molecular constitution (here, at the covalent level) upon alternate pH changes can also be seen as an adaptive response of dynamic libraries of aldehydes, amines and imines to external stimuli (here, the pH).

1.5 Preliminary overview

With the above considerations in mind, we report herein ([Section 2](#)) on the formation of (di)aldehyde-based aromatic and aliphatic (bis-)imines, and on (bis-)imine/amine exchanges in solution, as well as on the synthesis of a mono- and a dialdehyde. The key point consists of pH-modulated transiminations where an aromatic amine works as first (initial) amine, and an aliphatic one, as second amine. The difference of basicity and nucleophilicity between the two amines should make possible a better selectivity and its modulation through the pH. The aim of the first part is rather to illustrate this kind of covalent switch ([Zou et al., 2019](#)) based on transiminations, than to produce a study with a considerable number of examples.

We further wished to extend the investigation to other types of exchanges (namely, to imine/aldehyde exchanges) and to other conditions (namely, without solvent). A number of (tris-, bis-) imine/(di)aldehyde exchanges (Section 3) are also presented here, although a way to trigger them through external stimuli (e.g. pH changes) is not yet available.

Imine formation and transiminations, including sequential multistep processes, were tried under free-solvent conditions, as well (Section 4).

The first four parts of this work are complemented by a fourth one. The last part (Section 5) deals with calculations based on equilibrium constants, which include the determination of the composition at equilibrium starting from initial concentrations of amines and aldehydes, equilibrium-constants-based modeling of the pH-adaptive behavior of small dynamic libraries of imines and calculation of water-dependent distribution curves.

This work is mainly focused on dialdehydes. Monoaldehydes can serve as models or as competing aldehydes. A trialdehyde was used in a sequence of successive, multistep exchanges, and the corresponding tris-imine was used for an exchange in solution.

With one exception (ketimine **bzphim**; vide infra), all Schiff bases used in this work are imines derived from aldehydes, namely (mono-, bis- or tris-)aldimines. In the framework of this report, where all aldehydes are aromatic ones, “aromatic” imine means an imine derived from an aromatic amine, and an “aliphatic” imine is one derived from an aliphatic amine.

1.6 Experimental considerations

As preliminary experimental observations, one may notice that reactions in solution (except those where the imine products are isolated) are done in NMR tubes (0.5–1 mL of solution), on milligram scale. The starting mono- or bis-imine may directly be prepared in the tube and used without purification, or may be isolated by precipitation, or prepared in another convenient way (like the solvent-free methods, vide infra). In most cases of dialdehyde-based bis-imines prepared in the tube, we used an excess of monofunctional reagent (monoamine) to increase the yield of starting aromatic bis-imine (vide infra).

For the switches in solution, the reagents are usually added in small volumes of solvent, with appropriate microsyringes. In practice, depending on factors like the amount of water from the solvent, the amount of water from the reagents and the uncertainties associated to the preparation of the solutions, it might be necessary for the theoretically calculated volumes of reagent solutions, to be slightly adjusted. In order to keep the volume of the reaction mixture as constant as possible and to limit the external (undesired) inputs of water, one may, amongst other possibilities: i) use concentrated solutions of reagents, which lead to very small volumes of solution to add, so that the overall volume of the reaction mixture can be seen as constant; ii) add the reagent in a small volume of solvent, then, under Ar or N₂ flow, without heating, evaporate the corresponding volume of solvent from the reaction mixture.

Chloroform-d₃ (main NMR solvent) may contain traces of acid (Teipel et al., 2022). It is usually filtered through basic alumina; the kinetics may be affected by possible traces of acid, which may act as a catalyst.

The reaction mixtures in solution are generally equilibrated at room temperature. The equilibration can be accelerated by heating.

The working concentrations before reaction are usually between 3×10^{-3} M and 2×10^{-2} M. The yields and conversions were determined by ¹H NMR (integration uncertainties being, on average, of about ±5%).

The equilibrium constants associated to imine formation or exchange were roughly estimated through NMR spectroscopy. For reactions involving water, the concentration of water in the reaction mixture at equilibrium was included in the calculation of the constants. In our experiments, the concentration of water (before and after equilibration) is usually below the solubility (of about 7.2×10^{-2} M at 25°C) of water in chloroform (Horwath et al., 1995).

Chemicals from commercial sources were used without purification.

2 Exchanges between (bis-)imines and amines in solution. pH-modulated covalent switches

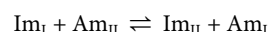
2.1 General principles. Choice of aldehydes and amines. Main equilibria

Such (bis-)imine/amine transiminations are covalent constitutional interconversions between two architectures, which occur through breaking and formation of C=N dynamic covalent bonds (Chakma and Konkolewicz, 2019; Wanasinghe et al., 2022), generally under equilibrium conditions. As covalent (non mechanical) constitutional switches, they should operate in a way that can be made reversible, should not be too slow, should be triggered by stimuli and it should be possible to modulate and implement them in a relatively accessible way.

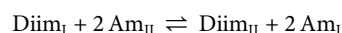
2.1.1 A short classification of (bis-)imine/(di) amine exchanges

This part of our work is limited to exchanges which are based on mono- or difunctional compounds and does not deal with macrocyclic or polymeric imines. An attempt of systematic presentation of the exchanges between (bis-)imines and (di) amines can be done on the basis of a short classification that includes the following types of reactions (Am = amine, Im = imine, Diam = diamine, Diim = bis-imine).

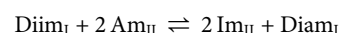
- i. imine I with amine II (formation of amine I and of target imine II)



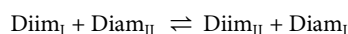
- ii. dialdehyde-based bis-imine I with amine II (formation of amine I and of target bis-imine II)



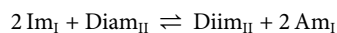
- iii. diamine-based bis-imine I with amine II (formation of diamine I and of target imine II)



- iv. diamine-based bis-imine I with diamine II (formation of diamine I and of target bis-imine II)



- v. imine I with diamine II (formation of amine I and of target diamine-based bis-imine II)



- vi. macrocyclic bis-imine I (from diamine I and dialdehyde) with diamine II (formation of diamine I and of target macrocyclic bis-imine II or of oligomeric or polymeric structures).

In terms of number of imine groups per imine-containing-molecule, between the starting (bis-)imine and the target one, there are cases where this number remains constant (e.g. amine/dialdehyde-based-bis-imine exchanges, namely from 2 (bis-imine) to 2 (bis-imine)), and cases where it changes (e.g. amine/diamine-based-bis-imine exchanges, namely from 2 (bis-imine) to 1 (imine)). This classification is of interest also for the choice of the mathematical model which is to be applied to the system.

One deals in this section with exchanges, in solution, between monoamines and bis-imines derived from dialdehydes (point ii of the above classification), and between monoamines and monoamines (point i of the classification). In the examples presented here, I from the previous classification corresponds to the aromatic nature of the amine, and II, to its aliphatic nature.

2.1.2 Choice of aldehydes

Reaction of an equimolar mixture of 1 equiv. of 2,6-pyridinedicarboxaldehyde **dialpy** and 1 equiv. of isophthalaldehyde **iphtal** with 2 equiv. of decylamine **L4** produces a reaction mixture where 2,6-pyridinedicarboxaldehyde is consumed, under kinetic conditions, faster than isophthalaldehyde (Figure 3a). A similar behavior is observed when a mixture of 1 equiv. of 2,6-pyridinedicarboxaldehyde **dialpy** and 2 equiv. of 2,4-dinitrobenzaldehyde **dinial** reacts with 2 equiv. of octadecylamine **L5** (Figure 3b). The bis-imine from pyridine-derived dialdehyde is the main kinetic product (yield >67%, depending on the reaction time). This seems however to be a rather kinetic situation, that may be different from that at equilibrium.

Reaction of mixtures consisting of 1 equiv. of a benzene-derived aldehyde and 1 equiv. of a homologous pyridine-derived one (3-bromobenzaldehyde and 6-bromo-2-pyridinecarboxaldehyde; salicylaldehyde and 3-hydroxy-2-pyridinecarboxaldehyde; 2-naphthaldehyde and 2-quinolinecarboxaldehyde) with p-toluidine, suggests that, for the same kinds of substituents, similarly disposed, the pyridine-derived aldehyde reacts faster than the homologous benzene-derived one (see **Supplementary Material** = SM, file synt-char, p. 129).

On the basis of these results and with the aim of reaching reasonable reaction rates, we decided to use, for the syntheses of (bis-) imines involved in the exchanges performed in this part of the work, (di)aldehydes derived from pyridine (or quinoline), rather than (di)aldehydes derived from benzene.

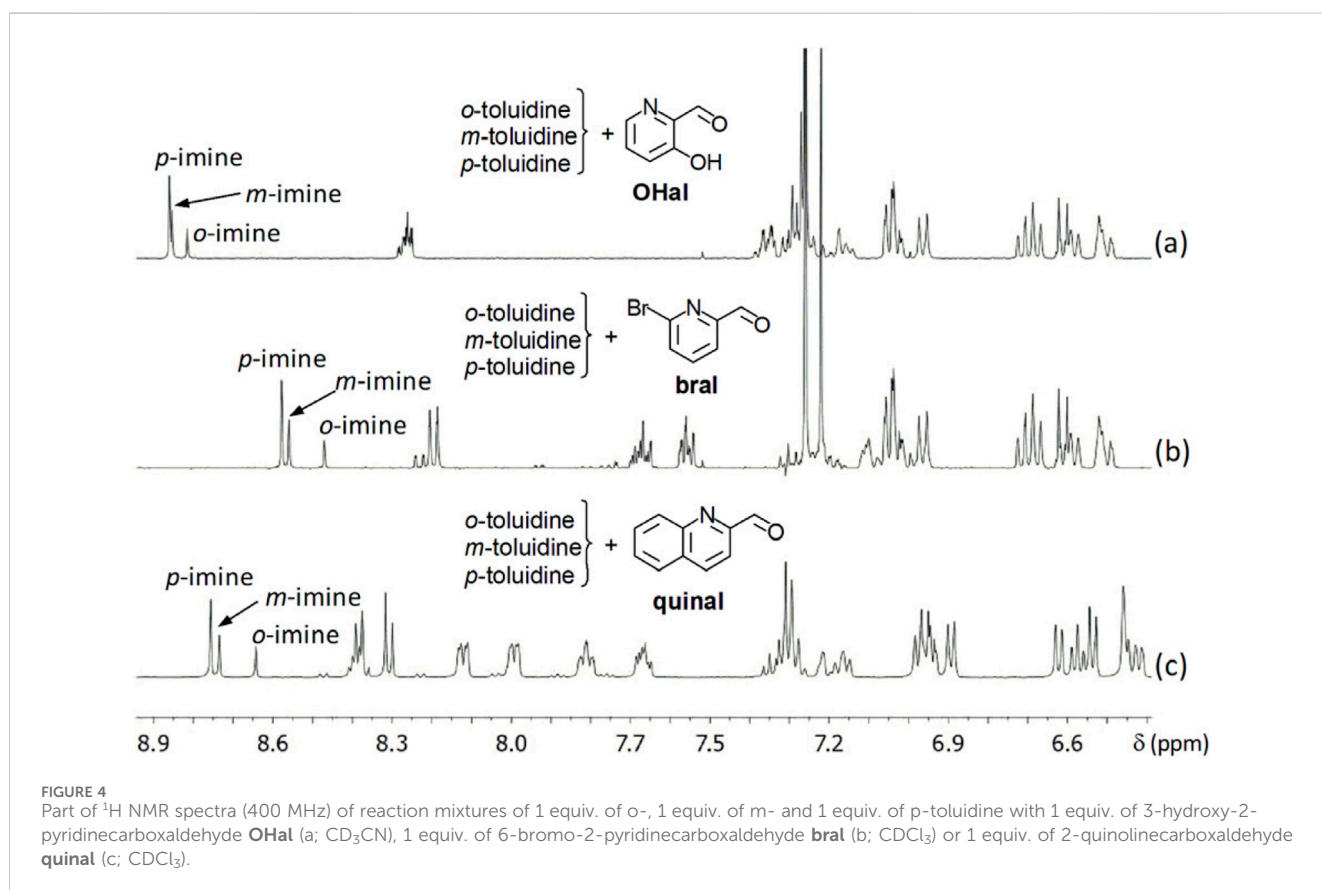
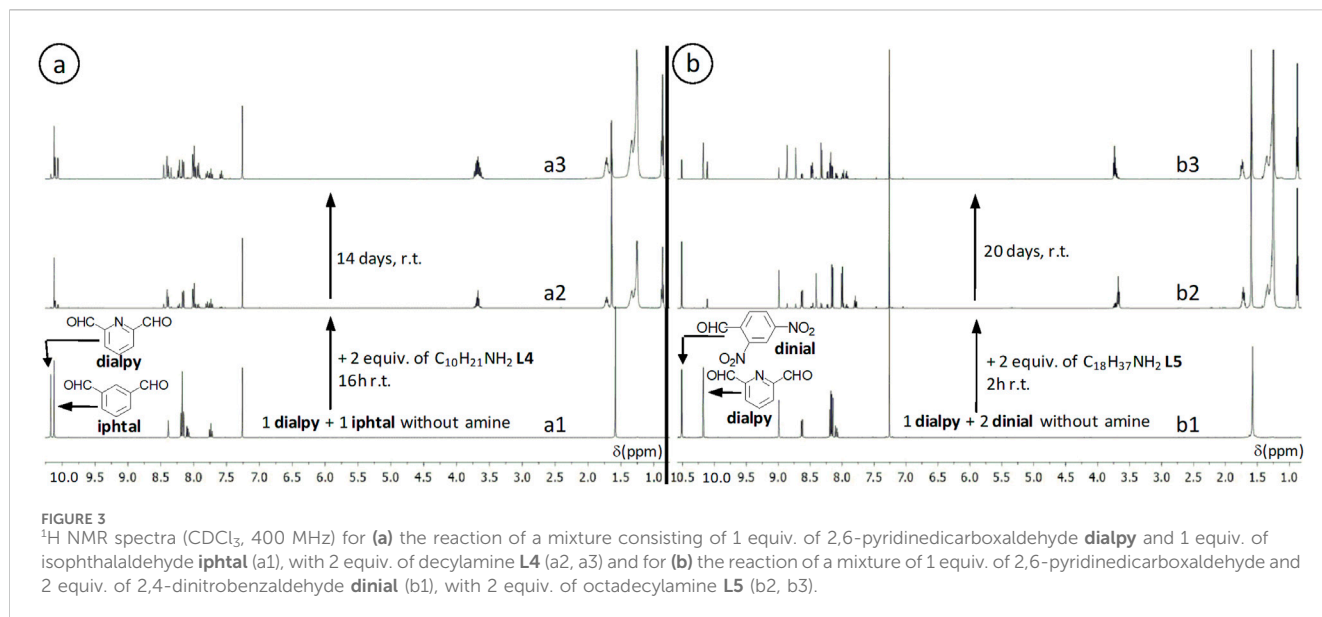
2.1.3 Choice of aromatic amines

In the framework of a qualitative screening, the choice of aromatic amines was done in several steps. We worked mainly with benzene-based amines and we tried to select, amongst a limited set of compounds, most of which are commercially available, those which would react faster.

Aldehydes may generate, as autoxidation products with oxygen (Liao et al., 2022), acids. Chloroform-d₃, which is the main solvent for this work (although several reactions were done in acetonitrile-d₃), may contain traces of hydrochloric acid (Teipel et al., 2022). In order to diminish the influence of such potential acid sources on the comparison of reaction rates, we decided to put two or three amines in competition for a same aldehyde, in order to purely qualitatively compare their reactivities.

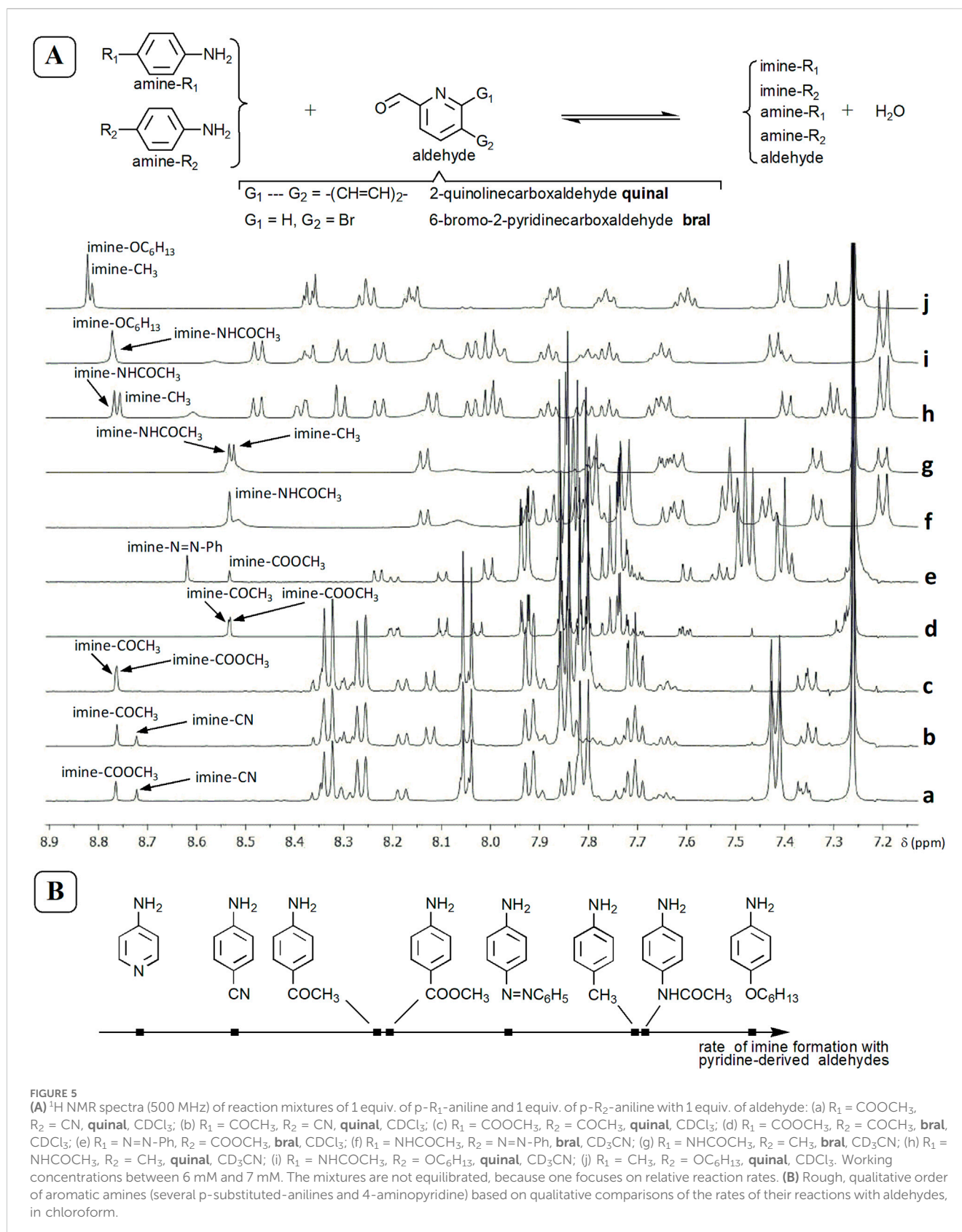
- i. Choice of positional isomers. Reaction of equimolar mixtures consisting of one equivalent of o-, m- and p-toluidine with one equivalent of 3-hydroxypyridine-2-carboxaldehyde **OHal**, 2-quinolinecarboxaldehyde **quinal** or 6-bromo-2-pyridinecarboxaldehyde **bral** (Figure 4) shows that p-toluidine is the most reactive. Reaction of a mixture of 1 equiv. of o- and 1 equiv. of p-anisidine, with 1 equiv. of 6-bromo-2-pyridinecarboxaldehyde, shows that p-anisidine reacts faster than o-anisidine.
 - ii. Choice of primary aromatic amines. Further, we comparatively tested seven p-substituted-anilines (4-acetylaniline, 4-aminoacetanilide, 4-aminoazobenzene, 4-aminobenzonitrile, methyl-4-aminobenzoate, 4-(hexyloxy)aniline **R4** and p-toluidine **R3**), by making subsets of two amines. To this purpose, equimolar mixtures of 1 equiv. of a first p-substituted-aniline and 1 equiv. of a second one were reacted with 1 equiv. of aldehyde (2-quinolinecarboxaldehyde **quinal** or 6-bromo-2-pyridinecarboxaldehyde **bral**; for a selection of spectra, see Figure 5A). These qualitative comparisons are mainly based on the relative intensity of peaks corresponding to the protons from CH=N imine groups. They lead to a qualitative and relative estimation of the order of p-substituted-anilines based on the rate of their reaction with pyridine- and quinoline-derived aldehydes (Figure 5B; preliminary results suggest that the same order would hold for the formation constants of the corresponding imines). 4-Aminopyridine was also tested, in chloroform-d₃. These results (Figure 5B) together with those from reactions of 2,6-pyridinedicarboxaldehyde with p-substituted-anilines possessing OC₆H₁₃, CH₃, CN, COCH₃ and COOCH₃ at the para position (see SM, file synt-char, pp. 111–115) led us to consider p-toluidine and p-(hexyloxy)aniline as good aromatic amine candidates, especially when starting imines are intended to be prepared in the NMR tube and to be further used without isolation.
- The nucleophilicity of these amines can, in most cases, be correlated with the inductive (I) and mesomeric (M) effects of substituents: CN, COCH₃, COOCH₃ (–I and –M), CH₃ (+I) and NHCOCH₃, OC₆H₁₃ (–I < +M).

Considering these results, we focused our work mainly on p-anilines. Only a few experiments with m-substituted anilines were performed.



2.1.4 Motivation for dialdehydes **A** and **dialpy**

- i. In the dialdehyde **A** (Figures 6A, 7), the sequence generated by pyridine rings together with the hydrazone groups adopts a linear conformation (Figures 6, 7). Such sequences can contract and become helical on reaction with metal ions (Figures 6, 7) (Stadler and Lehn, 2014), like Pb^{2+} . The contraction is reversible upon removal of the metal ions. This could provide our system with a potential mechanical motional function (not investigated here), which will be the basis of a future work dealing with contractile polymeric architectures (Figure 6B; see (Dattler et al., 2020)).
- ii. Dialdehyde **A** incorporates, as its central moiety, the **dialpy**-derived sequence 2,6-bis(imino)pyridine (Figure 6C), that



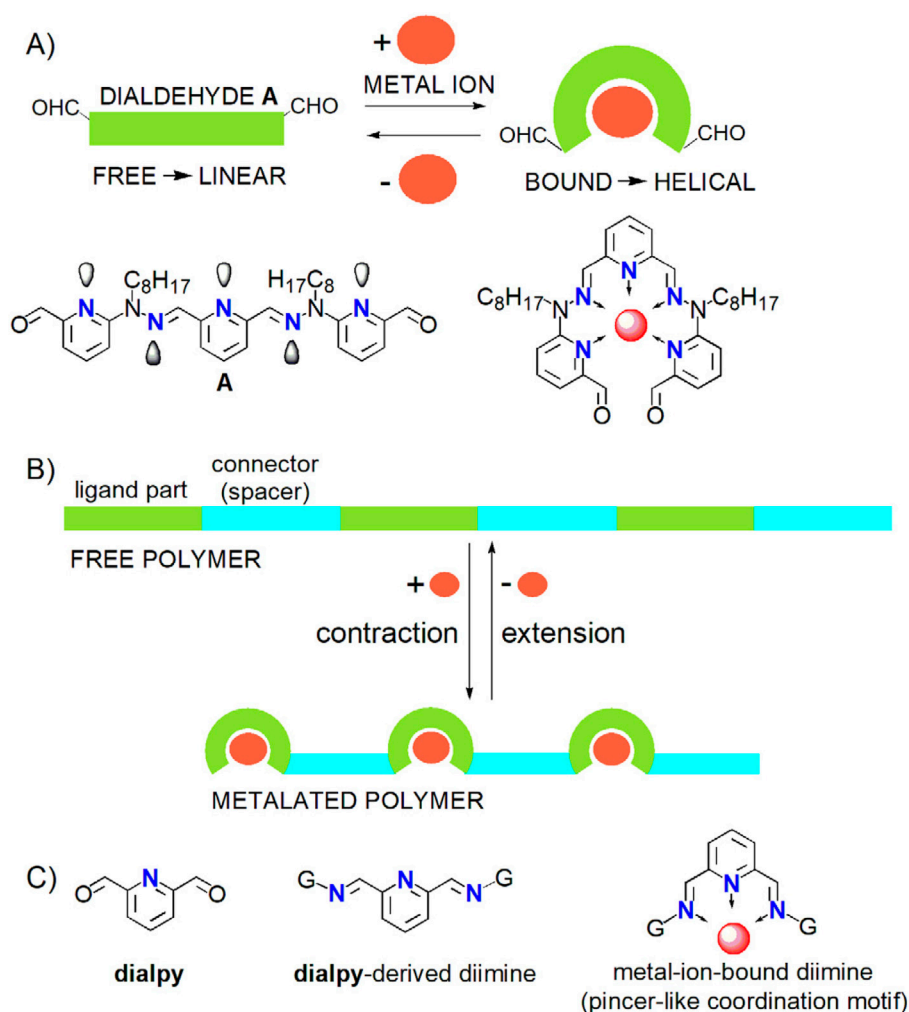


FIGURE 6
 (A) Dialdehyde **A** (Figure 7) possesses a metal-ion-dependent mechanical motional function: as a free ligand, it adopts a linear conformation, which becomes helical on reaction with metal ions (red circles), thus resulting in a contraction. (B) The polymers generated with **A** as a comonomer should undergo reversible contraction on reaction with metal ions. Stylized representations. (C) Structural formulae of dialdehyde **dialpy**, of its bis-imine (general case) and of the corresponding pincer-like coordination motif.

