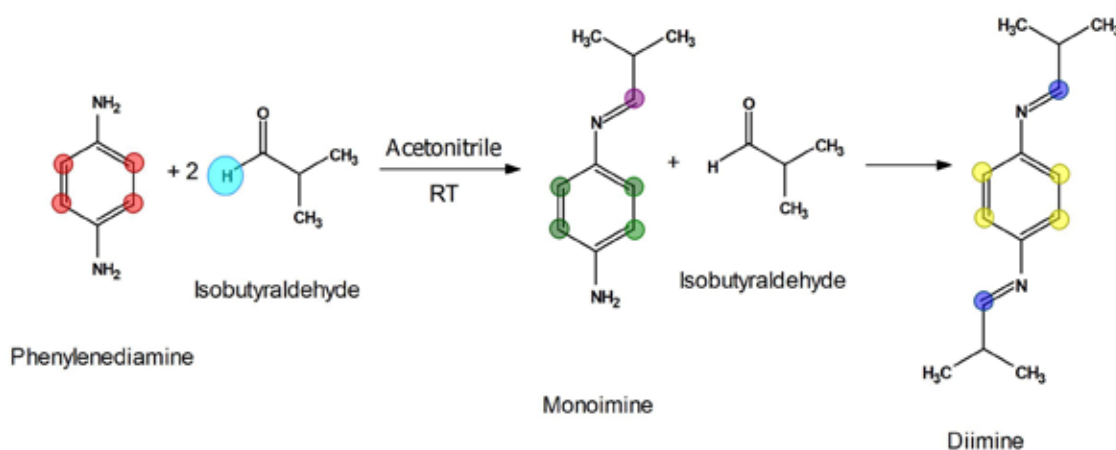# Online monitoring of the formation of a diimine

Fig. 1: Formation of diimine by the reaction between phenylenediamine and isobutyraldehyde in acetonitrile.

Imines, also named Schiff's bases, are easy to synthesize and allow the use of a large variety of starting materials (i.e. amine and aldehyde) for the condensation reaction. Therefore, these compounds are very popular in different areas. In coordination chemistry, Schiff's bases are used as ligands to obtain metal complexes, like the Salen ligand or the ligand of the Jacobsen´s catalyst [1]. In the dyes and pigments area [2], metal complex dyes of nickel with Schiff's bases are used [3]. On the other hand, porphyrin-Schiff's base ligand compounds have photoluminescence and/or electrochemical activity. [4] In pharmacy, numerous Schiff's bases are potential bioactive cores, that can have useful biological activities. [5] In biochemistry, Schiff's bases are commonly used as enzymatic intermediates. Therefore, online monitoring of this reaction is important to understand the mechanism and the formation of intermediates. In this note, the application of benchtop NMR to study this kind of reaction is demonstrated taking as an example the reaction between phenylenediame and isobutyraldehyde in acetonitrile to form the diimine product (see Fig. 1). The results reported in this note are in good agreement with data collected on a 400 MHz spectrometer previously reported in reference [6].

Experimental setup

The reaction was carried out in a round bottom flask, where 256 mg of phenylenediamine (2.35 mmol) were dissolved in anhydrous acetonitrile (22.5 mL). After phenylenediamine was completely dissolved, 0.42 ml of isobutyraldehyde (4.6 mmol) was added while the reaction mixture was stirred. The reaction kinetic was monitored by ^{1}H NMR spectroscopy using a Spinsolve Ultra 60 MHz benchtop NMR spectrometer equipped with a reaction monitoring kit 2 (RMK2). This setup makes it possible to measure in continuous or stop flow mode. For this experiment the stop flow mode was chosen. To pump the mixture from the reactor to the sensitive volume in the flow cell, the flow rate was set to 9 mL/min during a pumping time of 10 seconds. During the first 40 minutes, the reaction mixture was pumped every 2 minutes and after that the pumping interval was increased to 10 minutes. During the time the pump was off, 1D 1H spectra were recorded accumulating 4 scans with a recycling delay of 15 seconds.