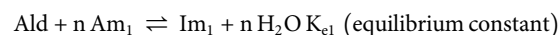
may act as a tridentate ligand and produce pincer like-coordination motifs or complexes (Gibson et al., 2007), a fact that motivates our interest in exploring such **dialpy**-derived bis-imines.

The study of the dicarbonyl species **A** is advantageously preceded by that of the model monoaldehyde **M**.

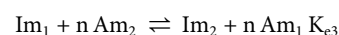
2.1.5 Overview of equilibriums

Control of imine exchanges through protonation/deprotonation of amines is a convenient one, given that acids and bases are easily available. The simplified sequence of exchanges for a molecule Ald bearing n aldehyde groups (when Ald = **A**, then $n = 2$) can be written as follows.

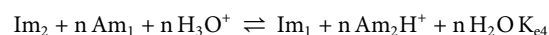
- Formation of the first imine Im_1 from aldehyde Ald and the first amine Am_1 :



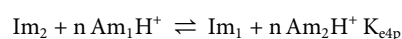
- First exchange:



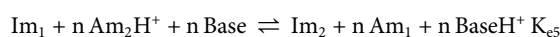
- Acid-triggered exchange:



If the protonation of amine Am_1 is considered, the reaction is as follows:



- Base-triggered exchange:



Considering the formation of the second imine

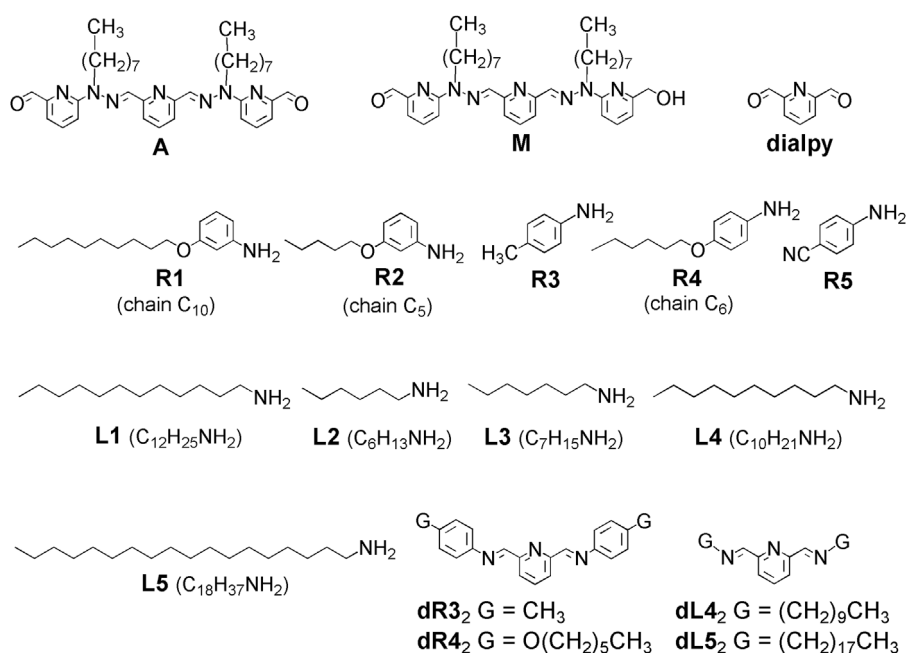
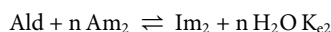
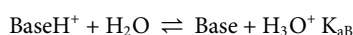
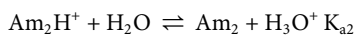
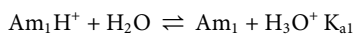


FIGURE 7
Structural formulae of monoaldehyde **M**, dialdehydes **A** and **dialpy**, aromatic amines **R1-R5**, aliphatic amines **L1-L5** and bis-imines **dR3₂**, **dR4₂**, **dL4₂** and **dL5₂**.



and the acidity constants:



the following equalities can be written

$$K_{e3} = K_{e2}/K_{e1}$$

$$K_{e4p} = (1/K_{e3}) \times (K_{a1}/K_{a2})^n$$

and

$$K_{e5} = K_{e3} \times (K_{a2}/K_{aB})^n$$

We notice that if $K_{a2} = K_{aB}$, then $K_{e5} = K_{e3}$.

In this simplified approach, equilibria like dissociation of the acid, intermediate reactions (formation of monoimine from dialdehyde, of hemiaminals) or side reactions (formation of animal, of aldehyde hydrates), possible partial protonation of the N_{pyridine} atom, have not been written.

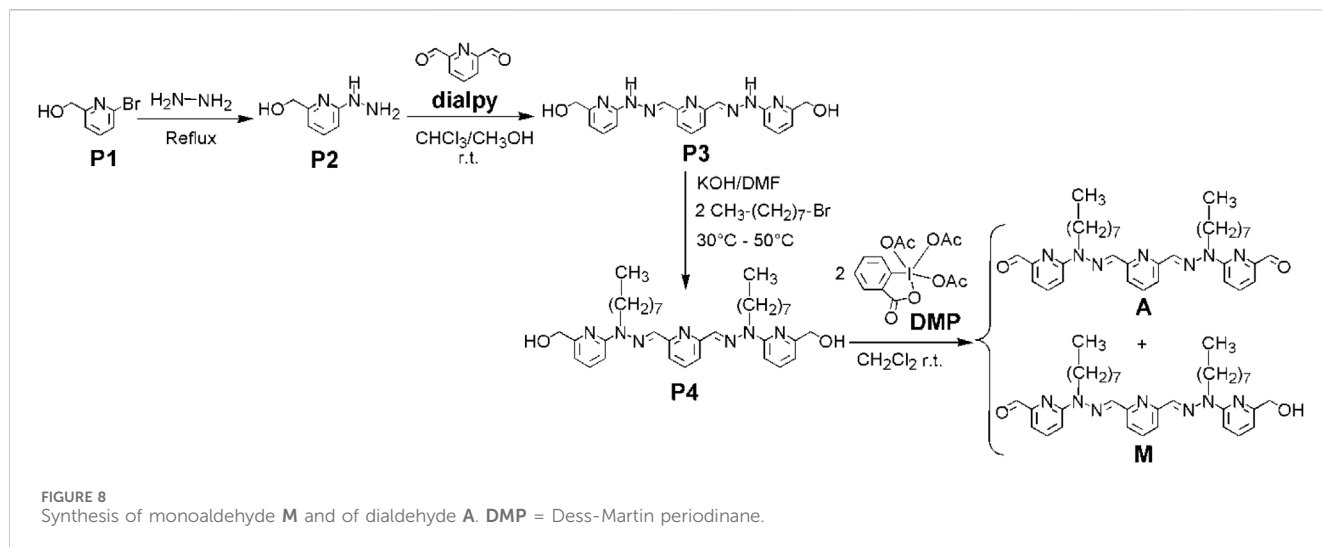
In the case of a dialdehyde ($n = 2$), starting from a 1:2 mixture of dialdehyde Ald and amine Am_1 , and assuming the only source of water would be that generated in this reaction, for a conversion of 90% of Ald into bis-imine Im_1 , with 5% of monoimine (or aldehyde-imine, not shown), K_{e1} should be of about 2.7×10^3 . Further, if to the previous equilibrated mixture one adds 2 equiv. of amine Am_2 , then, for the same conversion of 90% of Im_2 with respect to the starting dialdehyde Ald and with 5% of mixed bis-imine (derived from Am_1 , Am_2 and Ald; not shown) and 1% of monoimine (from Am_2 and Ald),

K_{e2} should be of about 1.1×10^7 (here, one assumes that the other Ald-based species in the equilibrated reaction mixture are only Ald itself (if still any), the bis-imine Im_1 and the aldehyde-amine from Am_1). Under similar conditions, but with conversions of 99% instead of 90%, 0.5% instead of 5% and 0.1% instead of 1%, one should have $K_{e1} \approx 3.5 \times 10^6$ and $K_{e2} \approx 1.7 \times 10^{13}$ (see SM, file l-simul-Ke1-Ke2).

pK_a values of primary alkylamines and of tertiary trialkylamines in water are generally between 10 and 11 (Hall, 1957). p-Toluidine has a pK_a of 5.07, p-methoxy-aniline one of 5.29 and m-methoxy-aniline, one of 4.20 (Brown et al., 1955). These values, although for water, suggest that aliphatic amines **L1-L5**, aromatic ones **R1-R4** (Figure 7) and triethylamine TEA should be, thank to the differences between their pK_a values, good candidates for the implementation of such acid/base-triggered switches. In addition, in an organic solvent like CH_3CN , primary aliphatic amines, such as n-propylamine and n-butylamine are more nucleophilic than p-anilines, like p-toluidine and p-anisidine. Indeed, in acetonitrile, n-butylamine has an $N_{\text{parameter}}$ of 15.27 and n-propylamine, one of 15.11 (Kanzian et al., 2009), while p-toluidine displays 13.19 and p-anisidine, 13.42 (Brotzel et al., 2007). The nucleophilicity of amines is, of course, relevant here, because the mechanism of imine formation (Ciaccia and Di Stefano, 2015), as well as that of imine/amine exchange starts with a nucleophilic attack of the amine to the C=O or C=N bond. One may however notice that the nucleophilicity is not always in correlation with the basicity.

2.2 Synthesis

2,6-Pyridinedicarboxaldehyde **dialpy** was obtained through oxidation of 2,6-di(hydroxymethyl)pyridine with selenium



dioxide SeO_2 (Alam, 2011). Reaction of 2-bromo-6-hydroxymethylpyridine **P1** with hydrazine under reflux produces the corresponding hydrazino-alcohol **P2**. 2 equiv. of compound **P2** react with 1 equiv. of 2,6-pyridinedicarboxaldehyde and generate the corresponding dihydrazone **P3**. Its NH groups are further alkylated with *n*-octylbromide (in the presence of KOH in DMF), in order to ensure a good solubility. The resulting diol **P4** (for a related compound, see (Lobo et al., 2019)) was reacted with the Dess-Martin periodinane (Dess and Martin, 1983) in order to oxidize the CH_2OH groups to aldehydes (Ulrich et al., 2009). This produced a mixture of monoaldehyde **M** and dialdehyde **A** (Figure 8; see SM, file synt-char, pp. 3–108).

Amines **R1**, **R2** and **R4** were prepared from 4- or 3-hydroxyacetanilide according to methods described in the literature (Bartulin et al., 1986; Sharma et al., 2017).

2.3 Imine formation

The reactions, mainly performed in CDCl_3 for the sake of the solubility (and only in a few cases in CD_3CN), were monitored through ^1H NMR.

Aromatic (bis-)imines used as first (starting) bis(imines) can be beforehand synthesized and isolated (by precipitation, like in the case of **AR3**₂) or obtained in the NMR tube and used without isolation. In the last situation, an excess of aromatic amine may be added in order to increase the yield of target (bis-)imine (like for the reaction of dialdehyde **dialpy** with amines **R3** or **R4**, vide infra). This excess can be calculated (vide infra, the calculations on constants) or added by titration until a satisfactory yield of (bis-)imine is reached. For example, a reaction mixture of **dialpy** (about 6.2 mM in CDCl_3 ; r.t.) with **R3** (2 equiv., 1 week) contains about 61–64% of bis-imine, while that with **R4** (2 equiv., about 3 days) has about 80% of bis-imine. Addition of an excess of amine (2.5 equiv. of **R3**; 0.75 equiv. of **R4**; about 12 days at r.t.), produces yields of bis-imine higher than 90%.

The yields of imine formation depend, of course, amongst other factors, also on the amount of water (vide infra, Section 5.2.4).

Uncertainties associated to equilibrium constants K_1 and K_2 were, roughly, estimated to be, on average, of about $\pm 20\%$ to $\pm 40\%$ and they should be higher for constants K_{e1} .

2.3.1 Imines from aldehyde **M**

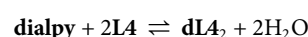
Reaction of monoaldehyde **M** (Figure 7) with 1 equiv. of aromatic amine **R1** produces the imine **MR1** with $K_{e1} = 10$ (yield: 57%). With the aliphatic amine **L1**, the reaction (Figure 9) of the monoaldehyde **M** is relatively fast ($t_{1/2} = 15$ min) and almost quantitative (98%), for a much higher equilibrium constant $K_{e1} = 9.8 \times 10^3$. For examples of reactions between aliphatic amines and pyridinealdehydes, see (French and Bruice, 1964; Green and Rogerson, 1968).

2.3.2 Bis-imines from dialdehyde **A**

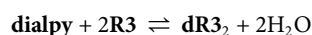
Dialdehyde **A** reacted with 2 equiv. of aromatic amine **R2** to form the corresponding bis-imine **AR2**₂ with a roughly estimated K_{e1} of 55 (yield: 66%) and a half-reaction time $t_{1/2}$ of about 4 h. Reactions of dialdehyde **A** with aliphatic amines **L1** (*n*-dodecylamine) and **L2** (*n*-hexylamine) were much faster ($t_{1/2}$ of about 10–15 min). The conversion to bis-imine was significantly higher (96–97%), where K_{e1} for **L1** is of 5.7×10^6 , and that for **L2**, of 2.8×10^6 . These data are in agreement with the idea that the aliphatic amines react faster than the aromatic ones and their imines have formation constants higher than those of the aromatic ones.

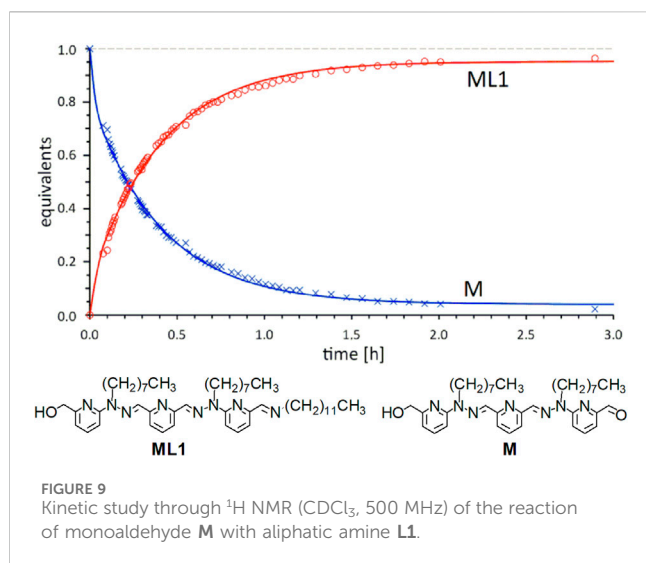
2.3.3 Bis-imines from dialdehyde **dialpy**

A good precursor of Schiff bases is 2,6-pyridinedicarboxaldehyde **dialpy** (vide supra). For the formation of bis-imine **dL4**₂ from **dialpy** and decylamine **L4**

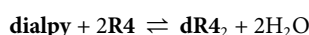


K_{e1} is greater than 10^7 , while for the reaction of **dialpy** with *p*-toluidine **R3**



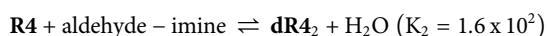
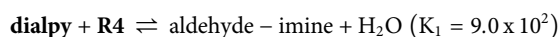


one has $K_{e1} = 10.9 \times 10^3$, and for the reaction of **dialpy** with 4-(hexyloxy)aniline **R4**

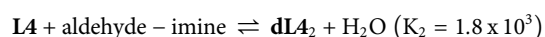
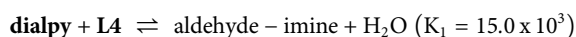


one has $K_{e1} = 14.4 \times 10^4$.

For the formation of bis-imines from dialdehyde **dialpy** and amines **L4** and **R4**, the formation constant of the bis-imine from aldehyde-imine (monoimine) and amine is lower than the formation constant of the aldehyde-imine (monoimine) from dialdehyde and amine, as suggested by the following reactions



and with amine **L4**



2.4 Transfer of structural units through transiminations (exchanges)

The work done in this subsection is focused mainly on the starting aromatic-aromatic- (e.g. **AR**₂) and final aliphatic-aliphatic-bis-imines (e.g. **AL**₂) from each reaction (Figures 10–12), rather than on the likely intermediate mixed aliphatic-aromatic-bis-imines (**ALR**).

The exchanges can be followed by ^1H DOSY NMR (see SM, file synt-char, pp. 120–121).

2.4.1 Bis-imines with amines

The global equation of the reaction of 2 equiv. of *n*-heptylamine **L3** with 1 equiv. of bis-imine **AR**₃ (beforehand synthesized from dialdehyde **A** and 2 equiv. of *p*-toluidine **R3**) and that with 1 equiv. of bis-imine **AR**₄ (obtained from **A** and 2 equiv. of *p*-(hexyloxy)aniline **R4**), can be written as follows:



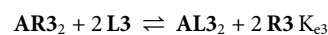
On that basis, one can calculate the equilibrium constant for the reaction



This example confirms a fact that should generally be true: considering the same bis-imine (here **AR**₃), the equilibrium constant for the cases where the displacing amine is an aliphatic one (like here, **L3** *n*-C₇H₁₅NH₂), is higher than where the displacing amine is an aromatic one (here, *p*-(hexyloxy)aniline **R4**).

The equilibration of such exchange reactions (aliphatic amine + aromatic (bis-)imine) usually requires several hours.

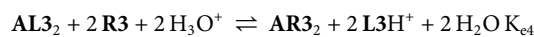
The increase of the amount of displacing amine, produces an increase, in agreement with Le Chatelier's principle, of the yield. For example, for the reaction



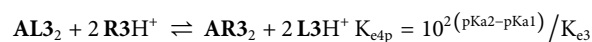
the yield was of about 95% for 3.6 equiv. of *n*-heptylamine **L3**, while it was of about 87% for 2 equiv. of *n*-heptylamine.

2.4.2 Addition of acid

In the last situation, subsequent addition of 2.2 equiv. of trifluoroacetic acid (TFA; Figure 10a), partly regenerates the starting bis-imine, according to the chemical equation:



or, considering the protonation of aromatic amines (although under these conditions, where **R3** is an aromatic and **L3** an aliphatic one-very weak)



with a yield of 68%, the reaction being quite fast (a few minutes). The protonation inverts the sense of the selectivity. Indeed, without acid, the aliphatic imine forms preferentially, while in presence of acid, the favored imine is the aromatic one (Stadler, 2013). For the amines used in our work, the difference $\Delta\text{p}K_a = \text{p}K_{a2} - \text{p}K_{a1}$ is of about 5–6 units, in water. The $\text{p}K_a$ values may be different in the cases herein reported, where the solvent is CDCl_3 .

Under these conditions, trifluoroacetic acid (TFA) not only acts as a protonating agent of - mainly - aliphatic amines, but it also catalyzes the exchanges. Indeed, the equilibration after addition of acid is particularly fast. Partial protonation of species (e.g. primary aromatic amines, pyridines) other than the primary aliphatic amine might also occur. This can, together with the chemical exchanges, affect the NMR chemical shifts of the species in solution. This should explain the slight differences between the ^1H NMR spectrum of the starting bis-imine and that obtained after addition of TFA (Figure 10a). The yield of this step may often be lower than those of other steps, and this can be due to acid-catalyzed hydrolytic processes. The excess (if any) of aromatic amine added in the initial steps can limit such hydrolytic effects.

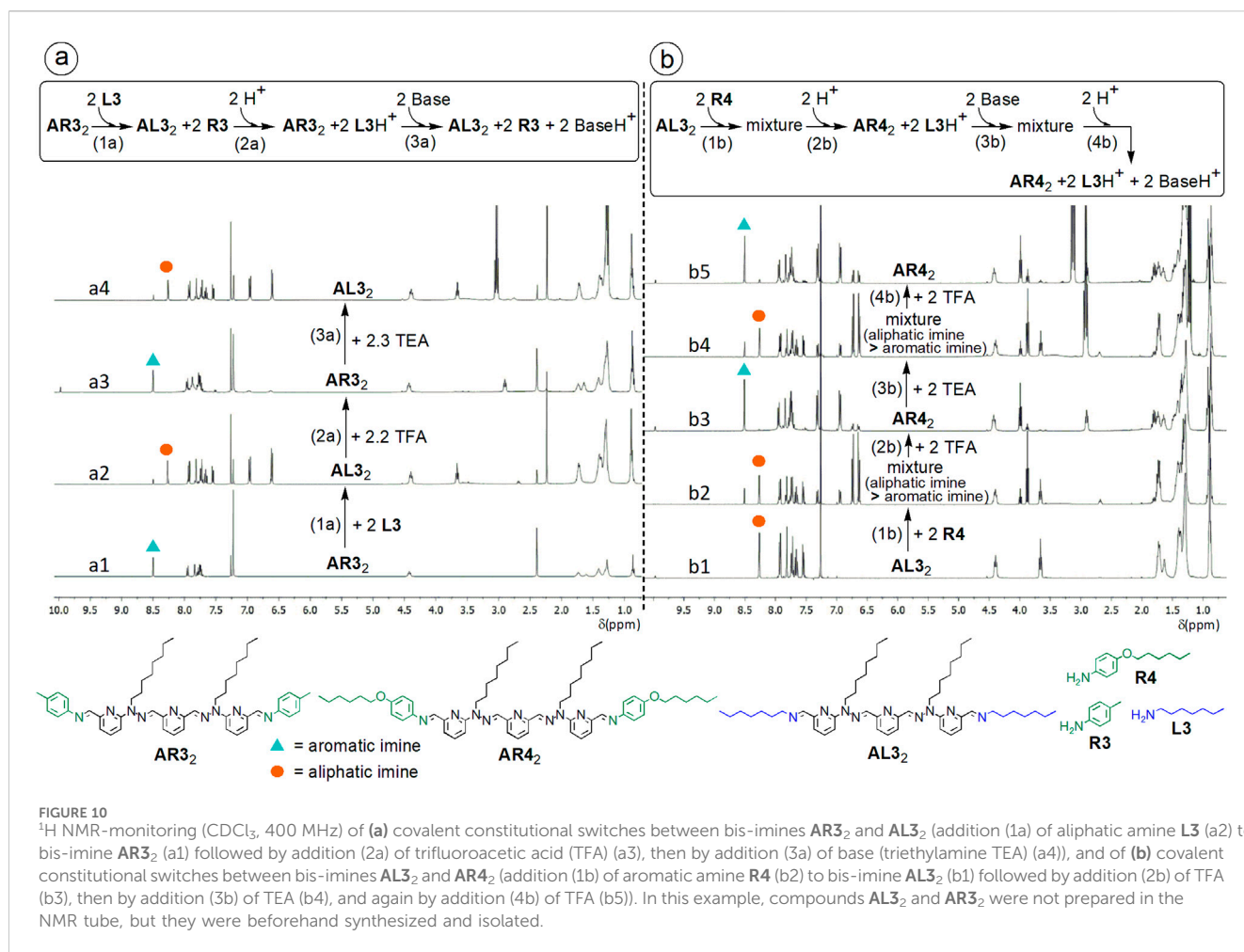
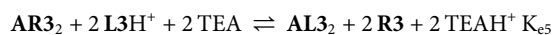


FIGURE 10

¹H NMR-monitoring (CDCl₃, 400 MHz) of (a) covalent constitutional switches between bis-imines AR₃₂ and AL₃₂ (addition (1a) of aliphatic amine L3 (a2) to bis-imine AR₃₂ (a1) followed by addition (2a) of trifluoroacetic acid (TFA) (a3), then by addition (3a) of base (triethylamine TEA) (a4)), and of (b) covalent constitutional switches between bis-imines AL₃₂ and AR₄₂ (addition (1b) of aromatic amine R4 (b2) to bis-imine AL₃₂ (b1) followed by addition (2b) of TFA (b3), then by addition (3b) of TEA (b4), and again by addition (4b) of TFA (b5)). In this example, compounds AL₃₂ and AR₃₂ were not prepared in the NMR tube, but they were beforehand synthesized and isolated.

2.4.3 Addition of base

Further addition of an organic base, triethylamine (TEA; in practice, usually, between 1 and 1.4 equiv. of base per equiv. of acid), regenerates the aliphatic bis-imine



with a yield of 92%. The sequence of pH-triggered switches can be represented in a cyclic manner (Figure 11). For two related examples, see Figures 12a, b.

The transfer of protons from the protonated second amine (e.g. L₄H⁺) to the base (e.g. Et₃N = TEA) makes possible—through transimination—the transfer of dialdehyde-derived structural units. This is represented here (Figure 12c) for the conversion of bis-imine dR₃₂ into bis-imine dL₄₂. The selectivity of imine formation is alternately reversed through addition of acid, than of base.

The aliphatic amines (e.g. n-hexyl-, n-heptyl- and n-dodecylamine) used as second amine to replace the first amine, have similar pK_a values (10.56 (Patel and Higuchi, 1980), 10.66 (Carlson et al., 1988) and 10.63 (Zhou et al., 2018)), which are close to that of TEA (10.75) (Tao et al., 2021) (values for water). In our previous work (Stadler and Lehn, 2014) we already used TEA as a basic trigger.

Acid and base are added as solutions in small volumes of solvent (chloroform-d₃). One may first add 90%–95% of the

calculated amount, then progressively, by titration, a bit less or a bit more than the remaining amount, until a convenient yield is reached. A same mixture of components (here, the one obtained after addition of the second amine) can be used to reversibly generate—upon addition of two different, alternate stimuli—two constitutional states, namely two alternate mixtures of constituents (which may be associated to two alternate properties). In this way, the mixture can be “reused” during a certain number of cycles. Such imine-based, pH-responsive switches, which undergo constitutional reorganization, can be seen as dynamic libraries with pH-adaptive behavior.

Similar sequences of covalent switches can also be performed even in reaction mixtures where the formation of the starting bis-imine is not complete, like in the example of dialdehyde A with m-(pentyloxy)aniline R₂ as a first amine, and hexylamine L₂, as a second amine (see SM, file synt-char, p. 130).

2.4.4 Number of acid-base cycles

It should be possible to perform pH-modulated transiminations a significant number of times. The switches fuelled through alternate additions of acid (CF₃COOH = TFA) and base (Et₃N = TEA) between dR₃₂ and dL₄₂, and those between dR₄₂ and dL₄₂ have been performed 12 times (6 cycles; only the acid-base cycles are considered here) (Figures 12a,b). The starting

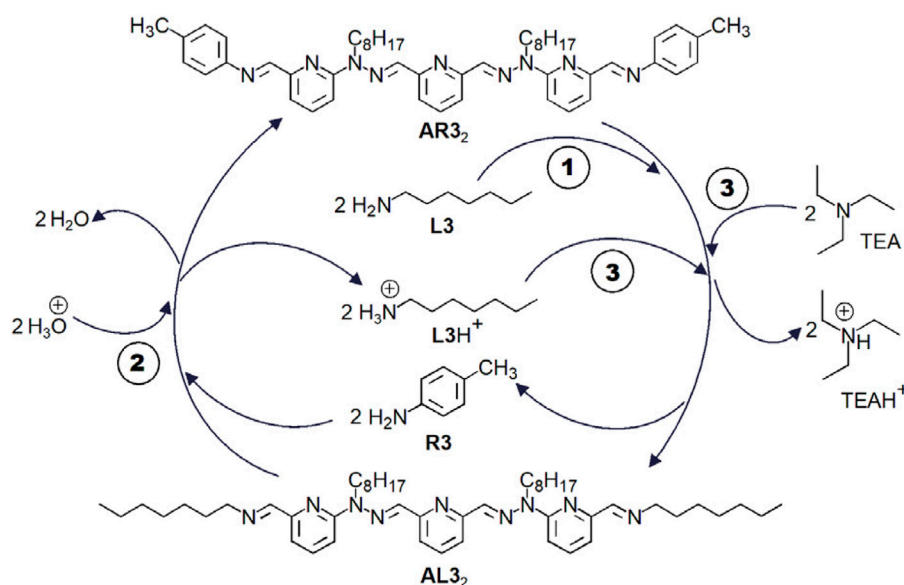


FIGURE 11

Cyclic representation of the switch presented in Figure 10a. In the first step (1), reaction of the bis-imine $AR3_2$ with the aliphatic amine $L3$ (*n*-heptylamine) produces the bis-imine $AL3_2$ and the aromatic amine $R3$ (*p*-toluidine). In the second step (2), addition of trifluoroacetic acid (TFA) to the reaction mixture regenerates the bis-imine $AR3_2$. In the third step (3), addition of triethylamine (TEA) to the reaction mixture produces the bis-imine $AL3_2$ together with amine $R3$ (*p*-toluidine).

aromatic bis-imines $dr3_2$ and $dr4_2$ were prepared in the NMR tubes. Aromatic and aliphatic amines are added in excess with respect to the dialdehyde **dialpy**. These are typical examples of the use of an excess of amine for the preparation of dialdehyde-derived bis-imines in NMR tubes.

If too much acid or base is accidentally added in a step, this excess can be corrected in the subsequent step (Figure 12b, spectra b7-b10).

The successive pH-triggered interconversions can be represented in a cyclic manner (Figure 11), as well as in a non-cyclic way (Figure 12d).

2.5 Inversion of steps

The first step of the above presented switches is the formation of the aromatic imine or, if it has previously been isolated, its reaction with the aliphatic amine. So, usually, the first (bis-)imine is the aromatic one (Figures 11, 12).

It is however possible to start with the aliphatic amine (or imine). The interest of this procedure is that aliphatic imines generally forms faster than aromatic ones and so, the starting aliphatic imine can rapidly be obtained in the NMR tube. Moreover, the subsequent step of the covalent switch (formation of the aromatic amine in the presence of TFA through transimination) is quite fast, thanks to acid catalysis.

In the example from Figure 13, an aromatic aldehyde **G** (here, **bral**) (1 equiv.) reacts with one equivalent of aliphatic amine **C** (here $C_{10}H_{21}NH_2 = L4$) and forms the imine **GC** (=bralL4, Figure 13a). After equilibration, one equivalent of aromatic amine **B** (here, *p*-toluidine **R3**) is added, followed by one equivalent of acid (TFA, Figure 13b). After a new equilibration,

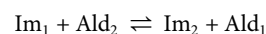
one adds a supplementary amount of **B** (β equiv.) until the desired amount of imine **GB** (=bralR3) is reached at equilibrium. Then, one adds one equivalent of base **E** (here, TEA = triethylamine). After equilibration (Figure 13d), one adds a supplementary amount of amine **C** (γ equiv.), until the desired amount of imine **GC** is reached (Figure 13e). To the equilibrated mixture, one adds an amount of acid that corresponds to the total amount of amine **C** (namely, in principle, $1 + \gamma$ equiv.; Figure 13f). After subsequent equilibration, one adds the amount of base **E** required to neutralize the previous amount of acid and to reach the previous amount of imine **GC** (Figure 13g). In our example, the alternate additions of acid and base were continued, each of them being done two more times, and, in this way, 2 supplementary cycles were performed (Figures 13g–k).

A simplified version of steps was used for the pH-triggered inversion of switch between the bis-imines $AL3_2$ and $AR4_2$ (Figure 10b), where the starting bis-imine was the aliphatic one, $AL3_2$. This bis-imine was beforehand synthesized and isolated, and no excess of amine was added in the NMR tube.

3 Exchanges between (mono-, bis-, tris-)imines and (di)aldehydes in solution

3.1 Overview and examples

Such exchanges correspond, in the case of a monoimine Im_1 (obtained from an amine Am and an aldehyde Ald_1) and an aldehyde Ald_2 , to the global equation:



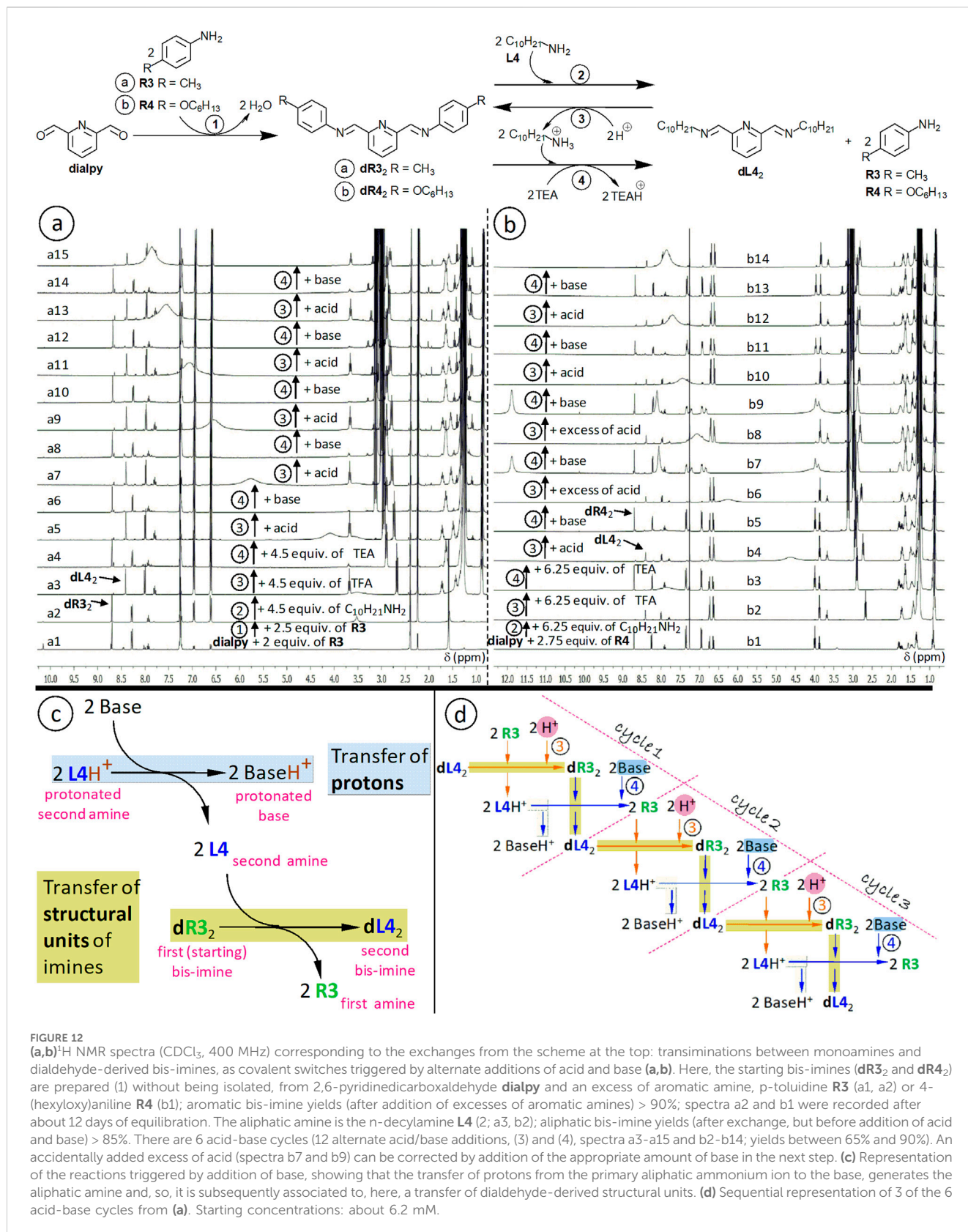
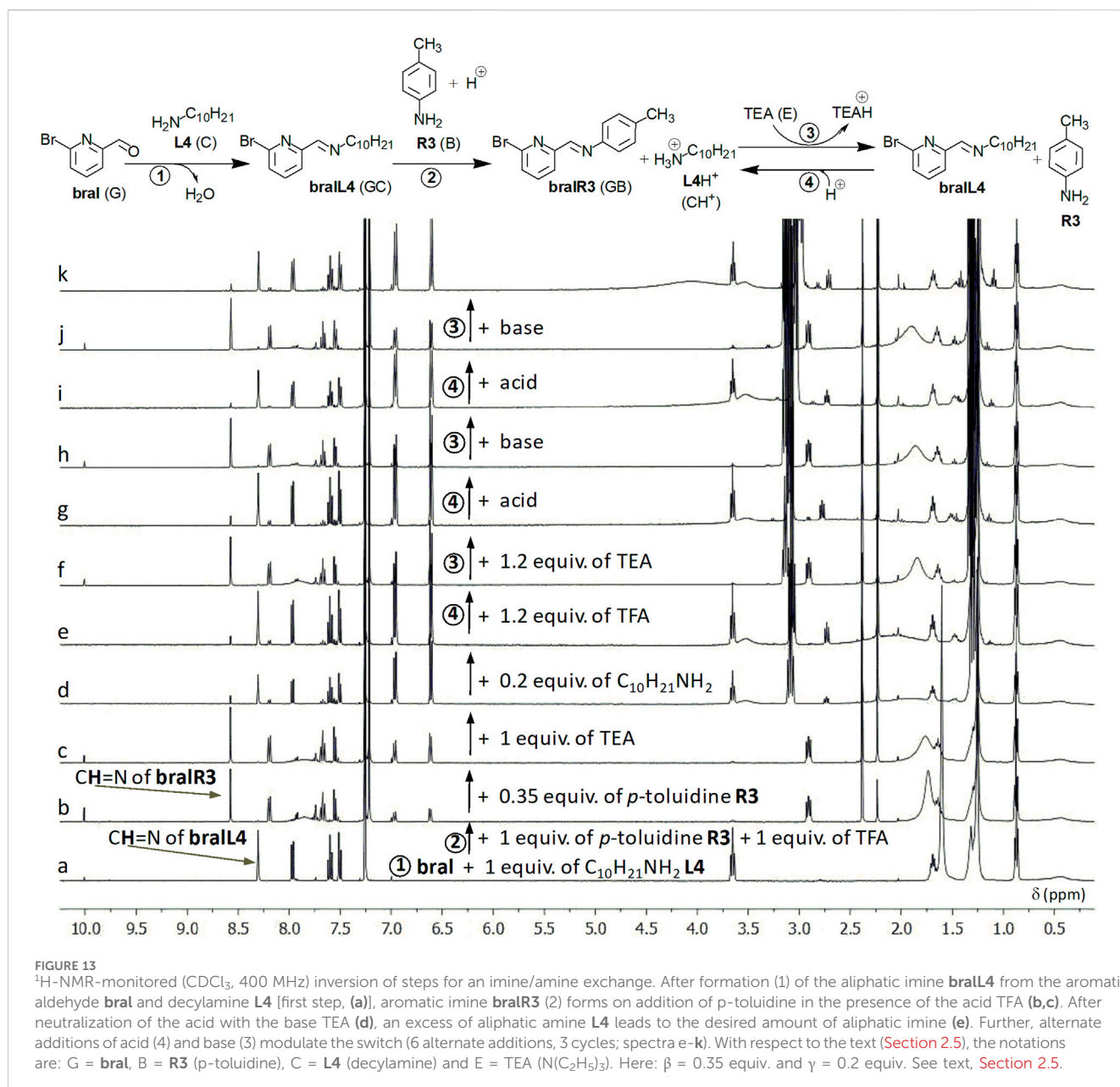
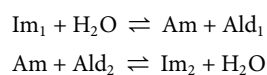


FIGURE 12

(a,b) ¹H NMR spectra (CDCl₃, 400 MHz) corresponding to the exchanges from the scheme at the top: transiminations between monoamines and dialdehyde-derived bis-imines, as covalent switches triggered by alternate additions of acid and base (a,b). Here, the starting bis-imines (dR₃₂ and dR₄₂) are prepared (1) without being isolated, from 2,6-pyridinedicarboxaldehyde dialpy and an excess of aromatic amine, p-toluidine R₃ (a1, a2) or 4-(hexyloxy)aniline R₄ (b1); aromatic bis-imine yields (after addition of excesses of aromatic amines) > 90%; spectra a2 and b1 were recorded after about 12 days of equilibration. The aliphatic amine is the n-decylamine L₄ (2; a3, b2); aliphatic bis-imine yields (after exchange, but before addition of acid and base) > 85%. There are 6 acid-base cycles (12 alternate acid/base additions, (3) and (4), spectra a3-a15 and b2-b14; yields between 65% and 90%). An accidentally added excess of acid (spectra b7 and b9) can be corrected by addition of the appropriate amount of base in the next step. (c) Representation of the reactions triggered by addition of base, showing that the transfer of protons from the primary aliphatic ammonium ion to the base, generates the aliphatic amine and, so, it is subsequently associated to, here, a transfer of dialdehyde-derived structural units. (d) Sequential representation of 3 of the 6 acid-base cycles from (a). Starting concentrations: about 6.2 mM.



They should most likely occur through the intermediate hydrolysis of the starting imine, followed by the subsequent reaction of the resulting amine with the second aldehyde

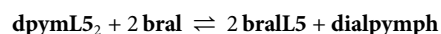


thus leading to an overall process of transimination.

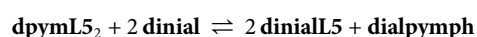
In an amine/imine exchange (vide supra), takes place the transfer of the aldehyde-derived moiety, while in an aldehyde/imine exchange, the moiety that is transferred, is the amine-derived one.

We explored such transiminations by performing the following kinds of (bis-, tris-)imine/(di)aldehyde exchanges in solution.

- i. dialdehyde-based bis-imine with aldehyde, exemplified here by the reaction of the bis-imine **dpymL5₂** (from 2-phenyl-4,6-pyrimidinedicarboxaldehyde **dialpymph** and octadecylamine **L5**), with i.a) 2 equiv. of 6-bromo-2-pyridinecarboxaldehyde **bral**, where forms the target imine **bralL5** (30% after 20 days; Figures 14a,b):



or with i.b) 2 equiv. of 2,4-dinitrobenzaldehyde **dinial**, where is generated the target imine **dinialL5** (57% after 20 days; Figures 14c,d):



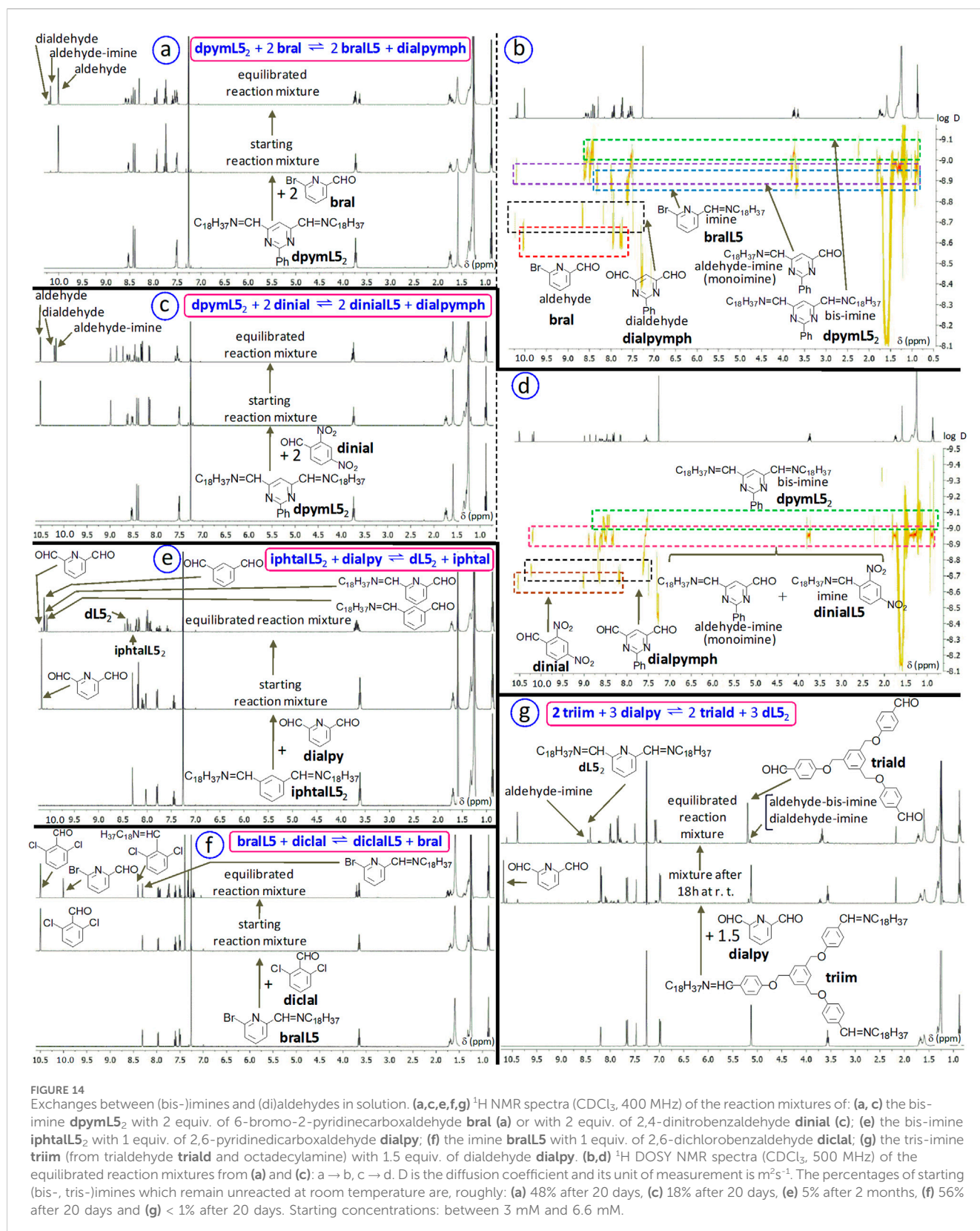


FIGURE 14

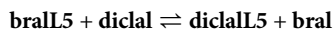
Exchanges between (bis-)imines and (di)aldehydes in solution. (a, c, e, f, g) ^1H NMR spectra (CDCl_3 , 400 MHz) of the reaction mixtures of: (a, c) the bis-imine dpymL_2 with 2 equiv. of 6-bromo-2-pyridinecarboxaldehyde **bral** (a) or with 2 equiv. of 2,4-dinitrobenzaldehyde **dinal** (c); (e) the bis-imine iphtalL_2 with 1 equiv. of 2,6-pyridinedicarboxaldehyde **dialpy**; (f) the imine **bralL}_5 with 1 equiv. of 2,6-dichlorobenzaldehyde **diclal**; (g) the tris-imine **triim** (from trialdehyde **triald** and octadecylamine) with 1.5 equiv. of dialdehyde **dialpy**. (b, d) ^1H DOSY NMR spectra (CDCl_3 , 500 MHz) of the equilibrated reaction mixtures from (a) and (c): a \rightarrow b, c \rightarrow d. D is the diffusion coefficient and its unit of measurement is m^2s^{-1} . The percentages of starting (bis-, tris-)imines which remain unreacted at room temperature are, roughly: (a) 48% after 20 days, (c) 18% after 20 days, (e) 5% after 2 months, (f) 56% after 20 days and (g) < 1% after 20 days. Starting concentrations: between 3 mM and 6.6 mM.**

- ii. dialdehyde-based bis-imine with dialdehyde, illustrated here by the reaction of the bis-imine iphtalL_2 (from isophthalaldehyde and octadecylamine), with 1 equiv. of 2,6-pyridinedicarboxaldehyde **dialpy**, with

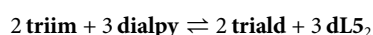
formation of target bis-imine dL_5 (41% after 2 months; Figure 14e):



- iii. imine with aldehyde, the example presented here being the reaction of the imine **brall5** (from 6-bromo-2-pyridinecarboxaldehyde **bral** and octadecylamine **L5**), with 1 equiv. of 2,6-dichlorobenzaldehyde **diclal**, the target imine being **diclalL5** (44% after 20 days; Figure 14f; see SM, file synt-char, p. 123):



- iv. trialdehyde-based tris-imine with dialdehyde, exemplified here by the reaction of the starting tris-imine **triim** (from trialdehyde **triald** (Rajakumar et al., 2006) and octadecylamine **L5**; see SM, file synt-char, p. 100), with 2,6-pyridinedicarboxaldehyde **dialpy** (Figure 14g):



The target bis-imine is, here, **dL5₂** (65%–70% after 20 days). In the equilibrated reaction mixture of **triim** with 1.5 equiv. of **dialpy**, the intermediates between **triim** et **triald**, namely the aldehyde-bis-imine (about 5%) and the dialdehyde-imine (about 23%), are also present along with the trialdehyde **triald** (about 70%–72%); they were roughly quantified through ¹H NMR thanks to the resonances of CH₂O groups. Trialdehydes (Nakada et al., 2017) are promising candidates for imine-based dynamic architectures, including cages (Giri et al., 2023; Pattillo and Moore, 2019) and fluorodynamers (Si et al., 2020).

Starting (mono-, bis-, tris-)imines were synthesized through a simple solvent-free procedure, where (mono-, di-, tri-)aldehydes were reacted, under solvent-free conditions, at 65°C–95°C, for, usually, 18–22 h, with the corresponding amines (vide infra, Section 4; see Supplementary Material, file synt-char, p. 4).

Exchange reactions were followed by 1D ¹H NMR and, quite often, by ¹H DOSY NMR (Figures 14b,d), that is a useful tool for the characterization of multicomponent reaction mixtures.

The differential of the number of imine groups between the starting imine-containing species and the target one is, here, 0, for reactions (ii) (bis-imine → bis-imine) and (iii) (imine → imine), or 1, for reactions (i) (bis-imine → imine) and (iv) (tris-imine → bis-imine). If the N atom of each imine bears a moiety possessing one of more (for example, n) functional groups, then the passage from a compound with p imines per molecule to one with q imines per molecule, leads to a differential (absolute value) of |p–q| imines and |n(p–q)| functional groups between the starting compound and the target one. This aspect can be of significance if the functional group plays a particular role, like a biological or an analytical one.

Results obtained in solution at room temperature suggest that the equilibration generally requires days, weeks or even months (Figure 15a), at room temperature (r.t.), without catalyst (of course, acid traces which may form in CDCl₃ may affect the reaction rate).

In preliminary attempts, we tested dihexylammonium p-toluenesulfonate (prepared from the corresponding amine and acid), as catalyst for imine/aldehyde exchanges, on the reaction between **dinialL5** and **bral** (that requires, without catalyst, about 6 weeks to reach the equilibrium at r.t.; Figure 15a). The promising results thus obtained will be deepened in further experiments.

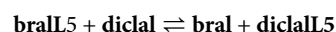
The means to modulate these exchanges through external stimuli (like the variations of the pH) remains to be found. For

an example of supramolecular modulation of imine dynamic libraries, see Gambaro et al. (2020).

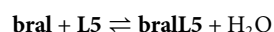
3.2 Order of aldehydes according to the formation constants of their aliphatic imines

The design of successive transiminations (switches or other related processes under equilibrium conditions) requires the knowledge of an at least qualitative and relative order of amines and aldehydes according to the formation constants of their imines. To this purpose, one can use exchange experiments, like in the following example.

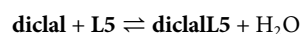
In a typical example, the equilibrium constant for the exchange equilibrium



was found, through NMR spectroscopy, to be $K_{iii} = 6.2 \times 10^{-1}$. If $K_{bral/bralL5}$ is associated to the equilibrium



and $K_{diclal/diclalL5}$ is associated to the equilibrium

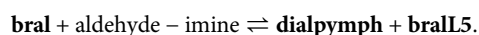


then one has $K_{iii} = K_{diclal/diclalL5}/K_{bral/bralL5}$, which gives $K_{diclal/diclalL5} = K_{iii}K_{bral/bralL5} = 0.62K_{bral/bralL5}$. The relative uncertainties associated to the constants were estimated to be, roughly, of about ±20%.

One determined the constants $K_{ia1} = 5.0 \times 10^{-1}$ for the equilibrium



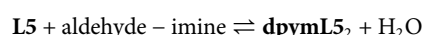
and $K_{ia2} = 4.0 \times 10^{-2}$ for the equilibrium



Let $K_{dialpymph/monoim}$ be associated to the equilibrium



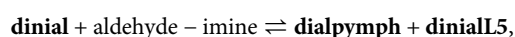
and $K_{monoim/dpymL5_2}$, to the equilibrium



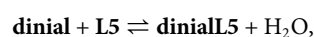
One obtains $K_{ia1} = K_{bral/bralL5}/K_{monoim/dpymL5_2}$ and $K_{ia2} = K_{bral/bralL5}/K_{dialpymph/monoim}$, or $K_{monoim/dpymL5_2} = K_{bral/bralL5}/K_{ia1} \approx 2K_{bral/bralL5}$ and $K_{dialpymph/monoim} = K_{bral/bralL5}/K_{ia2} \approx 25K_{bral/bralL5}$. For the reaction



the equilibrium constant is $K_{ib1} = 4.5$, and for the equilibrium



one has the constant $K_{ib2} = 4.2 \times 10^{-1}$. If $K_{dinial/dinialL5}$ is associated to the equilibrium



then, one obtains $K_{ib1} = K_{dinial/dinialL5}/K_{monoim/dpymL5_2}$ and $K_{ib2} = K_{dinial/dinialL5}/K_{dialpymph/monoim}$, or $K_{dinial/dinialL5} = K_{ib1}K_{monoim/dpymL5_2}$ and $K_{dinial/dinialL5} = K_{ib2}K_{dialpymph/monoim}$.

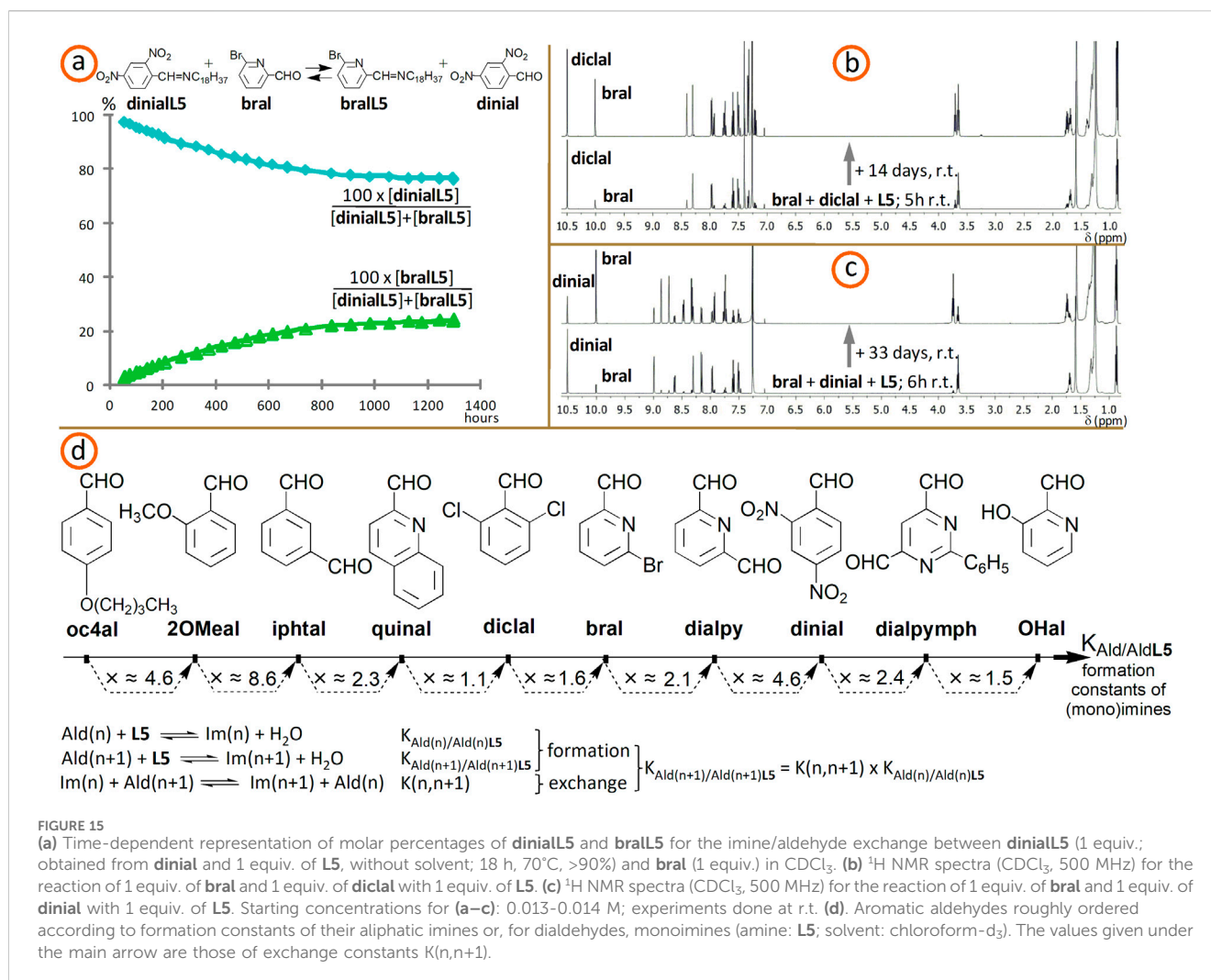


FIGURE 15

(a) Time-dependent representation of molar percentages of **dinalL5** and **bralL5** for the imine/aldehyde exchange between **dinalL5** (1 equiv.; obtained from **dinal** and 1 equiv. of **L5**, without solvent; 18 h, 70°C, >90%) and **bral** (1 equiv.) in CDCl_3 . (b) ^1H NMR spectra (CDCl_3 , 500 MHz) for the reaction of 1 equiv. of **bral** and 1 equiv. of **diclal** with 1 equiv. of **L5**. (c) ^1H NMR spectra (CDCl_3 , 500 MHz) for the reaction of 1 equiv. of **bral** and 1 equiv. of **dinal** with 1 equiv. of **L5**. Starting concentrations for (a–c): 0.013–0.014 M; experiments done at r.t. (d). Aromatic aldehydes roughly ordered according to formation constants of their aliphatic imines or, for dialdehydes, monoimines (amine: **L5**; solvent: chloroform- d_3). The values given under the main arrow are those of exchange constants $K(n,n+1)$.

With the above results $K_{\text{monoim}/\text{dpymL52}} \approx 2K_{\text{bral}/\text{bralL5}}$ and $K_{\text{dialpymph}/\text{monoim}} \approx 25K_{\text{bral}/\text{bralL5}}$, one obtains $K_{\text{dinal}/\text{dinalL5}} = 4.5 \times 2K_{\text{bral}/\text{bralL5}} \approx 9K_{\text{bral}/\text{bralL5}}$ and $K_{\text{dinal}/\text{dinalL5}} = 0.42 \times 25K_{\text{bral}/\text{bralL5}} \approx 10.5K_{\text{bral}/\text{bralL5}}$, expressions which lead to the average, rounded result $K_{\text{dinal}/\text{dinalL5}} \approx 9.8K_{\text{bral}/\text{bralL5}}$.

Now, taking into account the above results where $K_{\text{diclal}/\text{diclalL5}} (=0.62K_{\text{bral}/\text{bralL5}})$, $K_{\text{monoim}/\text{dpymL52}} (\approx 2K_{\text{bral}/\text{bralL5}})$, $K_{\text{dinal}/\text{dinalL5}} (\approx 9.8K_{\text{bral}/\text{bralL5}})$ and $K_{\text{dialpymph}/\text{monoim}} (\approx 25K_{\text{bral}/\text{bralL5}})$ are expressed as functions of $K_{\text{bral}/\text{bralL5}}$, the following order of the constants of imine formation can be established:

$$K_{\text{diclal}/\text{diclalL5}} < K_{\text{bral}/\text{bralL5}} < K_{\text{monoim}/\text{dpymL52}} < K_{\text{dinal}/\text{dinalL5}} < K_{\text{dialpymph}/\text{monoim}}$$

One notices that, for aliphatic amine **L5**, the constant of formation of the monoimine (aldehyde-imine) from the dialdehyde **dialpymph** is bigger than that of formation of bis-imine from monoimine. A similar trend, namely $K_{\text{monoimine}/\text{bis-imine}} < K_{\text{dialdehyde}/\text{monoimine}}$ (the constant of the formation of the bis-imine from monoimine is lower than that of the formation of monoimine from dialdehyde), was observed for **dialpy** and amines **L4** and **R4** (vide supra). For dialdehydes **iphtal**, **dialpy** and **dialpymph**, the

ratio $K_{\text{dialdehyde}/\text{monoimine}}/K_{\text{monoimine}/\text{bis-imine}}$ lies, when reacted with aliphatic amines, between 8 and 13 (average value of about 10.5).

During competing experiments (2 aldehydes + 1 amine; e.g. **bral** + **diclal** + **L5**, **Figure 15b**; **diclal** + **quinal** + **L5**; **bral** + **dinal** + **L5**; **dialpy** + **dinal** + **L5**, **Figure 15c**), we noticed that pyridine- and quinoline-derived aldehydes react faster than benzene-derived ones (with “kinetic” yields usually greater than 70%). The trend from this kinetic situation may be maintained (**Figure 15b**) or reversed (**Figure 15c**) at equilibrium.

On the basis of exchanges of this kind, as well as of competing experiments done on sets of two aldehydes and one amine (decyl- or octadecylamine), in CDCl_3 , and through calculations like those presented above, done on average values, we established a rough, qualitative order of some aldehydes, corresponding to the increase of formation constants of their aliphatic imines (for dialdehydes, is considered the formation of the monoimine; **Figure 15d**). Here, one looks at the thermodynamic aspect of imine formation, while in the precedent **Section 2.1.3** (vide supra), one focused rather on the kinetic aspect.

Thus, exchange constants $K(n,n+1)$ associated to the equilibrium

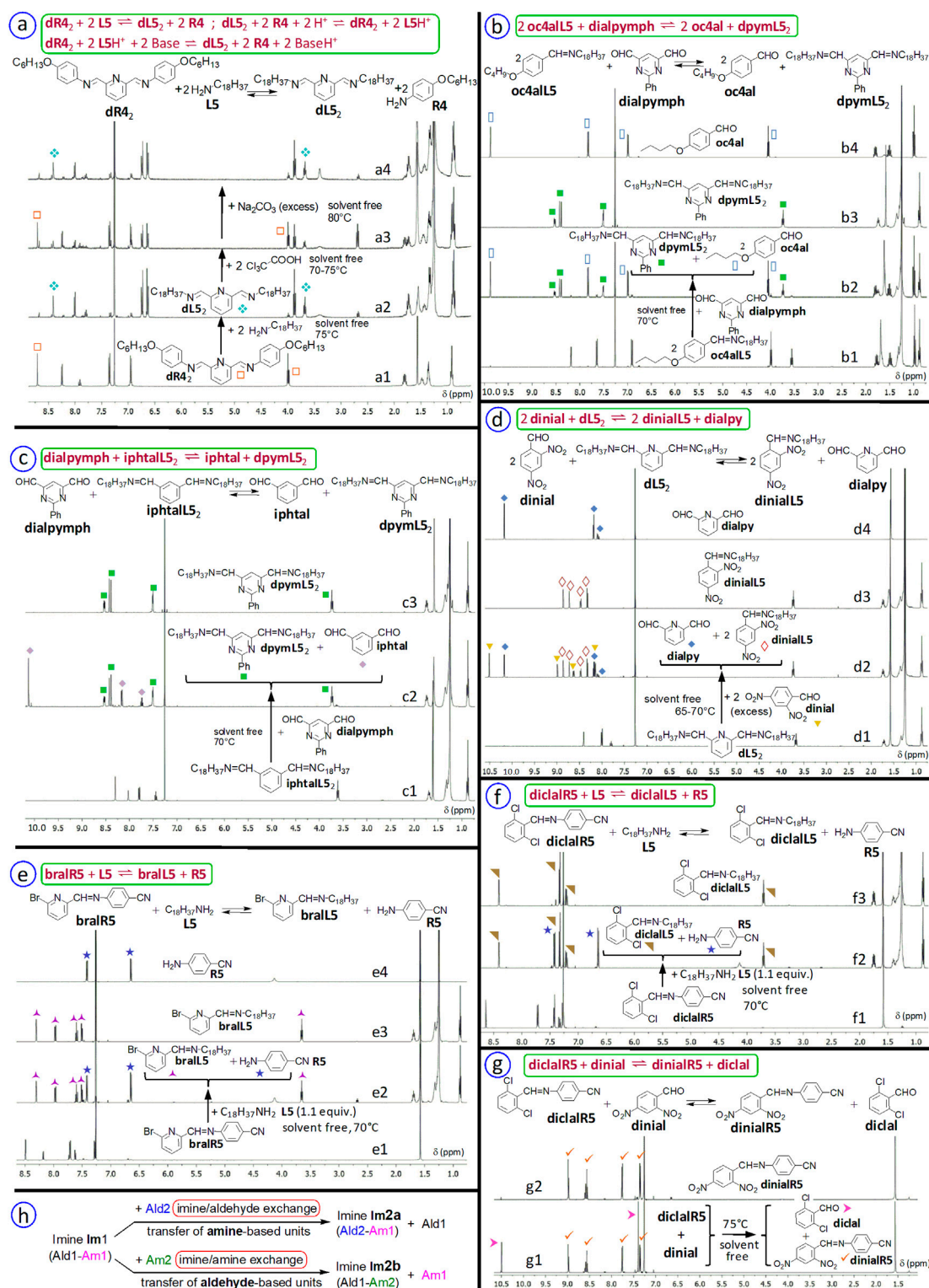


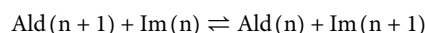
FIGURE 16

Solvent-free exchanges between (bis-)imines and (di)aldehydes or amines. 1H NMR spectra (400 MHz, $CDCl_3$) of samples recorded a few minutes after their dissolution. **(a)** Reaction mixture of bis-imine **dR4₂** (obtained from 2,6-pyridinedicarboxaldehyde **dialpy** and 2 equiv. of 4-(hexyloxy)aniline **R4**, 24h, 70°C, >95%; a1) with 2 equiv. of octadecylamine **L5** (a2, 18h, 75°C, 60–74%), followed by addition of trichloroacetic acid TCA (a3; 2 equiv. of acid, 16h, 70°C–75°C, 33–49%) and of sodium carbonate (a4; 9 equiv. of carbonate, 18h, 80°C, 66%); **(b)** Reaction mixture of imine **oc4alL5** (from 4-butoxybenzaldehyde **oc4al** and 1 equiv. of octadecylamine **L5**, 18h, 75°C, >90%; b1) with 0.5 equiv. of 2-phenyl-4,6-pyrimidinedicarboxaldehyde **dialpymph** (b2; 18h, 70°C, ≈80%) compared with bis-imine **dpymL5₂** (from 2-phenyl-4,6-pyrimidinedicarboxaldehyde and 2 equiv. of octadecylamine, 18h, 70°C, >95%; b3) and with 4-butoxybenzaldehyde **oc4al** (b4); **(c)** Reaction mixture of bis-imine **iphtalL5₂** (from isophthalaldehyde and 2.05 equiv. of octadecylamine, 22 h, 80°C–85°C, >95%; c1) with 1 equiv. of 2-phenyl-4,6-pyrimidinedicarboxaldehyde (16h, 70°C, 65–85%; c2) compared with bis-

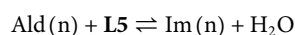
(Continued)

FIGURE 16 (Continued)

imine **dpymL5₂** (c3); (d) Reaction mixture of the bis-imine **dL5₂** (from 2,6-pyridinedicarboxaldehyde and 2 equiv. of octadecylamine, 6h, 70°C, >95%; d1) with an excess of 2,4-dinitrobenzaldehyde **dinial** (4 equiv., 24 h, 65°C–70°C, >95%; d2) compared with the imine **dinialL5** (obtained from 2,4-dinitrobenzaldehyde and 1 equiv. of octadecylamine, 18 h, 70°C, >90%; d3) and with 2,6-pyridinedicarboxaldehyde **dialpy** (d4). ¹H NMR spectra (500 MHz, CDCl₃). (e) Reaction mixture of imine **bralR5** (from 4-aminobenzonitrile **R5** and 1 equiv. of 6-bromo-2-pyridinecarboxaldehyde **bral**, 24h, 85°C, >90%; aminoral 4-8%; e1) with octadecylamine **L5** (1.1 equiv., 20h, 70°C, >90%; e2), compared with imine **bralL5** (obtained from 6-bromo-2-pyridinecarboxaldehyde **bral** and 1 equiv. of octadecylamine **L5**, 20h, 70°C, >95%; e3) and with 4-aminobenzonitrile **R5** (e4); (f) Reaction mixture of imine **diclalR5** (from 4-aminobenzonitrile **R5** and 1 equiv. of 2,6-dichlorobenzaldehyde **diclal**, 48h, 80°C, 80–90%; aminoral 4–12%; f1) with octadecylamine **L5** (1.1 equiv., 20h, 70°C, >90%; f2), compared with imine **diclalL5** (obtained from 2,6-dichlorobenzaldehyde **diclal** with 1 equiv. of octadecylamine **L5**, 18h, 70°C, >90%; f3); (g) Reaction mixture of imine **diclalR5** with 2,4-dinitrobenzaldehyde **dinial** (1 equiv., 18h, 75°C, >90%; g1), compared with imine **dinialR5** (from **dinial** and 1 equiv. of **R5**, 48h, 80°C, >90%; g2); (h) Two possibilities of transimination and transfer of structural units illustrated for a monoimine: imine/amine and imine/aldehyde exchanges. All starting imines were synthesized without solvent.



have been obtained and their average, rough values rounded to one digit after the decimal separator (relative uncertainties of about ±20%), are given under the main arrow from Figure 15d. *n* corresponds to an aldehyde Ald(*n*) from the ordered set (Figure 15d), and *n*+1, to the immediately next one Ald(*n*+1), in the increasing sense of formation constants. If $K_{\text{Ald}(n)/\text{Ald}(n+1)\text{L5}}$ is the formation constant associated to the equilibrium



then one has $K_{\text{Ald}(n+1)/\text{Ald}(n+1)\text{L5}} = K_{\text{Ald}(n)/\text{Ald}(n)\text{L5}} \times K(n,n+1)$.

One obtained (Figure 15d): $K_{2\text{OMeal}/2\text{OMealL5}} \approx 4.6K_{\text{oc4al}/\text{oc4alL5}}$, $K_{\text{iphtal}/\text{monoim}} \approx 8.6K_{2\text{OMeal}/2\text{OMealL5}}$, $K_{\text{quinal}/\text{quinalL5}} \approx 2.3K_{\text{iphtal}/\text{monoim}}$, $K_{\text{diclal}/\text{diclalL5}} \approx 1.1K_{\text{quinal}/\text{quinalL5}}$, $K_{\text{bral}/\text{bralL5}} \approx 1.6K_{\text{diclal}/\text{diclalL5}}$, $K_{\text{dialpy}/\text{monoim}} \approx 2.1K_{\text{bral}/\text{bralL5}}$, $K_{\text{dinial}/\text{dinialL5}} \approx 4.6K_{\text{dialpy}/\text{monoim}}$, $K_{\text{dialpymph}/\text{monoim}} \approx 2.4K_{\text{dinial}/\text{dinialL5}}$ and $K_{\text{OHal}/\text{OHalL5}} \approx 1.5K_{\text{dialpymph}/\text{monoim}}$. Of all formation constants, only $K_{\text{oc4al}/\text{oc4alL5}}$ (for the reaction of aldehyde **oc4al** with amine **L5**) has been determined directly; it has a value of, roughly, about 52 (uncertainties of about, roughly, ±20%).

4 Solvent-free imine formation and exchanges

We performed several reactions of imine formation and exchange in the absence of solvents (Figures 16–18).

4.1 Overview and examples

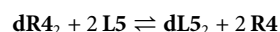
Amongst the advantages of such solvent-free reactions are the saving of organic solvents and the reduction of organic wastes (in a green chemistry, sustainable approach), the saving of the energy and time required to evaporate the solvents, a possible simplification of the work-up. Absence of solvent also means higher concentrations of starting materials, absence of the water that would have been contained in the solvent and therefore, limitation of hydrolysis and shift of equilibriums. In addition, without solvent (particularly when both water and imine reaction product are soluble in it), a better separation of the organic phase from the water generated in the reaction is achieved.

Such reactions have already been performed in the field of imine chemistry (Alvarez-Santamaría et al., 2019; Crawford et al., 2015; Crawford et al., 2017; Ferguson et al., 2014; León

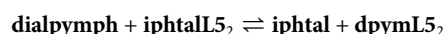
et al., 2023; Leoni et al., 2019; Shaw et al., 2018; Shaw et al., 2019; Shaw et al., 2024; Singh et al., 2021; Suzuki et al., 2018; Suzuki et al., 2019; Wang et al., 2016; Zuo et al., 2022). Here, we applied them to imine synthesis, to (bis-)imine/amine and (bis-)imine/(di)aldehyde exchanges (Figures 16, 17), as well as, in a multistep process, to a sequence of successive transiminations involving mono-, bis- and tris-imines (Figure 18).

The solvent-free transiminations performed in one step, which are reported herein, are of following types (Figure 16):

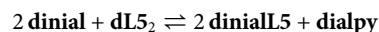
- dialdehyde-derived bis-imine with amine, here, aromatic bis-imine **dr4₂** with 2 equiv. of aliphatic amine **L5** (Figures 16a, 17a, b):



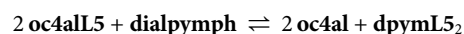
- dialdehyde-derived bis-imine with dialdehyde, namely bis-imine **iphtalL5₂** with 1 equiv. of dialdehyde **dialpymph** (Figure 16c; for the corresponding DOSY spectrum, see SM, file synt-char, p. 126):



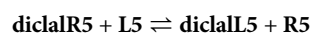
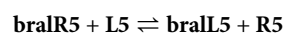
- dialdehyde-derived bis-imine with aldehyde, here, bis-imine **dL5₂** with 2 equiv. (in practice we used 4 equiv.) of 2,4-dinitrobenzaldehyde **dinial** as competing aldehyde (Figure 16d; for the corresponding DOSY spectrum, see SM, file synt-char, p. 125):



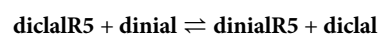
- imine with dialdehyde, namely 2 equiv. of imine **oc4alL5** with 1 equiv. of **dialpymph** (Figure 16b; for the corresponding DOSY spectrum, see SM, file synt-char, p. 127):



- imine with amine, e. g. imines **bralR5** or **diclalR5** with 1 equiv. of octadecylamine **L5** (Figures 16e,f; 17i–q):



- imine with aldehyde, here, imine **diclalR5** with 1 equiv. of 2,4-dinitrobenzaldehyde **dinial** (Figure 16g):



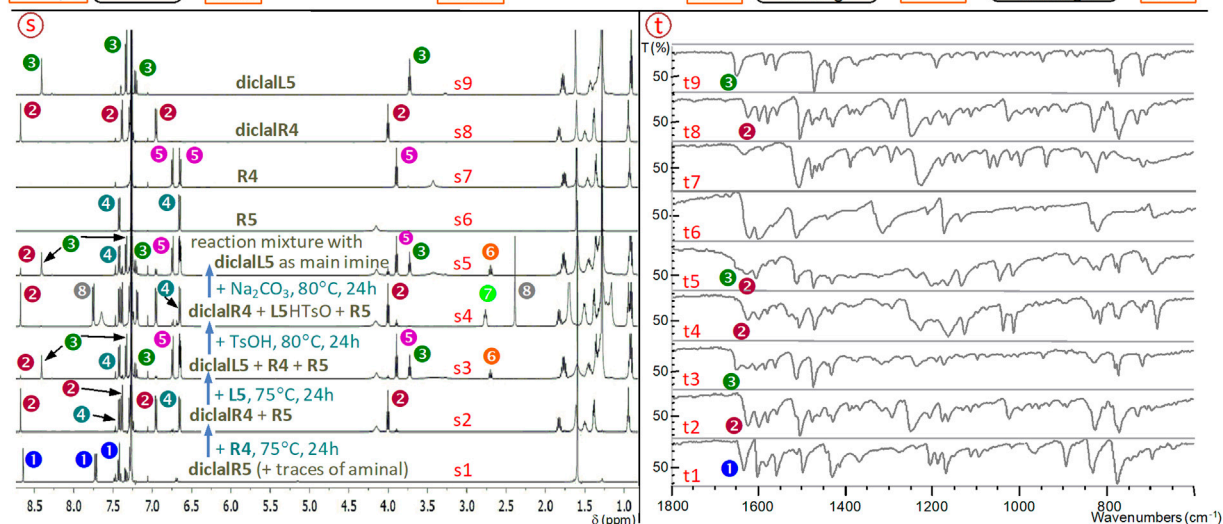
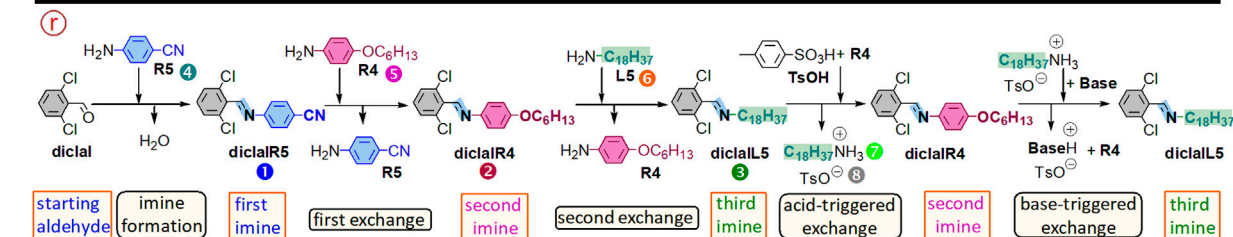
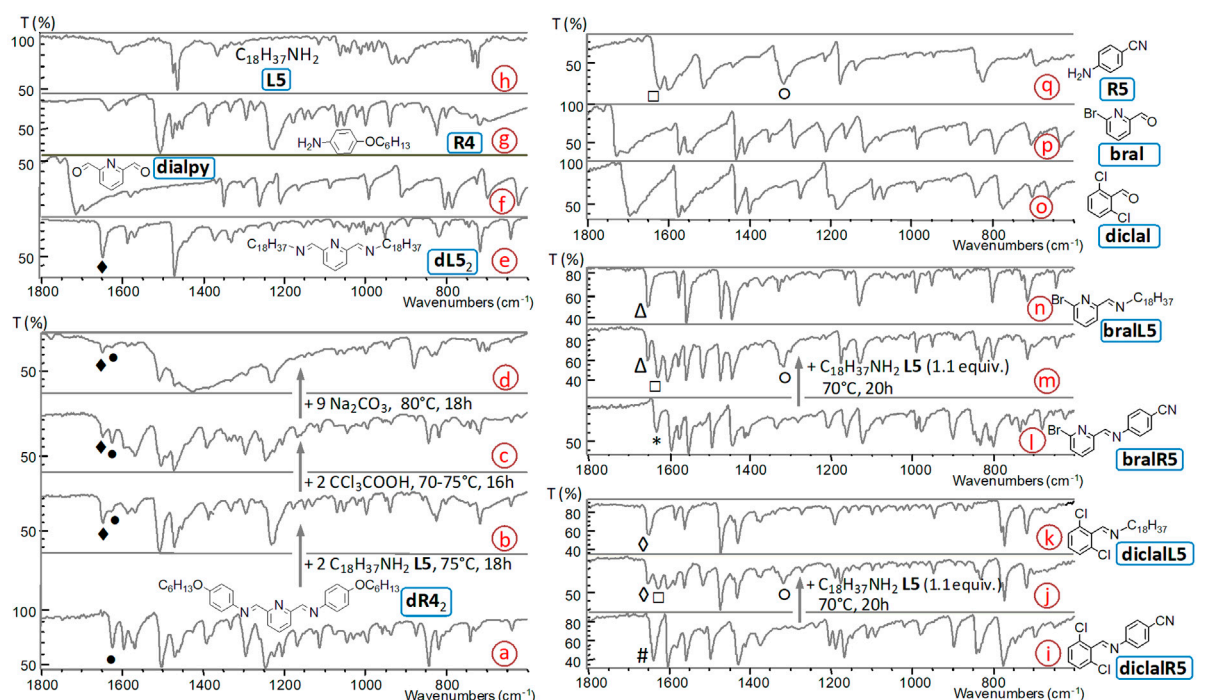


FIGURE 17 (a–h) Part of IR spectra (by Attenuated Total Reflectance = ATR) of the solvent-free reaction mixture of bis-imine dR_2 (from 2,6-pyridinedicarboxaldehyde dialpy and 4-(hexyloxy)aniline R4) (a) with 2 equiv. of octadecylamine L5 (b), then with acid (TCA; (c)) and base (Na_2CO_3 ; (d)), as well as those of starting materials (f–h) and of the bis-imine dL_5 from 2,6-pyridinedicarboxaldehyde and octadecylamine (e). \blacklozenge denotes stretching bands of $\text{C}=\text{N}$ bond in aliphatic imines $\nu_{\text{C}=\text{Nalkyl}}$ (here, $1,647\text{--}1,648\text{ cm}^{-1}$) and \bullet , those of the $\text{C}=\text{N}$ bond in aromatic imines $\nu_{\text{C}=\text{Naryl}}$ (here, $1,623\text{--}1,626\text{ cm}^{-1}$). One may notice that in (b) the height of \blacklozenge ($\nu_{\text{C}=\text{Nalkyl}}$) is greater than that of \bullet ($\nu_{\text{C}=\text{Naryl}}$), while in (c) the height of \bullet ($\nu_{\text{C}=\text{Naryl}}$) is greater than that of \blacklozenge ($\nu_{\text{C}=\text{Nalkyl}}$); in (d) the height of \blacklozenge ($\nu_{\text{C}=\text{Nalkyl}}$) is again greater than that of \bullet ($\nu_{\text{C}=\text{Naryl}}$). (i–k) Part of IR spectra (by ATR) of the reaction mixture of imine diclalR5 (i) with n-octadecylamine L5 (j), compared with that of imine diclalL5 (k); (l–n) Part of IR spectra (by ATR) of aldehyde diclal (o), aldehyde bral (p) and 4-aminobenzonitrile R5 (q). # and * denote imine stretching bands $\nu_{\text{C}=\text{Naryl}}$, \blacklozenge and Δ denote imine stretching bands $\nu_{\text{C}=\text{Nalkyl}}$. \square denotes the scissoring mode $\beta_3(\text{NH}_2)$, and \circ denotes the stretching mode $\nu_{\text{C}-\text{NH}_2}$ coupled with the bending $\delta(\text{NH}_2)$ in 4-aminobenzonitrile (Palafox et al., 2006). (r,s) A multistep sequence based on imine/amine exchanges: scheme (r) represents the whole process illustrated through the ^1H NMR spectra (500 MHz, CDCl_3 ; s) of: the starting (first) imine diclalR5 (s1), the mixture of the first exchange (s2), the mixture of the second exchange (s3), the

(Continued)

FIGURE 17 (Continued)

mixture of the acid-triggered exchange (**s4**), the mixture of the base-triggered exchange (**s5**), the two aromatic amines **R5** (**s6**) and **R4** (**s7**), and imines **diclalR4** (**s8**) and **diclalL5** (**s9**). The numbers associated to peaks correspond to compounds from (r). (t) t1 to t9 are IR spectra which correspond to NMR spectra s1 to s9. Only several key IR bands are denoted with numbers corresponding to compounds. T = transmittance.

The starting materials were roughly ground. Solvent-free reactions, usually on 2–20 mg of starting aldehyde or imine, were done in small glass vials with good caps.

The ^1H NMR spectra of samples of solvent-free reaction mixtures were recorded a few (generally, between 2 and 5) minutes after the dissolution of the samples. It is assumed (except for acid-triggered exchanges) that, during this short time and in the absence of (acid) catalysts, the transiminations do not (significantly) progress in solution and that, in this way, the composition of the mixture remains almost unchanged between the solvent-free sample and the corresponding solution in CDCl_3 .

Two of the amines used in solvent-free syntheses and exchanges are 4-(hexyloxy)aniline **R4** and octadecylamine **L5**, which are already molten under the reaction conditions (65°C – 95°C ; reaction time, depending on the case, between 6 h and 8 days; vide infra section 4.3.1 and Figure 16), a fact that improves the homogenization in the course of the reaction. The reaction times are, usually, not optimized. The yields were determined by ^1H NMR. Small amounts of compounds like 2,6-dichlorobenzaldehyde, may deposit, during the reaction, on the wall of the vial. The yields of syntheses of starting (bis-)imines **drR4**₂, **dlL5**₂, **iphtalL5**₂ and **oc4alL5** can be seen as very good (>90%). Most of the exchanges we tested (e.g. Figure 16 a2, b2, c2) worked rather satisfactorily, with yields between 70% and 85%. An appropriate excess of competing reagent, for example, aldehyde **dinial** (Figure 16 d2), may be used to improve the yield.

4.1.1 IR spectroscopy as an analytical tool for solvent-free reactions

The solvent-free final reaction mixtures were also investigated through infrared (IR) spectroscopy (Figures 17a–q, t), that can provide useful structural information for characterization of such mixtures. The IR data are in agreement with the NMR ones (vide infra, Sections 4.2 and 4.4).

For example, the stretching bands $\nu_{\text{C=Naryl}}$ observed in imines **diclalR5** ($1,636\text{ cm}^{-1}$; Figure 17i) and **bralR5** ($1,629\text{ cm}^{-1}$; Figure 17l) are replaced, upon reaction with n-octadecylamine **L5**, by bands with higher wavenumbers—the stretching bands $\nu_{\text{C=Nalkyl}}$ —in **diclalL5** ($1,648$ – $1,651\text{ cm}^{-1}$; Figures 17j, k) and **bralL5** ($1,651\text{ cm}^{-1}$; Figure 17m, n). In addition to these changes, these imine/amine exchanges without solvent are also confirmed through the formation of amine **R5**, which is suggested, amongst other bands, by the scissoring mode of the NH_2 group (β_s) at about $1,621$ – $1,625\text{ cm}^{-1}$, as well as by the stretching mode $\nu_{\text{C-NH}_2}$ coupled with the bending $\delta(\text{NH}_2)$, at about $1,315$ – $1,317\text{ cm}^{-1}$. For the attributions of the IR bands in amine **R5**, see (Palafox et al., 2006).

4.1.2 Two kinds of exchanges per imine group

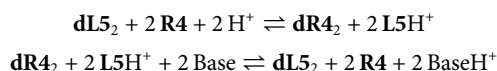
We are mentioning here only imine/amine and imine/aldehyde exchanges, namely exchanges between imines and

compounds possessing one (i.e., here, amine or aldehyde) of the functional groups which react together to form imines (and water). Indeed, an imine group (Figure 16h) offers the possibility of imine/amine exchanges associated to a transfer of aldehyde-derived units, as well as the possibility of imine/aldehyde exchanges associated to a transfer of amine-derived units. In the context of the work reported herein, both possibilities are illustrated, under solvent-free conditions, for imine **diclalR5**: the imine/amine exchange upon reaction with amine **L5** (Figure 16f), and the imine/aldehyde exchange upon reaction with aldehyde **dinial** (Figure 16g).

For pyridine-based, dialdehyde-derived bis-imines, were performed not only solvent-free bis-imine/amine exchanges (bis-imine **drR4**₂ with amine **L5**; Figure 16, spectra a1,a2), but also solvent-free bis-imine/aldehyde exchanges (bis-imine **dlL5**₂ with aldehyde **dinial**; Figure 16, spectra d1,d2).

4.2 Acid/base-modulated covalent switches

For the solvent-free acid/base-triggered switches between bis-imines **drR4**₂ and **dlL5**₂ (Figure 16 a3, a4)



we used trichloroacetic acid (TCA) and sodium carbonate (both being solid at room temperature), as acidic and basic triggers, respectively. TCA (CCl_3COOH) was chosen here because it is less volatile than TFA (CF_3COOH). The yields are lower than those of the corresponding solvent-free reactions without triggers (Figures 16a1, a2), and a possible optimization would be a better homogenization of the solvent-free solid reaction mixtures. These preliminary results will be further investigated.

The switches between bis-imines **drR4**₂ and **dlL5**₂ (Figure 16a) were also followed by IR (infrared) spectroscopy on solvent-free, solid samples (Figure 17), thanks to, for example, the stretching bands of the imine C=N bond which are, here, at $1,623$ – $1,626\text{ cm}^{-1}$ ($\nu_{\text{C=Naryl}}$, aromatic imine) and $1,647$ – $1,648\text{ cm}^{-1}$ ($\nu_{\text{C=Nalkyl}}$, aliphatic imine). See also SM, file synt-char, p. 128. Here, the starting bis-imine is **drR4**₂ (Figure 17a). In the IR spectrum of the mixture obtained after the first transimination (Figure 17b), the two stretching bands $\nu_{\text{C=Naryl}}$ and $\nu_{\text{C=Nalkyl}}$ have different intensities, which move - after each subsequent transimination step - in opposite directions (Figures 17c,d). IR spectra suggest, together with the NMR results, that the switch globally operates as expected. The IR spectra corresponding to the steps of the switch (Figures 17a–d), can be compared with that of bis-imine **dlL5**₂ (Figure 17e) and with those of starting reagents (Figures 17f–h).

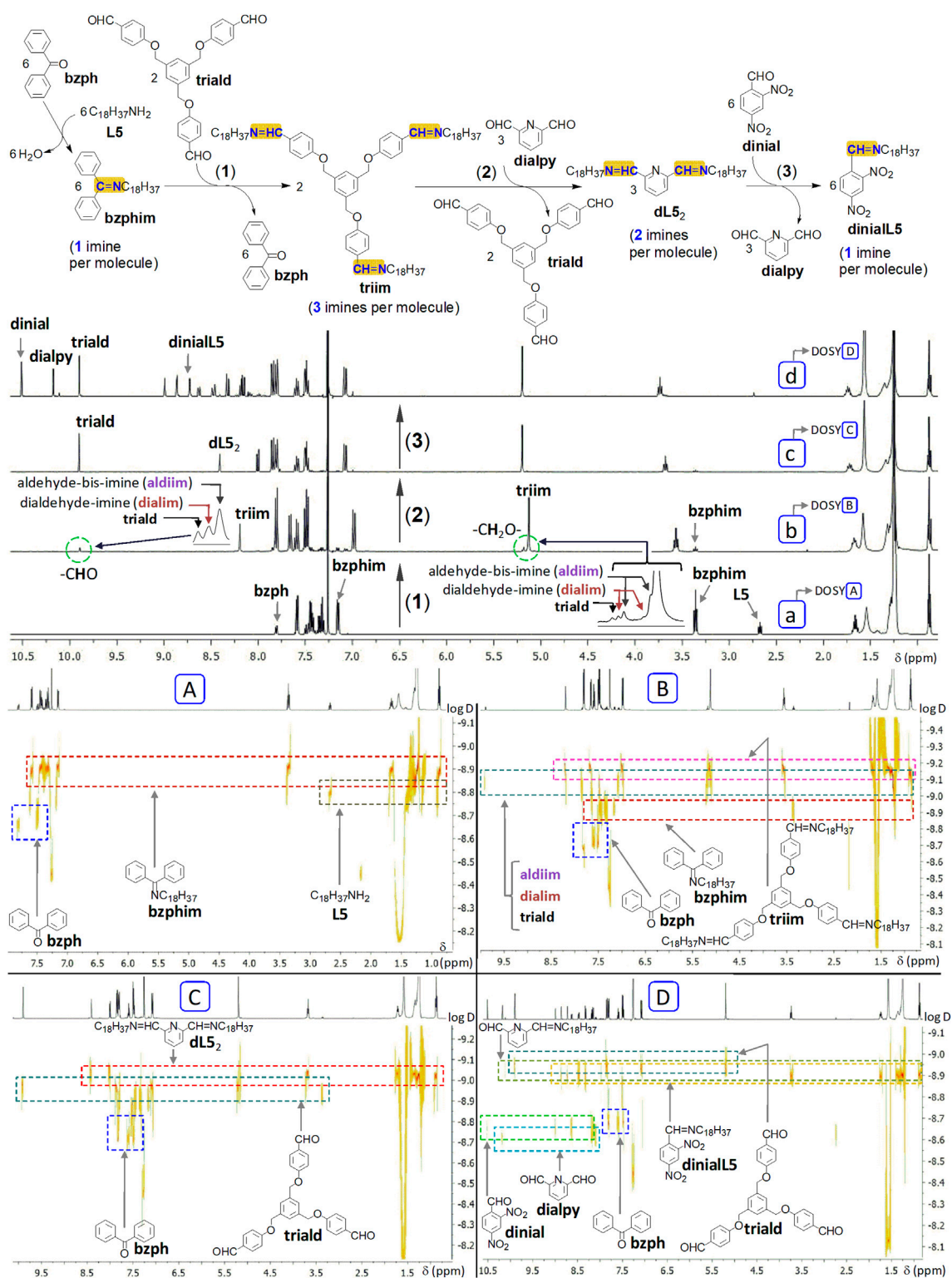


FIGURE 18

A sequential multistep process: solvent-free successive transiminations (top scheme). (a-d) ^1H NMR spectra (400 MHz, CDCl_3) of reaction mixtures, recorded a few minutes after dissolution of samples, and (A–D) the corresponding ^1H DOSY NMR spectra (500 MHz, CDCl_3): reaction of benzophenone **bzph** with octadecylamine **L5** (a, A), followed by addition (1) of trialdehyde **triald** (b, B), then (2) of 2,6-pyridinedicarboxaldehyde **dialpy** (c, C) and, in the final step (3), of 2,4-dinitrobenzaldehyde **dinal** (d, D). During this process, one passes from a monoimine (**bzphim**) to a tris-imine (**triim**), then to a bis-imine (**dl52**), and, finally, again to a monoimine (**dinalL5**). For conditions and discussion, see the text. D is the diffusion coefficient, measured in m^2s^{-1} .

4.3 A multistep sequence of transiminations based on imine/aldehyde exchanges

The series of successive transiminations previously presented (vide supra, Sections 2.4, 2.5) were performed in a switch-like manner, between two (bis-)imines ($\text{Im1} \rightarrow \text{Im2} \rightarrow \text{Im1} \rightarrow \text{Im2} \rightarrow \text{Im1} \dots$), and they were modulated by additions of acid and base. The example presented hereafter shows that successive transiminations can also be implemented as a multistep process, namely from an imine to a second one, then to a third one, and, in the final step, to a fourth one, in just one direction ($\text{Im1} \rightarrow \text{Im2} \rightarrow \text{Im3} \rightarrow \text{Im4}$), without modulation through stimuli (pH changes). The solvent-free multistep sequence presented hereafter was designed on the basis of the order from Figure 15. For another example of multistep process in imine chemistry (but performed in solution), see (Schultz and Nitschke, 2006).

4.3.1 Operation

Solvent-free reaction of benzophenone **bzph** with octadecylamine **L5** (1 equiv., 5 days, 75–80°C) produces the corresponding ketimine N-octadecyl-1,1-diphenylmethanimine **bzphim** (72%–82%) (Figure 18A a). This reaction mixture, used without purification, was treated with trialdehyde **triald** (for its synthesis, see (Rajakumar et al., 2006); 1/3 equiv. of **triald** with respect to the total initial amount of amine **L5**; 6–8 days, 80 °C–90 °C) and produced the tris-imine **triim** (yield of 66%–80% with respect to the total initial amount of **L5**; Figure 18B b). Intermediate aldehyde-bis-imine and dialdehyde-imine are also present. Treatment of this mixture with dialdehyde **dialpy** (1/2 equiv. with respect to the total amount of **L5**; 1–1.5 days, 70 °C–75 °C) produces the expected bis-imine **dL5₂** (about 80–90%; Figure 18C c). This mixture was reacted with 2,4-dinitrobenzaldehyde **dinial** (4 equiv., so an excess of 2 equiv. with respect to **L5**, 1–1.5 days, 65 °C–70 °C) to produce the corresponding imine **dinialL5** (77%–85% with respect to **L5**; Figure 18D d), together with observable traces of the intermediate aldehyde-imine (monoimine). Reagents like benzophenone and dinitrobenzaldehyde may partly deposit on the vial wall. The reactions were followed by 1D ¹H NMR (recorded a few minutes after the dissolution of the samples) and by ¹H DOSY NMR (Figure 18); chemical exchanges in solution may affect the values of the diffusion coefficients.

4.3.2 Change of the number of imine groups per molecule

In this sequence of successive transiminations (although not with quantitative yields), the amine-derived unit is transferred from an imine-containing species to another. The multistep process consists of three subsequent solvent-free reactions done in the same pot. Correlatively, the number of imine groups per imine-containing species changes from a step to another (Figure 18), namely from 1 (**bzphim**) to 3 (**triim**), then to 2 (**dL5₂**) and, finally, again to 1 (**dinialL5**). Vide supra, Section 3.1.

4.4 A multistep sequence of transiminations based on imine/amine exchanges

In this solvent-free sequence, the **R5**-derived unit from imine **dicalR5** is replaced by a unit derived from 4-(hexyloxy)aniline **R4**. Further, the **R4**-derived unit from **dicalR4** is replaced by that derived from n-octadecylamine **L5**, when forms imine **dicalL5** (Figure 17r). In this way takes place a 2-step transfer of the unit derived from aldehyde **dical**.

Practically, solvent-free reaction of the first monoimine **dicalR5** of the sequence (obtained from **dical** and **R5**, without solvent; 48 h, 80°C, 80–90%; Figure 17sl) with 1.1 equiv. of 4-(hexyloxy)aniline **R4** (24 h, 75°C, Figure 17s2) generates the second imine **dicalR4** (> 90%). Reaction of the mixture obtained in this way, with 1.25 equiv. of n-octadecylamine **L5** (24 h, 75°C, Figure 17s3) produces **dicalL5**, the third imine of the sequence (92%), with about 8% of imine **dicalR4**. Comparison with spectra of amines **R4** and **R5** (Figures 17s4,s5) and with those of imines **dicalR4** (from 2,6-dichlorobenzaldehyde **dical** and amine **R4**, without solvent; 24 h, 75°C, > 90%; Figure 17s6) and **dicalL5** (from **dical** with 1 equiv. of **L5**, without solvent; 18 h, 70°C, > 90%; Figure 17s7), confirms the formation of expected imines and amines.

Addition of p-toluenesulfonic acid monohydrate (TsOH·H₂O; 1.25 equiv.) to this reaction mixture (80 °C, 24 h), leads to compound **dicalR4** as main imine (92%; acid-triggered exchange; Figure 17r,s4). Subsequent treatment with an excess of Na₂CO₃ (5 equiv.) under similar conditions, generates **dicalL5** as main imine (84%; base-triggered exchange; Figure 17r,s5).

The whole process is one of type $\text{Im1} \rightarrow \text{Im2} \rightarrow \text{Im3} \rightarrow \text{Im2} \rightarrow \text{Im3}$, namely a combined (mixed) one consisting of a multistep sequence of exchanges without stimuli ($\text{Im1} \rightarrow \text{Im2} \rightarrow \text{Im3}$) and a stimuli-triggered switch ($\text{Im3} \rightarrow \text{Im2} \rightarrow \text{Im3}$).

One may wish to reuse, in new acid-base cycles, the imines and amines from the final solvent-free reaction mixture. To this end, they can be extracted in accordance with the following steps, thanks to the low solubility of NaTsO and Na₂CO₃ in chloroform: addition of chloroform to the final mixture, stirring, centrifugation, filtration, removal of the solvent.

The sequence was monitored by ¹H NMR (the spectra being recorded 2–5 min after the dissolution of samples; Figures 17s1–s9) and IR spectroscopy (Figures 17t1–t9).

In all intermediate steps of sequences presented in Sections 4.2–4.4, the reagents are added as ground solids, without solvents. Before heating, the solid reaction mixtures are ground again with the added reagents.

5 Mathematical models

This part is focused on calculations with and simulations of equilibrium constants in solution, for the reaction of a dialdehyde with a monoamine, followed by the addition of a second amine.

In this way, these calculations deal with the formation and exchange of dialdehyde-based bis-imines and they are intended to complement the experimental work. One can, for example:

- Estimate the composition at equilibrium starting from initial concentrations of reagents and from the corresponding equilibrium constants. See, for example, (Crerar, 1975) and references cited herein;
- Calculate the excess of a reagent required to reach a desired yield;
- Calculate concentration-versus-pH distribution curves, which represent the composition of an equilibrated reaction mixture as a function of the pH, and are relevant for pH-adaptive dynamic libraries;
- Estimate/simulate the values of equilibrium constants starting from desired yields. From such constants, one can estimate (but this was not done here) the corresponding Gibbs free energies ($\Delta G = -RT \ln K$), which could further be used in the framework of structure-free energy relationships (Liu et al., 1994). One notices also that, on the basis of quantitative determination of relationships between the rate and equilibrium constants, in the framework of structure-reactivity relationships for Schiff base formation, was developed a model to predict the macroscopic behavior of dynamic covalent materials (hydrogels) (Morgan et al., 2024);
- Quantitatively investigate the effect of the amount of water on the concentration of imine-containing compounds;
- Generalize or extend such calculations to other classes of chemical reactions similar to those discussed herein (i.e. reaction of a difunctional compound with a complementary monofunctional one, followed by an exchange with a second, competing, monofunctional compound).

Key points would be: the quantitative description of reaction mixtures at equilibrium, the solving of the corresponding systems of (polynomial) equations and the possible simplifications of the mathematical treatment.

For the sake of simplification, we assumed that, in this mathematical model, molar concentrations are equal to activities, and that the volume of solution does not significantly change on addition of various reagents. Hydration of aldehydes, formation of (hemi)aminals, protonation of N_{sp^2} atom of pyridines or other possible protonation equilibria (except the protonation of NH_2 groups of amines B and C), dissociation of water, and other reactions, except those written herein, were not taken into account for the calculations.

One deals here with an (aromatic) dialdehyde A, that reacts with a first primary (aromatic) amine B. To this reaction mixture is added a second primary amine C, then acid. A, B and C denote also, in calculations, parameters.

For simplification, all kinds of hydrated or solvated protons are denoted H^+ .

The meaning of the term “yield” is the ratio between the number of moles of (aldehyde- or bis-)imine of interest, and the number of moles of dialdehyde A present initially, i.e., for a derivative of A, the molar fraction of A that generated that derivative.

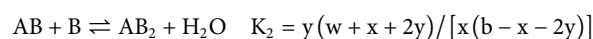
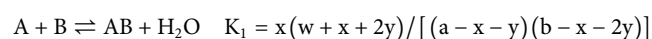
For the calculations, the only notations which keep their meaning from a subsection to another one, are those for the initial concentrations of dialdehyde A (a), amine B (b), amine C (c) and water (w) and those for the following concentrations at

equilibrium: x, y, z, t, u, v, s and h. The other notations may change their meanings from a subsection to another. In such cases, they are explicitly associated to their respective new formulae or meanings.

One assumes that the reactions between aldehydes and amines take place in the sense of formation of imines, so that x, y, z, t, u, v and s should be positive. The multiplication sign was omitted in the literal expressions.

5.1 Formation of the first bis-imine

Dialdehyde A (that may be, but is not only the dialdehyde A), of initial molar concentration in the reaction mixture a, reacts with the primary (aromatic) monoamine B (of concentration b) to form, as a final target product, the bis-imine AB_2 . The equilibrium constants being K_1 and K_2 , the reactions are:



where the initial concentrations (prior to formation of any imine) are $[A]_{in} = a$, $[B]_{in} = b$, $[AB]_{in} = 0$, $[AB_2]_{in} = 0$, $[H_2O]_{in} = w$, and the concentrations at equilibrium are $[A]_{eq} = a - x - y$, $[B]_{eq} = b - x - 2y$, $[AB]_{eq} = x$, $[AB_2]_{eq} = y$, $[H_2O]_{eq} = w + x + 2y$. The concentrations x and y at equilibrium, the excess of B required to obtain a desired concentration of AB_2 , and equilibrium constants from yields, can be calculated as follows.

5.1.1 Calculation of K_1 and K_2 from yields

If the ratios (yields at equilibrium) $[AB]_{eq}/[A]_{in} = x/a = m$ and $[AB_2]_{eq}/[A]_{in} = y/a = n$ are known, then we have $x = ma$, $y = na$ and, finally, $K_1 = [m/(1-m-n)]\{[w/a + (m + 2n)]/[b/a - (m + 2n)]\}$, $K_2 = (n/m)\{[w/a + (m + 2n)]/[b/a - (m + 2n)]\}$ and $K_{e1} = K_1 K_2 = [n/(1-m-n)]\{[w/a + (m + 2n)]/[b/a - (m + 2n)]\}^2$. See SM, file l-simul-K1-K2.

5.1.2 Composition at equilibrium

If the initial concentrations (before formation of any imine) $[A]_{in} = a$, $[B]_{in} = b$, $[AB]_{in} = [AB_2]_{in} = 0$, $[H_2O]_{in} = w$, and K_1 and K_2 are known, one may wish to calculate the concentrations of species at equilibrium. One needs x and y. From $K_1/K_2 = x^2/[y(a-x-y)]$ one obtains the equation in x, $K_2x^2 + K_1yx + K_1(y-a)y = 0$, with the discriminant $\Delta = K_1(K_1 - 4K_2)y^2 + 4K_1K_2ay$ and $x_{1,2} = (-K_1y \pm \Delta^{1/2})/(2K_2)$. One notices that $-K_1y < 0$ and $-(\Delta^{1/2}) < 0$, and so $(-K_1y - \Delta^{1/2})/(2K_2) < 0$. The positive solution is $x = (\Delta^{1/2} - K_1y)/(2K_2) > 0$. This expression is introduced into K_2 and gives the equation $(\Delta^{1/2} - K_1y)[- \Delta^{1/2} - (4K_2 - K_1)y + 2K_2b] = 2(4K_2 - K_1)y^2 + 4K_2wy + 2y\Delta^{1/2}$, which, after rewriting and simplification, becomes $Ay^2 + By = (Dy + E)(Fy^2 + Gy)^{1/2}$, where $A = K_1(4K_2 - K_1 + 1) - 4K_2 = (4K_2 - K_1)(K_1 - 1)$, $B = -K_2[K_1(2a + b) + 2w]$, $D = 2K_2 - K_1 + 1$, $E = -K_2b$, $F = K_1(K_1 - 4K_2)$ and $G = 4K_1K_2a$. After elimination of radicals, simplification and rewriting, one obtains the cubic (third degree) equation $\alpha y^3 + \beta y^2 + \gamma y + \delta = 0$, that can be solved analytically (Pettis, 1942; Zucker, 2008; vide infra) and where $\alpha = A^2 - D^2F$, $\beta = 2AB - 2DEF - D^2G$, $\gamma = B^2 - E^2F - 2DEG$, $\delta = -E^2G$. Example of verification key (for 1 real root): for $a = 5$, $b = 8$, $w = 2$, $K_1 = 0.6$, $K_2 = 2.25$, one obtains $x = 1$, $y = 1.5$. See SM, files g-S1-Num-expl, g-S1-St1-comp-after-add-B, g-S1-St3-comp-after-add-exc-B, v-key-ABW, v-verif-ABW.

Sections 5.1.2, 5.1.3 are, here, treated independently of each other.

5.1.3 Calculation of the supplementary amount (excess) of amine B

Let $[A]_{in} = a$, $[B]_{in} = b$, $[AB]_{in} = 0$, $[AB_2]_{in} = 0$, $[H_2O]_{in} = w$ be the initial concentrations of reagents for which the equilibrium is reached at the ratios $m = [AB]_{eq}/a$ and $n = [AB_2]_{eq}/a$. In this case, K_1 and K_2 can be calculated as done before. We now wish to know which is the supplementary amount (the excess) of B, which is to be added to the mixture at equilibrium, so that the yield of AB_2 increases from s to p , which means $[AB_2]_{eq}/a = p$ (where $p > n$). Let this excess of B be, in terms of concentration, $g_B = [B]_{ex}$. With $[AB_2]_{eq} = pa$, $[AB]_{eq} = x$, $[A]_{eq} = a - x - pa$, $[B]_{eq} = b - x - 2pa + g_B$, and $[H_2O]_{eq} = w + x + 2pa$, we have $K_1 = x(w + x + 2pa)/[(a - x - pa)(b - x - 2pa + g_B)]$ and $K_2 = pa(w + x + 2pa)/[x(b - x - 2pa + g_B)]$. We obtain $K_1/K_2 = x^2/\{pa[(1-p)a - x]\}$, which leads to the quadratic equation $x^2 + pa(K_1/K_2)x - p(1-p)(K_1/K_2)a^2 = 0$, with the discriminant $\Delta = p^2a^2(K_1/K_2)^2\{1 + 4[(1-p)/p](K_2/K_1)\} = p^2a^2(K_1/K_2)^2\{1 + 4(1/p-1)(K_2/K_1)\}$ and $x_{1,2} = a[(p/2)(K_1/K_2)]\{\pm[1 + 4(1/p-1)(K_2/K_1)]^{1/2} - 1\}$. The positive value of x being to be chosen, we have $x = a[(p/2)(K_1/K_2)]\{[1 + 4(1/p-1)(K_2/K_1)]^{1/2} - 1\}$.

Then, from K_2 we have $g_B = [pa(w + x + 2pa)/(K_2x)] - (b - x - 2pa)$ or from K_1 , $g_B = \{x(w + x + 2pa)/[K_1(a - x - pa)]\} - (b - x - 2pa)$, which gives g_B/a equivalents of B with respect to A or g_B/b equivalents of B with respect to B. See SM, files g-S1-Num-expl, g-S1-St2-calc-exc-B.

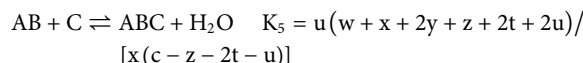
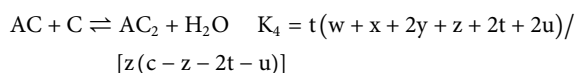
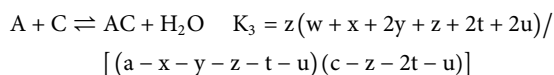
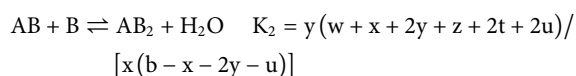
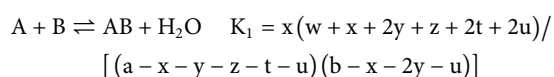
The expression of the excess of B is not included in the calculations hereafter.

5.1.4 Influence of the amount of water

Depending on the values of imine formation constants, the amount of water may, more or less considerably, affect the composition at equilibrium (vide infra, Section 5.2.4).

5.2 Exchange with monoamine. General approach

On addition of primary (aliphatic) monoamine C, that should be - if good transimination yields are wished - more nucleophilic than B, the following exchanges are expected to occur, the target compound being the bis-imine AC_2 : $AB_2 + C \rightleftharpoons ABC + B$ and $ABC + C \rightleftharpoons AC_2 + B$. If one does not consider the equations of formation of aldehyde hydrates, amins or hemiaminals, the system can be described through the following equations:



where the following was added or changed in the concentrations from the introductory part of Section 5.1: $[C]_{in} = c$, $[AC]_{in} = [AC_2]_{in} = [ABC]_{in} = 0$, $[C]_{eq} = c - z - 2t - u$, $[AC]_{eq} = z$, $[AC_2]_{eq} = t$, $[ABC]_{eq} = u$, $[A]_{eq} = a - x - y - z - t - u$ and $[B]_{eq} = b - x - 2y - u$.

The initial concentrations of compounds A, B, C and H_2O are their total molar concentrations prior to the formation of any imine. In this framework, the initial concentrations of compounds AB, AB_2 , AC, AC_2 and ABC are 0. The relation between initial concentrations and concentrations before reaction can be exemplified as follows. If a solution containing A, AB_2 , AB, ABC and B is mixed with a solution containing AC_2 , AC and C, so that the molar concentrations in the reaction mixture before reaction are $[A]_{bfr}$, $[AB]_{bfr}$, $[AB_2]_{bfr}$, $[B]_{bfr}$, $[AC]_{bfr}$, $[ABC]_{bfr}$, $[AC_2]_{bfr}$, $[C]_{bfr}$ and $[H_2O]_{bfr}$, then the initial, total concentrations prior to the formation of any imine, are $[A]_{in} = [A]_{bfr} + [AB]_{bfr} + [AB_2]_{bfr} + [AC]_{bfr} + [ABC]_{bfr} + [AC_2]_{bfr}$, $[B]_{in} = [B]_{bfr} + [AB]_{bfr} + 2[AB_2]_{bfr} + [ABC]_{bfr}$, $[C]_{in} = [C]_{bfr} + [AC]_{bfr} + 2[AC_2]_{bfr} + [ABC]_{bfr}$ and $[H_2O]_{in} = [H_2O]_{bfr} - ([AB]_{bfr} + [AC]_{bfr}) - 2([AB_2]_{bfr} + [ABC]_{bfr} + [AC_2]_{bfr})$. In a shortened numerical example, we consider a mixture consisting of 1 equiv. of imine AB_2 of molar concentration n , 0.005 equiv. of AB, 0.6 equiv. of B and 0.4 equiv. of water, that reacts with 1.4 equiv. of amine C. In this case, the concentrations (in mole/L) before reaction are $[AB_2]_{bfr} = n$, $[AB]_{bfr} = 0.005n$, $[B]_{bfr} = 0.6n$, $[H_2O]_{bfr} = 0.4n$ and $[C]_{bfr} = 1.4n$, and the initial concentrations (before formation of any imine) are $[A]_{in} = 1.005n$, $[B]_{in} = 2n + 0.005n + 0.6n = 2.605n$, $[C]_{in} = 1.4n$ and $[H_2O]_{in} = 0.4n - 2n - 0.005n = -1.595n$.

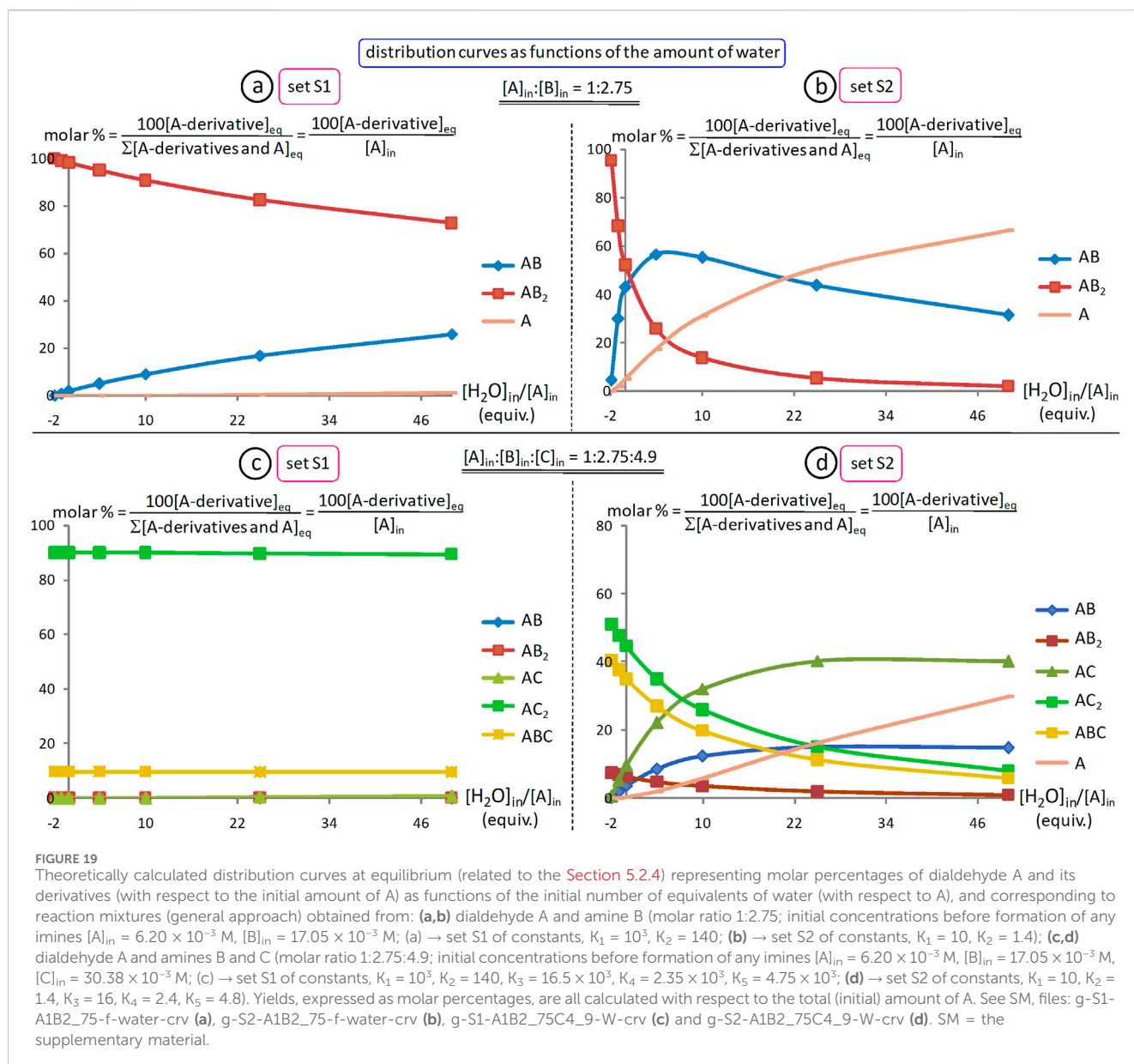
$[H_2O]_{in}$ is generally positive or zero. $[H_2O]_{in} < 0$ is a mathematical way to indicate that a part of the amount of water that forms in the reaction, starting from the initial concentrations, leaves the system during the equilibration. $[H_2O]_{eq}$ should however be positive. See SM, files g-S1-A1B2_75C4_9-W-1, g-S1-A1B2_75C4_9-W-1_9. Typically, $[H_2O]_{in}$ may be negative when one starts from compound AB_2 (beforehand synthesized and isolated), that is treated with compound C in a solution where the concentration of water before reaction is less than twice the concentration of AB_2 before reaction $[H_2O]_{bfr} < 2[AB_2]_{bfr}$.

One does not need to consider the equilibrium $AC + B \rightleftharpoons ABC + H_2O$ in addition to the above listed equations, because it and its constant (K_1K_5/K_3) can be deduced from the equilibria $AB + C \rightleftharpoons ABC + H_2O$ (K_5), $AC + H_2O \rightleftharpoons A + C$ (K_3) and $A + B \rightleftharpoons AB + H_2O$ (K_1).

These calculations can be applied to any couple of two amines which react with a dialdehyde, as well as to any exchange between a bis-imine and an amine, regardless of the aliphatic or aromatic nature of the two amines.

5.2.1 Simulation of constants K_3 , K_4 and K_5

In this section, the constants K_1 and K_2 are considered to be known. One may wish to estimate the values of constants K_3 , K_4 and K_5 that produce desired or known yields at equilibrium for the initial concentrations a , b , c and w . One assumes that the yields (and the concentrations) of three of the products AB, AB_2 , AC, AC_2 and ABC are known (or desired) at equilibrium and have a numerical value.



There are three main situations which depend on the groups $\{x, y\}$ or $\{z, t, u\}$ to which may belong the two remaining unknown concentrations.

- The unknown concentrations are x and y (1 possibility). Let the known (or desired) yields be $n = t/a$, $m = z/a$ and $o = u/a$. We have $K_1/K_2 = x^2/\{y [a(1-m-n-o)-x-y]\}$ which gives $x_{1,2} = (\pm\Delta^{1/2} - K_1y)/2K_2$, with $\Delta = Dy^2 + Ey$, $D = K_1(K_1 - 4K_2)$ and $E = 4K_1K_2(a-z-t-u) = 4aK_1K_2(1-m-n-o)$. The positive value of $x = (\Delta^{1/2} - K_1y)/2K_2$ is introduced into the expression of K_2 . After rewriting and simplification, one gets the equation $Ay^2 + By = (Fy + G)(Dy^2 + Ey)^{1/2}$, with $A = 4K_2 + K_1(K_1 - 4K_2 - 1)$, $B = K_2\{K_1[2(a-z-t-u) + b-u] + 2(w+z+2t+2u)\} = K_2\{K_1[2a(1-m-n-o) + b-ao] + 2[w+a(m+2n+2o)]\}$, $F = K_1 - 2K_2 - 1$, $G = K_2(b-u) = K_2(b-ao)$, $a-z-t-u = a(1-m-n-o)$ and $z+2t+2u = a(m+2n+2o)$. Elimination of radicals and simplification lead to the cubic equation $\alpha y^3 + \beta y^2 + \gamma y + \delta = 0$,

where $\alpha = A^2 - DF^2$, $\beta = 2AB - 2DFG - EF^2$, $\gamma = B^2 - DG^2 - 2EFG$ and $\delta = -EG^2$;

- One unknown concentration from $\{x, y\}$ and one from $\{z, t, u\}$ (6 possibilities). Let the known (desired) yields be, for example, $r = y/a$, $n = t/a$ and $o = u/a$. The following notations are introduced $J = w + 2(y + t + u)$, $K = a - (y + t + u)$ and $L = b - (2y + u)$. From K_2 , we obtain $z = -(K_2/y)x^2 + (K_2L/y - 1)x - J$. z is introduced into the expression of K_1 and leads to the cubic equation $\alpha x^3 + \beta x^2 + \gamma x + \delta = 0$, where $\alpha = [K_2(1 - K_1)]/y$, $\beta = [K_2L(2K_1 - 1)]/y$, $\gamma = -K_1(J + K + K_2L^2/y)$ and $\delta = K_1L(J + K)$;
- Both unknown concentrations from $\{z, t, u\}$ (3 possibilities). Let the known (desired) yields be, for example, $q = x/a$, $r = y/a$ and $m = z/a$, along with the notations $M = w + x + 2y + z$, $N = a - (x + y + z)$ and $O = b - (x + 2y)$. From K_1/K_2 we obtain $t + u = N - K_2x^2/(K_1y) = P$. From K_2 , we have $u = O - y(M + 2P)/(K_2x)$, then we obtain $t = P - u$.

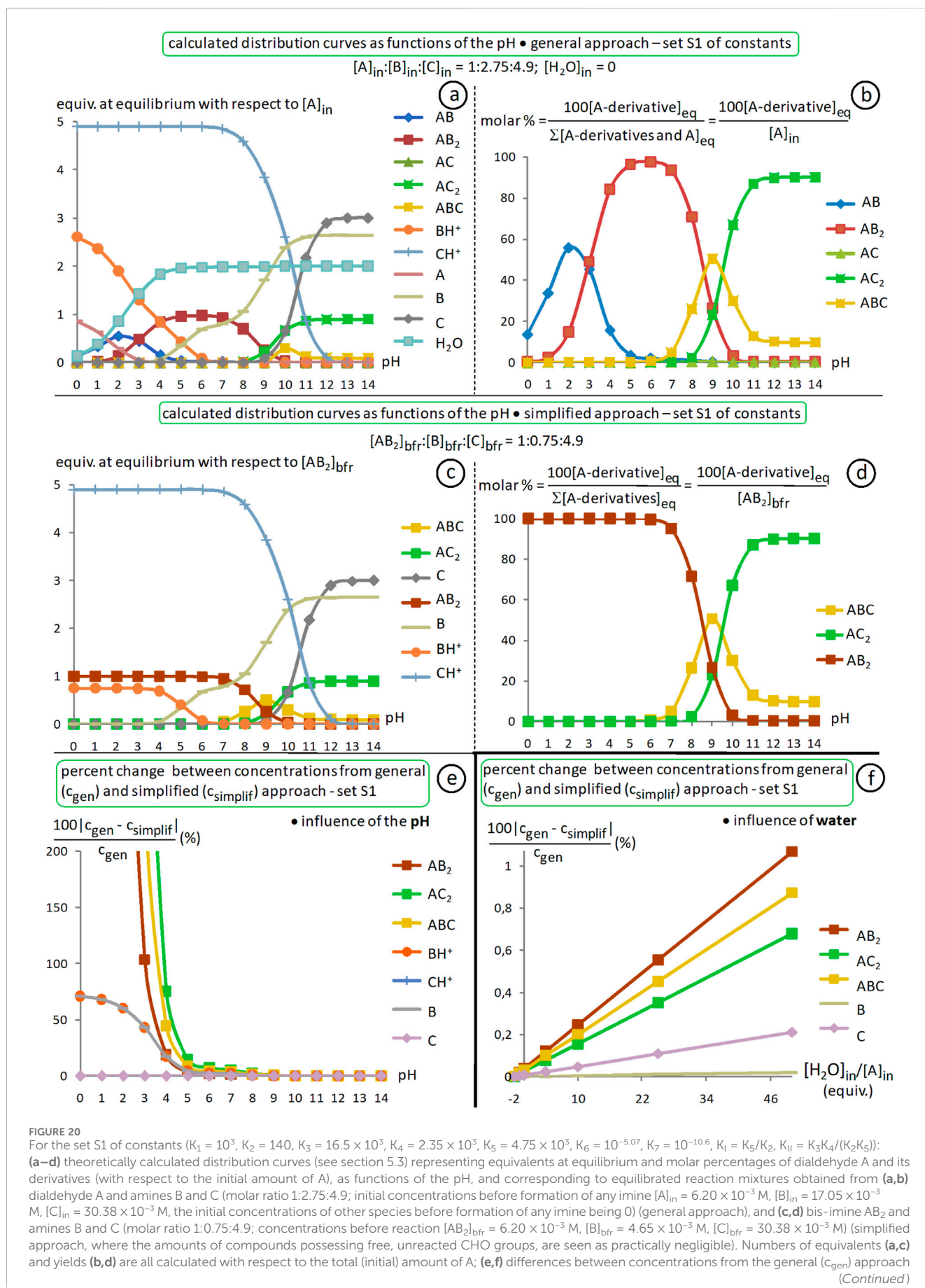


FIGURE 20 (Continued)

and those from the simplified ($c_{\text{simplified}}$) approach expressed as a percentage from c_{gen} , namely $100|c_{\text{gen}} - c_{\text{simplified}}|/c_{\text{gen}}$, and plotted as functions of the pH (e; $[\text{H}_2\text{O}]_{\text{in}} = 0$) and as functions of the initial number of equivalents of water with respect to A, before formation of imines and in the absence of acid (f; $[\text{H}_2\text{O}]_{\text{in}}/[\text{A}]_{\text{in}}$ (general approach) = -1.9, -1, 0, 4, 10, 25, 50). See SM, files g-S1-St7-pH-crv (a,b), s-S1-pH-crv (c,d), c-S1-perc-chg-f-pH (e) and c-S1-perc-chg-f-water-graph (f).

With the known concentrations and the appropriate roots determined as shown in paragraphs i-iii), one can calculate the expected values of K_3 , K_4 and K_5 . See SM, file l-simul-K3-K4-K5.

5.2.2 Composition at equilibrium

For constants K_1 to K_5 supposed to be known and for initial concentrations in the reaction mixture before formation of imines, a, b, c and w, one wishes to know the concentrations of the species in the equilibrated reaction mixture.

1. We could not find the analytical solution of the system consisting of the equations from K_1 to K_5 with the unknowns x , y , z , t and u , and we solved it numerically for $t = ar$, where $0 < r < 1$. We proceed as above and from K_4/K_5 , we have $x = Gzu$, where $G = K_4/(K_5t)$. We also have $K_1K_4/(K_2K_3) = (t/y)(x/z)^2$ and $K_4/(K_5t) = (1/u)(x/z)$, which leads to $y = Fu^2$, where $F = K_2K_3K_4/(tK_1K_5^2)$. From $K_1/K_3 = \{Gu[(c-2t)-(z+u)]\}/\{z[b-u(Gz-1-2Fu)]\}$, we obtain the equation $Hu^2 + Iu + J = Kuz$, where $H = K_3G-2K_1F$, $I = -[K_1 + GK_3(c-2t)]$, $J = K_1b$ and $K = G(K_1-K_3)$, which gives $z = (Hu^2 + Iu + J)/(Ku)$ and, further, $x = Gzu = G(Hu^2 + Iu + J)/K$. We can calculate the following expressions in t and u : $a-x-y-z-t-u = a-Gzu-Fu^2-z-t-u = \{-(FK+GH)u^3-(GI+H+K)u^2 + [K(a-t)-GJ-I]u\}/(Ku)$ and $z^2 = [H^2u^4 + 2HJu^3 + (I^2 + 2HJ)u^2 + 2IJu + J^2]/(K^2u^2)$, which can be introduced into $K_3/K_4 = z^2/[t(a-x-y-z-t-u)]$ and lead, after rewriting, to the quartic (fourth degree) equation $\alpha u^4 + \beta u^3 + \gamma u^2 + \delta u + \varepsilon = 0$, where $\alpha = -K_4H^2-tK_3K(FK+GH)$, $\beta = -tK_3K(GI+H+K)-2K_4HI$, $\gamma = tK_3K[K(a-t)-GJ-I]-K_4(I^2+2HJ)$, $\delta = -J(2K_4I+tK_3K)$ and $\varepsilon = -K_4J^2$. Quartic equations can be solved analytically (Yacoub and Fraidenraich, 2012). Each of the roots of this quartic equation is introduced into the expressions of x , y and z (in Excel). The expressions of x , y , z and u (which depend on $t = ar$) are now introduced into the equation obtained from K_1 , namely $K_1[(a-x-y-z-t-u)(b-x-2y-u)]-x(w+x+2y+z+2t+2u) = 0$. This equation can be solved numerically (in Excel), for r between 0 and 1. A shortened example of verification key (for 2 real roots): for $a = 8$, $b = 18$, $c = 32$, $w = 4$, $K_1 = 0.2$, $K_2 = 2$, $K_3 = 1.2$, $K_4 = 1.875$, $K_5 = 3$, $r = t/a = 0.5$, one obtains, amongst 2 real solutions, the following one: $x = 0.2$, $y = 0.4$, $z = 1.6$, $t = 4$, $u = 0.8$. See SM, files g-S1-Num-expl, g-S1-St4-comp-after-add-C, g-S1-St6-comp-after-add-exc-C, v-key-ABCW, v-verif-ABCW.
2. Alternatively, the system consisting of equations obtained from K_1 to K_5 can be solved numerically for $z = ma$, with m between 0 and 1; m is the yield of AC with respect to A. From the ratio K_4/K_5 , we have

$u = txF$, where $F = K_5/(K_4z)$, and from $K_1K_4/(K_2K_3) = (x/z)^2(t/y)$, we have $y = x^2tE$, where $E = K_2K_3/(K_1K_4z^2)$. Now, the ratio $K_1/K_3 = (x/z)[(c-z-2t-u)/(b-x-2y-u)]$ becomes $K_1/K_3 = (x/z)[c-z-t(Fx+2)]/[b-x-t(2Ex+Fx)]$ and the solution of this equation in t is $t = (Ax-B)/[x(Cx+D)]$, where $A = K_3c + ma(K_1-K_3)$, $B = K_1mab$, $C = K_3(K_5-2K_2)/(K_4ma)$ and $D = (2K_3K_4-K_1K_5)/K_4$. From this expression of t , we obtain $y = tx^2E = xE(Ax-B)/(Cx+D)$ and $u = txF = F(Ax-B)/(Cx+D)$. The expressions (in x) of y , t and u are introduced into the ratio $K_3/K_4 = z^2/[t(a-x-y-z-t-u)]$. This leads to the following equation in x : $(Ax-B)[(a-z)(Cx^2+Dx)-x^2(Cx+D)-(Ex^2+Fx+1)(Ax-B)] = Gx^2(Cx+D)^2$, where $G = K_4z^2/K_3$. This quartic equation becomes, after replacement of z by ma and rewriting, $\alpha x^4 + \beta x^3 + \gamma x^2 + \delta x + \varepsilon = 0$, where $\alpha = -A(AE+C)-C^2G$, $\beta = A[aC(1-m)-AF+2BE-D] + C(B-2DG)$, $\gamma = A[aD(1-m)-A+2BF] + B[D-aC(1-m)-BE]-D^2G$, $\delta = B[2A-BF-aD(1-m)]$ and $\varepsilon = -B^2$. Each of the roots of this quartic equation is introduced (in Excel) into the expressions of y , u and t , which become, like x , functions of z and, consequently, of m . The expressions of x , y , t and u are introduced (in Excel) into the equation obtained from K_5 , namely $K_5[x(c-z-2t-u)]-u(w+x+2y+z+2t+2u) = 0$. Now, in this last equation, all unknowns are functions of m . It can be solved numerically (in Excel) for $m \in (0,1)$. See SM, files g-S1-Num-expl, g-S1-St4-comp-after-add-C-altern, g-S1-St6-comp-after-add-exc-C-altern.

Sections 5.2.1, 5.2.2 and 5.2.3 are, here, treated independently of each other.

5.2.3 Supplementary amount (excess) of amine C

We now suppose that the reaction mixture with the constants K_1 to K_5 and the initial concentrations a , b , c and w , is equilibrated and that this equilibrium state is associated to the yield $n = t/a$. One wishes to calculate the supplementary amount of amine C that is to be added to the mixture, so that the yield at equilibrium be $p = t/a$. To this purpose, i) one may calculate the composition of the equilibrated reaction mixture for initial concentrations a , b , c and w , and, starting from that composition, calculate the supplementary amount of C that leads to the yield p , or ii) thanks to the dynamic character of the equilibria, one may consider the initial reaction mixture, before the formation of any imine, and calculate the amount of compound C, so that $t/a = p$.

1. We use here the second method. The initial concentrations in the reaction mixture are a , b , $c + g_C$ and w , where g_C is the supplementary amount of amine C, expressed as a

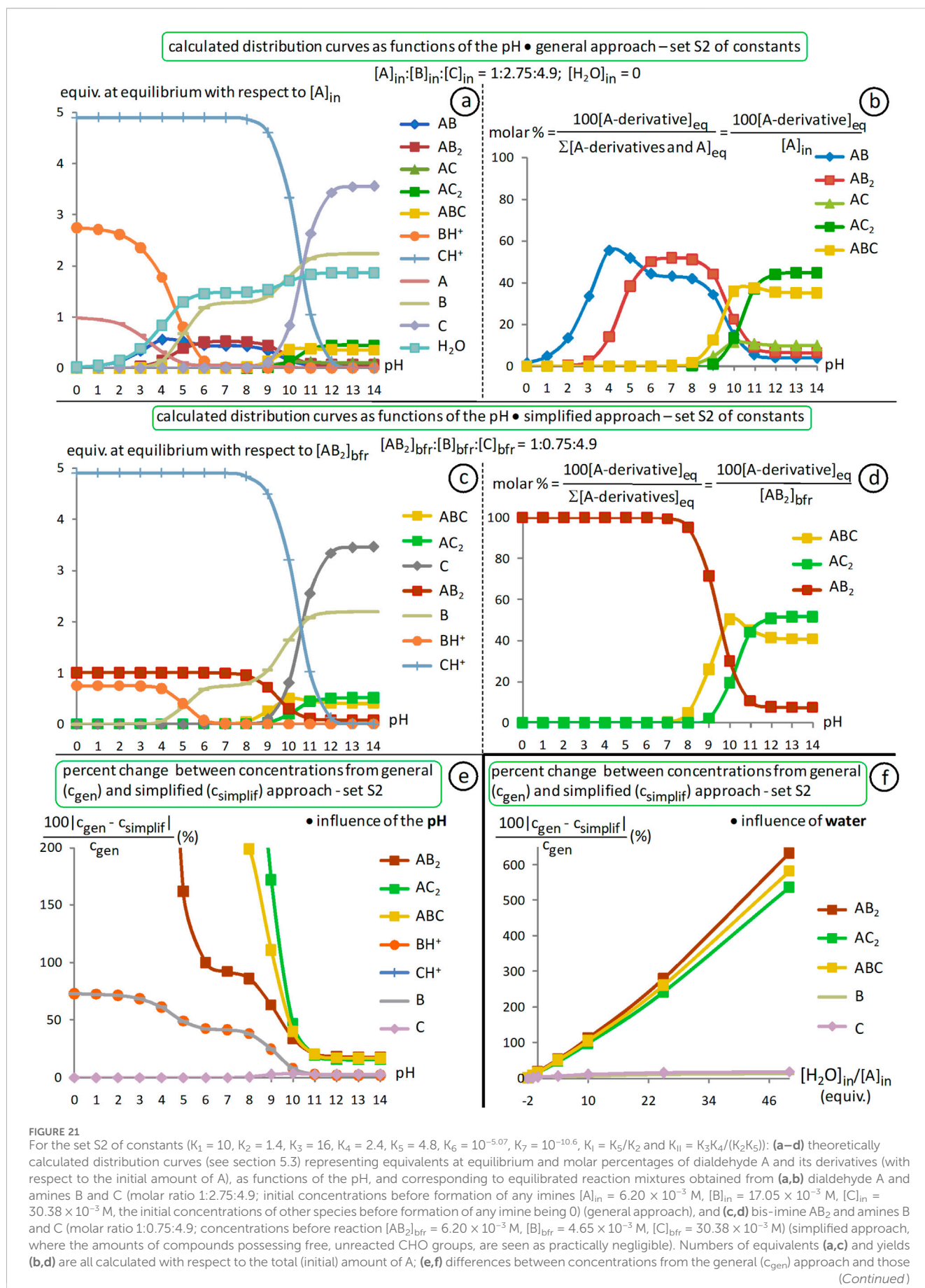


FIGURE 21 (Continued)

from the simplified (C_{simplif}) approach expressed as a percentage from C_{gen} , namely $100|C_{\text{gen}} - C_{\text{simplif}}|/C_{\text{gen}}$, and plotted as functions of the pH (e ; $[H_2O]_{\text{in}} = 0$) and as functions of the initial number of equivalents of water with respect to A, before formation of imines and in the absence of acid (f ; $[H_2O]_{\text{in}}/[A]_{\text{in}}$ (general approach) = -1.9, -1, 0, 4, 10, 25, 50). See SM, files g-S2-St7-pH-crv (a,b), s-S2-pH-crv (c,d), c-S2-perc-chg-f-pH (e) and c-S2-perc-chg-f-water-gaph" (f).

concentration. We have $t = ap$ and $K_1K_4/(K_2K_3) = (x/z)^2 t/y = (x/z)^2 ap/y$. From the ratio K_4/K_5 we obtain $x = uzK_4/(apK_5)$, which is introduced into the expression of $K_1K_4/(K_2K_3)$ and leads to $y = u^2K_2K_3K_4/(K_1K_5^2ap)$. x and y are introduced into the expression of K_3/K_4 , which leads, after rewriting, to the quadratic equation in z : $z^2 + \{[1 + uK_4/(K_5ap)]K_3ap/K_4\}z + K_3ap\{u[1 + uK_2K_3K_4/(K_1K_5^2ap)] - a(1-p)\}/K_4 = 0$ or $z^2 + Pz + Q = 0$, where $O = uK_4/(K_5t)$, $P = (O + 1)K_3t/K_4$ and $Q = K_3ap\{u[1 + uK_2K_3K_4/(K_1K_5^2ap)] - a(1-p)\}/K_4 = -K_3(a-t-u-y)t/K_4$, with the roots $z_{1,2} = [-P \pm (P^2 - 4Q)^{1/2}]/2$. Now $x = Oz$, $y = K_2K_3O^2t/(K_1K_4)$ and z are all functions of $u = ar$ and they can be introduced into the expression of K_2 . The resulting equation $K_2[x(b-x-2y-u)] - y(w+x+2y+z+2t+2u) = 0$ can be solved numerically for $u = ar$, where $0 < r < 1$. The supplementary amount of C, g_C can be calculated from K_4 , $g_C = t(w+x+2y+z+2t+2u)/(K_4z) + z+2t+u-c$, or from K_1/K_3 , $g_C = (K_1/K_3)(z/x)(b-x-2y-u) + z+2t+u-c$. See SM, files g-S1-Num-expl, g-S1-St5-calc-suppl-amt-C.

2. Alternatively, in view of a numerical solution, one can express z as ma , where m is the yield $[AC]_{\text{eq}}/a = z/a$ and lies between 0 and 1. We still have $t = ap$. We also have $K_4/K_5 = xt/zu$ or $x = uA$, where $A = (K_4/K_5)(z/t)$. From K_3/K_4 , we obtain, after rewriting, $x + y + z = B$, where $B = a-z-t-(K_4/K_3)(z^2/t)$. Both A and B are functions of z and, consequently, of $m = z/a$. Further, $x = uA$ is introduced into the expression of B, that becomes $B = y + uC$, where $C = A + 1$; $y = B - uC$. The expressions $x = Au$ and $y = B - uC$ are introduced into that of K_2 and lead, after rewriting, to the following quadratic equation in u , $u^2D + uE + F = 0$, where $D = K_2A(2C-A-1) + C(A-2C+2) = (K_2-1)A(A+1)$, $E = K_2A(b-2B) - B(A-2C+2) + C(w+2B+z+2t) = A[K_2(b-2B) + B] + C(w+2B+z+2t)$ and $F = -B(w+2B+z+2t)$. The discriminant is $\Delta = E^2 - 4DF$ and the roots are $u_{1,2} = [-E \pm (E^2 - 4DF)^{1/2}]/2D$, which are all functions of z . All expressions of unknowns x , y and t as functions of z are now introduced in that of the equation obtained from K_1/K_2 , i.e. $K_1y(a-x-y-z-t-u) - K_2x^2 = 0$. This equation can be solved numerically (in Excel) for m between 0 and 1. Further, the supplementary amount of amine C, g_C (expressed as a concentration), is calculated as described above. See SM, file g-S1-St5-calc-suppl-amt-C-altern.

5.2.4 Influence of water. A numerical example

- i. Framework. In a numerical example (see SM, file g-S1-Num-expl) we theoretically modeled, through calculations, several of the steps we follow in practice, when implementing a pH-controlled covalent switch. The imine formation constants (set S1: $K_1 = 10^3$, $K_2 = 140$, $K_3 = 16.5 \times 10^3$, $K_4 = 2.35 \times 10^3$, $K_5 = 4.75 \times 10^3$) which we considered, are in or close to the order of magnitude of those roughly determined for reactions of dialdehyde

dialpy with amines **L4** and **R4** ($K_1 = 9.0 \times 10^2$, $K_2 = 1.6 \times 10^2$, $K_3 = 15.0 \times 10^3$, $K_4 = 1.8 \times 10^3$, $K_5 = 3.2 \times 10^3$; vide supra, Section 2.3), and the concentrations of compounds A, B and C are in the range of our working concentrations. For a mixture of dialdehyde A and amine, B with $[B]_{\text{in}}/[A]_{\text{in}} = 2$ and $[A]_{\text{in}} = 6.20$ mM, we calculated the composition at equilibrium (step 1), the excess of B required to reach a desired yield of AB_2 (which led to $[B]_{\text{in}}/[A]_{\text{in}} = 2.75$; step 2) and the new composition at equilibrium after addition of the excess of B (step 3). We further calculated the composition at equilibrium after addition of 2.75 equiv. of amine C (step 4), the supplementary amount of C required to reach a desired yield of AC_2 (which led to $[C]_{\text{in}}/[A]_{\text{in}} = 4.9$; step 5) and the new composition at equilibrium after the addition of the excess of C (step 6). See SM, file g-S1-Num-expl. The seventh step deals with the influence of the pH (vide infra).

- ii. Method. In order to look at the influence of the amount of water on the concentration of bis-imines in equilibrated reaction mixtures, we considered the calculated initial concentrations (before formation of imines) resulted from the sixth step of this numerical example ($[A]_{\text{in}} = 6.20$ mM, $[B]_{\text{in}} = 17.05$ mM, $[C]_{\text{in}} = 30.38$ mM; $[A]_{\text{in}}:[B]_{\text{in}}:[C]_{\text{in}} = 1:2.75:4.9$). For these concentrations, we calculated the composition at equilibrium for reaction mixtures of A and B (for the formation of AB_2) and of A, B and C (for the formation of AC_2 upon addition of C to the equilibrated mixture of A and B), where $[H_2O]_{\text{in}}/[A]_{\text{in}} = -1.9, -1, 0, 4, 10, 25$ and 50. Comparatively, to the same concentrations $[A]_{\text{in}}$, $[B]_{\text{in}}$ and $[C]_{\text{in}}$ and ratio $[H_2O]_{\text{in}}/[A]_{\text{in}}$, we associated a second set S2 of lower imine formation constants: $K_1 = 10$, $K_2 = 1.4$, $K_3 = 16$, $K_4 = 2.4$, $K_5 = 4.8$. The set S2 is a hypothetical one obtained by simply lowering (through division by 10^2 or 10^3 and rounding) the constants from the set S1.
 - iii. Results.
 1. Mixture of A and B. For the set S1, in the equilibrated reaction mixture of A and B (Figure 19a), when the ratio $[H_2O]_{\text{in}}/[A]_{\text{in}}$ increases from -1.9 to 50, the percentage $100[AB_2]_{\text{eq}}/[A]_{\text{in}}$ decreases from practically 100% to about 73%. In parallel, the percentage $100[AB]_{\text{eq}}/[A]_{\text{in}}$ increases from, roughly, 1%–26%, while $100[A]_{\text{eq}}/[A]_{\text{in}}$ remains lower than 1.3%. For the set S2 (Figure 19b), the yield of bis-imine AB_2 dramatically diminishes from about 95% to about 2%, that of AB increases from about 5% to a maximum of about 57%, then decreases to about 32%, while $100[A]_{\text{eq}}/[A]_{\text{in}}$ increases from about 0% to about 66%.
- See SM, files g-S1-A1B2_75-f-water-crv, g-S2-A1B2_75-f-water-crv

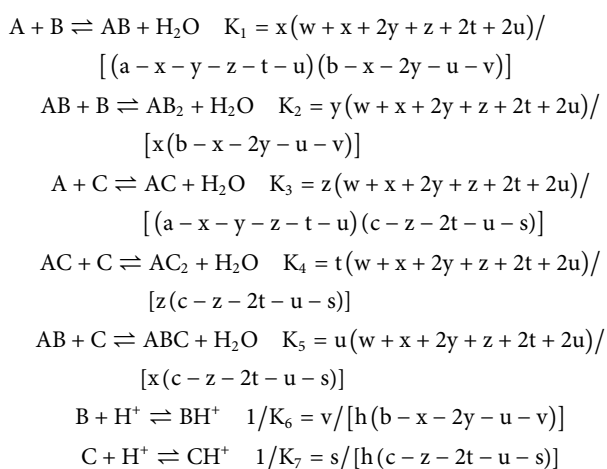
2. Mixture of A, B and C. In the equilibrated reaction mixture of A, B and C, in the case of set S1, when the ratio $[H_2O]_{in}/[A]_{in}$ increases from -1.9 to 50 , the percentages $100[bis-imine]_{eq}/[A]_{in}$ for the three bis-imines AB_2 , ABC and AC_2 remain, practically, unchanged (percent change $100|conc_{1.9}-conc_{50}|/conc_{1.9}$ is less than 1.1%) (Figure 19c). For the set S2, the percentage $100[bis-imine]_{eq}/[A]_{in}$ considerably diminishes (Figure 19d), namely, roughly, AB_2 from 7% to 1%, AC_2 from 51% to 8%, and ABC from 41% to 6%, with an average percent change $100|conc_{1.9}-conc_{50}|/conc_{1.9}$ of 85%. In parallel, $100[compound]_{eq}/[A]_{in}$ increases from less than 1% to, roughly, 15% (AB), 40% (AC) and 30% (A).

See SM, files g-S1-A1B2_75C4_9-W ... (8 files), g-S2-A1B2_75C4_9-W ... (8 files).

5.3 Influence of the pH. General approach. Equilibrium-constants-based modeling of the pH-adaptive behavior of a small dynamic library of imines

Reaction of a mixture of A, AB, AB_2 and B with amine C, leads to a mixture containing, in principle, the 8 following organic species: 1 dialdehyde (A), 2 aldehyde-imines (AB, AC), 3 bis-imines (AB_2 , AC_2 , ABC) and 2 amines (B, C). The same holds for the reaction of dialdehyde A with a mixture of amines B and C. The ways to modulate such dynamic covalent libraries of imines include supramolecular interactions (Gambaro et al., 2020), distillation (Osowska and Miljanić, 2011), crystallization (Chow et al., 2007), phase separation (Hafezi and Lehn, 2012; Pérez-Fernández et al., 2008), and the pH (Giuseppone and Lehn, 2006).

If one wishes to represent, in a rather quantitative manner, the composition of the equilibrated reaction mixture as a function of the pH (concentration = $f(\text{pH})$), then, one may consider that the system can be described, thanks to its dynamic character, through the following equations:



where the following was added or changed in the above notations for concentrations: $[B]_{eq} = b - x - 2y - u - v$, $[C]_{eq} = c - z - 2t - u - s$, $[BH^+]_{eq} = v$, $[CH^+]_{eq} = s$ and $[H^+]_{eq} = h$. This approach does

not include equations which describe the protonation of pyridines and imines, the dissociation of water or the formation of aminals, hemiaminals and hydrates from aldehydes.

From K_6 , we obtain $v = (b - x - 2y - u)h / (K_6 + h)$ and from K_7 , we have $s = (c - z - 2t - u)h / (K_7 + h)$, which lead to $b - x - 2y - u - v = (b - x - 2y - u)K_6 / (K_6 + h)$ and $c - z - 2t - u - s = (c - z - 2t - u)K_7 / (K_7 + h)$.

Now, the expressions of K_1 to K_5 become

$$\begin{aligned}
 K_1 K_6 / (K_6 + h) &= K_{1h} = x(w + x + 2y + z + 2t + 2u) / \\
 & [(a - x - y - z - t - u)(b - x - 2y - u)] \\
 K_2 K_6 / (K_6 + h) &= K_{2h} = y(w + x + 2y + z + 2t + 2u) / \\
 & [x(b - x - 2y - u)] \\
 K_3 K_7 / (K_7 + h) &= K_{3h} = z(w + x + 2y + z + 2t + 2u) / \\
 & [(a - x - y - z - t - u)(c - z - 2t - u)] \\
 K_4 K_7 / (K_7 + h) &= K_{4h} = t(w + x + 2y + z + 2t + 2u) / \\
 & [z(c - z - 2t - u)] \\
 K_5 K_7 / (K_7 + h) &= K_{5h} = u(w + x + 2y + z + 2t + 2u) / \\
 & [x(c - z - 2t - u)]
 \end{aligned}$$

The roots of this system are all functions of $h = [H^+]_{eq} = 10^{-\text{pH}}$ and could be used to express the concentrations of the components of the reaction mixture at equilibrium as functions of the pH (concentration-pH distribution curves). To this end, one may choose a range of pH values (for example, those values from 0 to 14 which are natural numbers) and, for each of these pH values, one may numerically solve the system based on K_{1h} to K_{5h} (like in the case of the system based on K_1 to K_5). Vide supra, Section 5.2.2.1. It may happen, like in our examples, that a root of the quartic equation is appropriate only for one or two pH intervals (e.g. for $0 \leq \text{pH} \leq 1$ and $10 \leq \text{pH} \leq 14$), while another root is appropriate for the remaining pH interval (e.g. for $2 \leq \text{pH} \leq 9$). See SM, file g-S1-St7-pH-crv.

In order to establish pH-dependent distribution curves, we applied this general approach to the above mentioned (vide supra, Section 5.2.4) set of initial molar concentrations (before formation of any imine) $[A]_{in} = 6.2$ mM, $[B]_{in} = 17.05$ mM (2.75 equiv.), $[C]_{in} = 30.38$ mM (4.9 equiv.) and $[H_2O]_{in} = 0$, which can be seen as a typical example. To them are associated the two sets S1 and S2 of constants $K_1 - K_5$ and the constants $K_6 = 10^{-5.07}$ and $K_7 = 10^{-10.6}$ (average acidity constants of protonated amines in water; acidity constants are expected to have different values between water and chloroform; however, those for water were used here for the sake of approximation, those for chloroform being unavailable). The results obtained for natural pH values from 0 to 14, were used to plot distribution curves (Figures 20a,b, 21a,b). For the set S1 of constants, the highest amount of aromatic bis-imine AB_2 forms at a pH between 5 and 7 (96% with respect to the total amount of A), while the highest amount of aliphatic bis-imine AC_2 (89%) appears for pH values greater than 10. Correlatively, for the set S2, a maximum of AB_2 (about 51%) is noticed for $6 \leq \text{pH} \leq 8$, and a maximum of AC_2 (about 44%), for $12 \leq \text{pH} \leq 14$ (the percentages are average values). See SM, files g-S1-Num-expl, g-S1-St7-pH0 to g-S1-St7-pH14, g-S1-St7-pH-crv, g-S2-St7-pH0 to g-S2-St7-pH14, g-S2-St7-pH-crv.

Such pH-dependent distribution curves make possible the theoretical exploration of pH domains of interest.

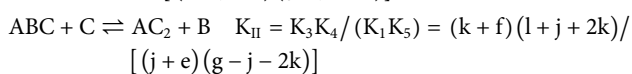
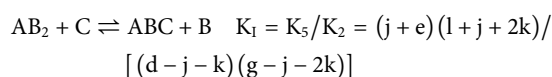
5.4 Simplification of the treatment of exchanges

If the equilibria in which compounds (here, A, AB and AC) possessing aldehyde groups are involved, could be seen, under particular conditions, as playing only a minor role, then the equilibrated reaction mixture can be described in a simplified way, where these equilibria do not longer appear. This may be done when the reaction mixture contains practically no compounds possessing carbonyl groups capable of reacting with amines (all CHO groups appear, in this framework, as imines) and the formation of such compounds through hydrolysis could be seen as negligible (presence of water, but enough high formation constants of imines or a significant excess of amines, or “absence” of water).

Hereafter we present an example of such calculations. The mathematical treatment (based on 2 polynomial equations corresponding to K_1 and K_{II} ; for the composition at equilibrium before addition of acid, the equation of highest degree to be solved is a cubic one, which can be solved analytically) of the mixture at equilibrium is simplified by comparison with the general approach (5 polynomial equations corresponding to K_1 - K_5). This can be, for example, the case when one starts from anhydrous bis-imine AB_2 (which is further treated with amine C), under the assumption that hydrolysis of imines can be seen as negligible.

5.4.1 Composition at equilibrium. Simplified approach

Under such conditions, for the reaction of a dialdehyde-based bis-imine with a primary amine (see Section 5.2), instead of equilibria A (dialdehyde) + B (amine) \rightleftharpoons AB + H_2O (K_1), $AB + B \rightleftharpoons A_2B + H_2O$ (K_2), $A + C$ (amine) \rightleftharpoons $AC + H_2O$ (K_3), $AC + C \rightleftharpoons AC_2 + H_2O$ (K_4) and $AB + C \rightleftharpoons ABC + H_2O$ (K_5), we have



with the concentrations before reaction $[AB_2]_{bfr} = d$, $[C]_{bfr} = g$, $[ABC]_{bfr} = e$, $[AC_2]_{bfr} = f$, $[B]_{bfr} = l$ and the concentrations at equilibrium $[AB_2]_{eq} = d - j - k$, $[C]_{eq} = g - j - 2k$, $[ABC]_{eq} = j + e$, $[AC_2]_{eq} = k + f$, $[B]_{eq} = 1 + j + 2k$. j and k are unknowns: $j = [ABC]_{formed}$, $k = [AC_2]_{formed}$.

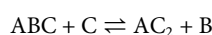
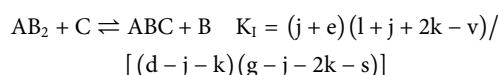
In order to calculate the composition at equilibrium, one introduces the notations $\chi = j + e = [ABC]_{eq}$ and $\zeta = k + f = [AC_2]_{eq}$ and one obtains $K_1/K_{II} = \chi^2 / \{\zeta[(d + e + f) - \chi - \zeta]\}$. This leads to the equation (in χ) $K_{II}\chi^2 + K_1\zeta\chi + K_1\zeta(\zeta - d - e - f) = 0$ with the discriminant $\Delta = E\zeta^2 + F\zeta$, where $E = K_1(K_1 - 4K_{II})$ and $F = 4K_1K_{II}(d + e + f)$. $\chi_{1,2} = (-K_1\zeta \pm \Delta^{1/2}) / (2K_{II})$. The positive χ should be $\chi = (\Delta^{1/2} - K_1\zeta) / (2K_{II})$. Introduced into the expression of K_{II} , it leads to the equation (in ζ) $G\zeta^2 + H\zeta = (I\zeta + J)(E\zeta^2 + F\zeta)^{1/2}$, where $G = K_1(4K_{II} - K_1 + 1) - 4K_{II}$, $H = -K_{II}[K_1(g + 2d + 3e + 4f) + 2(1 - e - 2f)]$,

$I = -K_1 + 2K_{II} + 1$ and $J = -K_{II}(g + e + 2f)$. After elimination of radicals, simplification and rewriting, one obtains the cubic equation (in ζ) $\alpha\zeta^3 + \beta\zeta^2 + \gamma\zeta + \delta = 0$, where $\alpha = G^2 - EI^2$, $\beta = 2GH - 2EIJ - FI^2$, $\gamma = H^2 - EJ^2 - 2FIJ$, $\delta = -FJ^2$. This equation can be solved analytically. From the solution $\zeta = k + f = [AC_2]_{eq}$, we obtain $k = \zeta - f = [AC_2]_{formed}$, as well as $\chi = j + e = (\Delta^{1/2} - K_1\zeta) / (2K_{II}) = [ABC]_{eq}$ and $j = \chi - e = [ABC]_{formed}$. See SM, files s-comp-equil, s-S1-S2-Num-expl, s-S1-comp-equil, s-S2-comp-equil. The imine exchange constants from the set S1 are $K_1 = K_5/K_2 \approx 33.9$ and $K_{II} = K_3K_4/(K_1K_5) \approx 8.2$ and those from the set S2 are $K_1 = K_5/K_2 \approx 3.4$ and $K_{II} = K_3K_4/(K_1K_5) = 0.8$ (for K_1 - K_5 from each set, vide supra, section 5.2.4).

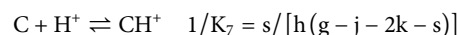
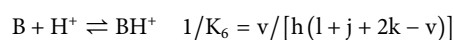
If $[A]_{in} = a$, $[B]_{in} = b$, $[C]_{in} = c$ and $[H_2O]_{in} = w$ are the total, initial (\rightarrow in) concentrations before the formation of any imine, and $[AB_2]_{bfr} = d$, $[AC_2]_{bfr} = f$, $[ABC]_{bfr} = e$, $[B]_{bfr} = l$, $[C]_{bfr} = g$ and $[H_2O]_{bfr} = w_{bfr}$ are the starting concentrations before reaction (\rightarrow bfr), then the following relationships of equivalence hold: $a = d + e + f$, $b = 2d + e + l$, $c = g + e + 2f$ and $w = w_{bfr} - 2(d + e + f)$. One notices that $[H_2O]_{bfr}$ does not appear in the simplified approach.

5.4.2 Influence of the pH

In addition to the two transiminations, one considers the protonation of amines B and C, as follows



$$K_{II} = (k + f)(1 + j + 2k - v) / [j(g - j - 2k - s)]$$

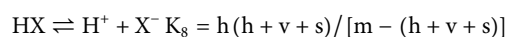


with the following changes in the concentrations at equilibrium $[BH^+]_{eq} = v$, $[B]_{eq} = 1 + j + 2k - v$, $[CH^+]_{eq} = s$, $[C]_{eq} = g - j - 2k - s$ and $[H^+]_{eq} = h$.

From K_6 and K_7 , we have $v = h(1 + j + 2k) / (K_6 + h)$ and $s = h(g - j - 2k) / (K_7 + h)$, which, introduced into the expressions of K_1 and K_{II} lead to $(j + e)(1 + j + 2k) / [(d - j - k)(g - j - 2k)] = K_1K_7(K_6 + h) / [K_6(K_7 + h)] = K_{Ih}$ and $(k + f)(1 + j + 2k) / [j(g - j - 2k)] = K_{II}K_7(K_6 + h) / [K_6(K_7 + h)] = K_{IIh}$. In order to establish distribution curves (concentrations as functions of the pH; Figures 20c,d, 21c,d), one may consider (natural) pH values between 0 and 14, and solve the system of equations obtained from K_{Ih} and K_{IIh} , for these values of the pH. See SM, files s-S1-S2-Num-expl, s-S1-pH, s-S1-pH-crv, s-S2-pH, s-S2-pH-crv.

5.4.3 Addition of an amount of acid

A known amount of acid HX (here, usually, CF_3COOH ; $K_a = K_8$) is added (in a small volume of solvent, that makes possible the approximation that the volume of the reaction mixture remains constant) to the equilibrated reaction mixture obtained after addition of amine C. The molar concentration of HX in the reaction mixture before reaction is m and one wishes to calculate the concentrations of species at equilibrium. The equation to be added to those from section 5.4.2, is



with $[HX]_{bfr} = m$, $[X^-]_{eq} = h + v + s$ and $[HX]_{eq} = m - (h + v + s)$.

The equation to be solved is that obtained from K_8 , namely $(h + v + s)(K_8 + h) - mK_8 = 0$. This was done numerically, in Excel, for $r = h/m$ with $0 < r < 1$ (r is, here, the degree of dissociation of HX). h is a function of r , but v and s are functions of h and, consequently, of r , and so, the whole expression $(h + v + s)(K_8 + h) - mK_8$ is a function of $r \in (0,1)$. See SM, files s-S1-S2-Num-expl, s-S1-aj-acid.

5.4.4 Addition of an amount of base

A known amount of base (usually triethylamine TEA) is added to the equilibrated reaction mixture obtained after addition of acid, the volume being seen as constant. The molar concentration of base before reaction is p . The supplementary equilibrium to be considered, in addition to those from sections 5.4.2 and 5.4.3, is



with $[\text{Base}]_{\text{bfr}} = p$, $[\text{HX}]_{\text{bfr}} = m$, $[\text{Base}]_{\text{eq}} = i$, $[\text{X}^-]_{\text{eq}} = h + v + s + i$ and $[\text{HX}]_{\text{eq}} = m - (h + v + s + i)$. From K_9 , we have $h = K_9 i / (p - i)$. We also have $K_8 = h(h + v + s + i) / [m - (h + v + s + i)]$ and the equation to be solved is $(h + v + s + i)(K_8 + h) - mK_8 = 0$. i can be written as $i = qp$, where $q \in (0,1)$ is the degree of protonation of the base. In this way, unknowns h , v , s and i are functions of q and the above equation from K_8 can be solved numerically (in Excel) for q between 0 and 1. See SM, files s-S1-S2-Num-expl, s-S1-aj-base.

5.4.5 Comparison between general and simplified approaches

- Set S1 of constants. Thanks to excesses of amines and to enough strong constants from set S1, the distribution of bis-imines AB₂, ABC and AC₂ is, for $7 \leq \text{pH} \leq 14$ (e), quite similar between the general approach, with $[\text{H}_2\text{O}]_{\text{in}} = 0$, and the simplified one. For a quantitative comparison, we used the percentage change $100|c_{\text{gen}} - c_{\text{simplif}}|/c_{\text{gen}}$ which is, for that pH range, lower than 5.6%. At pH = 6, this percentage change for bis-imines is between 2% and 7.5%, at pH = 5, it lies between 3.9% and 14.5%, and for $0 \leq \text{pH} \leq 4$, it is superior to 18.8% (Figure 20e; see SM, file c-S1-perc-chg-f-pH). The influence of water from the general approach - water does not appear in the calculations from the simplified approach -, in the absence of acid, is very weak (Figure 20f). Indeed, for $[\text{H}_2\text{O}]_{\text{in}}/[\text{A}]_{\text{in}}$ from -1.9 – 50 equiv., the difference $100|c_{\text{gen}} - c_{\text{simplif}}|/c_{\text{gen}}$ lies between $3.8 \times 10^{-5}\%$ and 1.1%. See SM, files s-S1-S2-Num-expl, c-S1-perc-chg-f-water, c-S1-perc-chg-f-water-graph.
- Set S2 of constants. In the case of set S2, the formation constants of imines are quite low, and even with an excess of 0.75 equiv. of amine B and an excess of 2.9 equiv. of amine C, the difference $100|c_{\text{gen}} - c_{\text{simplif}}|/c_{\text{gen}}$ for AB₂, ABC and AC₂ is, in the pH range from 0 to 14 and for $[\text{H}_2\text{O}]_{\text{in}} = 0$, greater than 15% (Figure 21e). See SM, file c-S2-perc-chg-f-pH. In such cases, it is better to consider the general approach. The influence of water (in systems without acid) on the difference between the concentrations of imines calculated in the general approach and those calculated in the simplified

approach (Figure 20f), can be seen as weak only for $[\text{H}_2\text{O}]_{\text{in}}/[\text{A}]_{\text{in}} = -1.9$ (the negative sign means that 1.9 equiv. of water leave, in the general approach, the system during the equilibration), with the percentage change $100|c_{\text{gen}} - c_{\text{simplif}}|/c_{\text{gen}}$ for AB₂, ABC and AC₂ between 0.76% and 0.88%. However, $100|c_{\text{gen}} - c_{\text{simplif}}|/c_{\text{gen}}$ lies between 7.7% and 8.8% for $[\text{H}_2\text{O}]_{\text{in}}/[\text{A}]_{\text{in}} = -1$ and it is bigger than 15% for $[\text{H}_2\text{O}]_{\text{in}} > 0$. See SM, files s-S1-S2-Num-expl, c-S2-perc-chg-f-water, c-S2-perc-chg-f-water-graph.

5.5 Solving of equations and systems

5.5.1 Solutions of systems

The systems of polynomial equations were solved by substitution. In order to avoid very long or too complicated mathematical expressions in the solving of equations, we introduced notations (usually, capital or Greek letters) corresponding to intermediate parameters or coefficients. In the solving of equations and systems, it is assumed that coefficients, parameters, their combinations and other expressions are nonzero, when they appear as divisors.

5.5.2 Stop-criteria

In the cases where we had to solve equations and/or systems of equations in a numerical way, the variable or unknown (e.g. the concentration of a bis-imine or of an aldehyde-amine) convenient for the solving was expressed as a function of its yield with respect to the difunctional compound (dialdehyde). This yield (let it be, here, r) is necessarily between 0 and 1. One gives to this yield values between 0 and 1, and looks at the sign and general trend of the polynomial function of the equation $\text{eq}(r)$, which is to be solved. We did this manually in Excel. If a sign change is found for two values r_1 and r_2 of the yield, this means that a root of the equation is between r_1 and r_2 . One should find, between r_1 and r_2 , values of r for which $\text{eq}(r)$ is as closest to zero as possible. This process is stopped thank to criteria defined by the chemist. One may use, as a stop-criterion related to numerical values of the yield, the number of digits after the decimal separator. To this criterion one should add a second one, which can be the closest to 0 value of $\text{eq}(r)$, namely the smallest absolute value of $\text{eq}(r)$.

A supplementary means to verify the solutions obtained through numerical methods is the value of the equilibrium constants recalculated on the basis of the roots of the equation. One may consider the sum of the percentages of differences between the starting constants (K) and the recalculated ones ($K_{\text{recalculated}}$), namely $\Sigma 100\Delta K_i/K_i$, where $\Delta K = |K_{\text{recalculated}} - K|$. If several numerical solutions which may have a real chemical meaning, are found, one should retain that for which $\Sigma 100\Delta K_i/K_i$ is the smallest.

One can, of course, use other numerical methods. See, for example, (Crerar, 1975).

For the sake of mathematical accuracy, when numerically solving the equations in Excel, we sought to obtain a value of the left-hand side, as close as possible to 0, which may lead to mathematical solutions with numerous (sometimes more than 8) digits after the decimal separator. However, in practice such

solutions should be rounded (to ones with only 2-3 digits after the decimal separator), considering also the uncertainty associated to the inputs (concentrations, constants).

5.5.3 Verification keys

Sets of arbitrary chosen numerical values of the initial concentrations and of those of newly formed products at equilibrium were used to calculate constants without particular chemical meaning. In this way, one is sure that at least one set of mathematically right roots of the system is known. We use such sets as verification keys, to check if the formulae we wrote in Excel are mathematically right. See SM, files v-key-ABCW, v-key-ABW, v-verif-ABCW, v-verif-ABW.

5.5.4 Analytical solving of cubic equations

For the equation $\alpha x^3 + \beta x^2 + \gamma x + \delta = 0$, one defines its discriminant discr3 (or discrIII) = $18\alpha\beta\gamma\delta - 4\beta^3\delta - 27\alpha^2\delta^2 - 4\alpha\gamma^3 + \beta^2\gamma^2$, $\mu = (3\alpha\gamma - \beta^2)/(3\alpha^2)$ and $v = (27\alpha^2\delta - 9\alpha\beta\gamma + 2\beta^3)/(27\alpha^3)$. If $\text{discr3} < 0$, the cubic equation has one real root and two non-real roots. The real root is the real algebraic one $x_r = [-v/2 + (\mu^3/27 + v^2/4)^{1/2}]^{1/3} + [-v/2 - (\mu^3/27 + v^2/4)^{1/2}]^{1/3} - \beta/(3\alpha)$. If $\text{discr3} > 0$, the cubic equation has three distinct real roots. Its trigonometric solution is based on $\varphi = \arccos [(-v/2)/(-\mu^3/27)^{1/2}]$. In this case (said casus irreducibilis), one has $x_{1,2,3} = -\beta/(3\alpha) + 2(-\mu/3)^{1/2} \cos[(\varphi + 2k\pi)/3]$, where $k = 0, 1, 2$. In our Excel files, the discriminant may appear, but it is not systematically calculated. We preferred to introduce the numerical data into the formulae for both algebraic and trigonometric solutions and to check directly which solution (algebraic or trigonometric) is the convenient one (Fettis, 1942; Zucker, 2008).

5.5.5 Analytical solving of quartic equations

We used here the method established by Yacoub and Fraidenaich (2012). For the equation $\alpha x^4 + \beta x^3 + \gamma x^2 + \delta x + \varepsilon = 0$, these authors defined (with other notations) the parameters τ_0, τ_1, τ_2 and τ_3 : $\tau_0 = -\alpha\delta^2 + \beta^2\varepsilon$, $\tau_1 = \beta^2\delta - 4\alpha\gamma\delta + 8\alpha\beta\varepsilon$, $\tau_2 = \beta^2\gamma - 4\alpha\gamma^2 + 2\alpha\beta\delta + 16\alpha^2\varepsilon$ and $\tau_3 = \beta^3 - 4\alpha\beta\gamma + 8\alpha^2\delta$. If $\tau_2 = \tau_3 = 0$, then $x_1 = x_2 = [-\beta + (3\beta^2 - 8\alpha\gamma)^{1/2}]/(4\alpha)$ and $x_3 = x_4 = [-\beta - (3\beta^2 - 8\alpha\gamma)^{1/2}]/(4\alpha)$. If $\tau_2 \neq 0$ and $\tau_3 = 0$, then $x_{1,2} = -\{\beta + [\pm 2(\beta^4 - 8\beta^2\alpha\gamma + 16\alpha^2\gamma^2 - 64\alpha^3\varepsilon)^{1/2} + 3\beta^2 - 8\alpha\gamma]^{1/2}\}/(4\alpha)$ and $x_{3,4} = -\{\beta - [\pm 2(\beta^4 - 8\beta^2\alpha\gamma + 16\alpha^2\gamma^2 - 64\alpha^3\varepsilon)^{1/2} + 3\beta^2 - 8\alpha\gamma]^{1/2}\}/(4\alpha)$. If $\tau_2 \neq 0$ and $\tau_3 \neq 0$, then the following cubic equation is to be solved: $\tau_3\lambda^3 + \tau_2\lambda^2 + \tau_1\lambda + \tau_0 = 0$. Yacoub and Fraidenaich consider any of the three possible roots of this cubic equation. We focused here only on its real roots. Are also defined discr3 (or discrIII) = $18\tau_3\tau_2\tau_1\tau_0 - 4\tau_2^3\tau_0 - 27\tau_3^2\tau_0^2 - 4\tau_3\tau_1^3 + \tau_2^2\tau_1^2$, $\mu = (3\tau_3\tau_1 - \tau_2^2)/3\tau_3^2$ and $v = (27\tau_3^2\tau_0 - 9\tau_3\tau_2\tau_1 + 2\tau_2^3)/(27\tau_3^3)$. If $\text{discr3} < 0$, the cubic equation has one real root and two non-real roots. The real root is $\lambda_r = [-v/2 + (\mu^3/27 + v^2/4)^{1/2}]^{1/3} + [-v/2 - (\mu^3/27 + v^2/4)^{1/2}]^{1/3} - \tau_2/(3\tau_3)$. If $\text{discr3} > 0$, the cubic equation has three real roots. Its trigonometric solution is based on $\varphi = \arccos [(-v/2)/(-\mu^3/27)^{1/2}]$. In this case, $\lambda_{\text{trig}1,2,3} = -\tau_2/(3\tau_3) + 2(-v/3)^{1/2} \cos[(\varphi + 2k\pi)/3]$, where $k = 0, 1, 2$. For the solving of the quartic equation, Yacoub and Fraidenaich also defined $\eta = [\tau_3/(\beta + 4\alpha\lambda_s)]^{1/2}$ and $\rho = (\beta^3 - 4\alpha^2\delta - 2\alpha\beta\gamma + 6\alpha\beta^2\lambda_s - 16\alpha^2\gamma\lambda_s)/(\beta + 4\alpha\lambda_s)$, where λ_s is λ_r (if $\text{discr3} < 0$) or any of the roots $\lambda_{\text{trig}1,2,3}$ (if $\text{discr3} > 0$). The solutions of the quartic equation are: $x_{1,2} = \{-\beta - \eta \pm 2^{1/2}[\rho + \eta(\beta + 4\alpha\lambda_s)]^{1/2}\}/(4\alpha)$ and $x_{3,4} = \{-\beta + \eta \pm 2^{1/2}[\rho - \eta(\beta + 4\alpha\lambda_s)]^{1/2}\}/(4\alpha)$.

These formulae can be computed (in Excel) in a quite accessible way.

6 Conclusion

The present study sustains the concept of (non mechanical) covalent constitutional switches based on imine/amine exchanges (transiminations), where, in the presence of a (di) aldehyde, the use of an aromatic amine as first amine (to produce the first (bis-)imine) and of an aliphatic amine as second amine (to produce the second (bis-)imine), makes possible the modulation through alternate additions of acid and base, in the same "pot". One can also start with an aliphatic amine in the presence of a (di)aldehyde (or with the corresponding (bis-)imine) and go further with the aromatic imine and acid, then with base.

The carbonyl compound that generates the imines is, for the (bis-)imine/amine exchanges in solution, a pyridine-derived (di)aldehyde, which has a good reactivity towards imines. The main aromatic amines used here are aniline-based ones, while the aliphatic ones are primary alkylamines. Trifluoroacetic acid (TFA) and triethylamine (TEA) were used as pH-triggers, the equilibration after addition of acid being particularly fast. The calculated amounts of reagents should sometimes be slightly increased, in order to reach optimal yields. No metal ions are needed to perform the exchanges.

For most dialdehydes investigated here, a general trend seems to be that the ratio between the constant of formation of aldehyde-imine from dialdehyde and amine, and the constant of the subsequent formation of the bis-imine from aldehyde-imine and amine, lies, when the amine is an aliphatic one, between 8 and 13, with an average of 10.5.

For the same kind of substituents, similarly disposed, pyridine-derived aldehydes reacted, with identical amines, generally faster than the corresponding aldehydes derived from benzene.

(Bis-)imines can undergo exchanges with (di)aldehydes as well, and several examples of this kind are reported herein.

In a green chemistry approach, both (bis-)imine/amine and (bis-, tris-)imine/(di)aldehyde exchanges can be implemented under solvent-free conditions. IR spectroscopy was used as an analytical tool for such reactions without solvents.

Successive transiminations can not only be performed in a switch-like, back and forth manner between two (bis-)imines, and triggered by pH changes ($\text{Im1} \rightarrow \text{Im2} \rightarrow \text{Im1} \rightarrow \text{Im2} \rightarrow \text{Im1} \dots$), but also from an imine to a second one, then to a third and, finally, to a fourth one, in just one direction ($\text{Im1} \rightarrow \text{Im2} \rightarrow \text{Im3} \rightarrow \text{Im4}$), in a multistep process (the modulation through pH changes being not compulsory). In this last case, the transimination can be associated to a change of the number imine groups per imine-containing molecule, namely, in the example reported here (vide supra, Section 4.3), from 1 to 3, then to 2 and, finally, again to 1. This sequence of three transiminations is based on imine/aldehyde exchanges and was done without solvent.

A solvent-free sequence based on imine/amine exchanges is also reported here: a second imine is obtained from a first one through transimination, and a third one, from the second imine. Upon

addition of acid is regenerated the second imine, while subsequent addition of base produces the third imine.

Ordered sets of amines (based on a qualitative estimation of their relative rate of reaction with aldehydes) and aldehydes (based on the formation constants of their imines) were established.

Mathematical models applied to calculate the composition at equilibrium on systems based in a dialdehyde and two competing amines, the excess of amines or the distribution of species as a function of the pH or of the amount of water, lead to systems of polynomial equations, for which analytical or numerical solutions were proposed. Under particular conditions (e.g. excess of amines, strong formation constants), where dialdehyde and aldehyde-imines can practically be seen as consumed, the mathematical treatment can be simplified.

In perspective, such switches could be introduced in more complex structures. The preliminary work on (di)aldehyde/(bis-)imine exchanges, as well as that on mathematical models will be continued. Amongst the perspectives of interest are also a comparison, at equilibrium, between the solvent-free exchanges and those in various solvents, a deep kinetic study of imine/aldehyde exchanges, and the identification of catalysts for such exchanges.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#), further inquiries can be directed to the corresponding author.

Author contributions

JR: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review and editing. A-MS: Conceptualization, Funding acquisition, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fchem.2025.1241625/full#supplementary-material>

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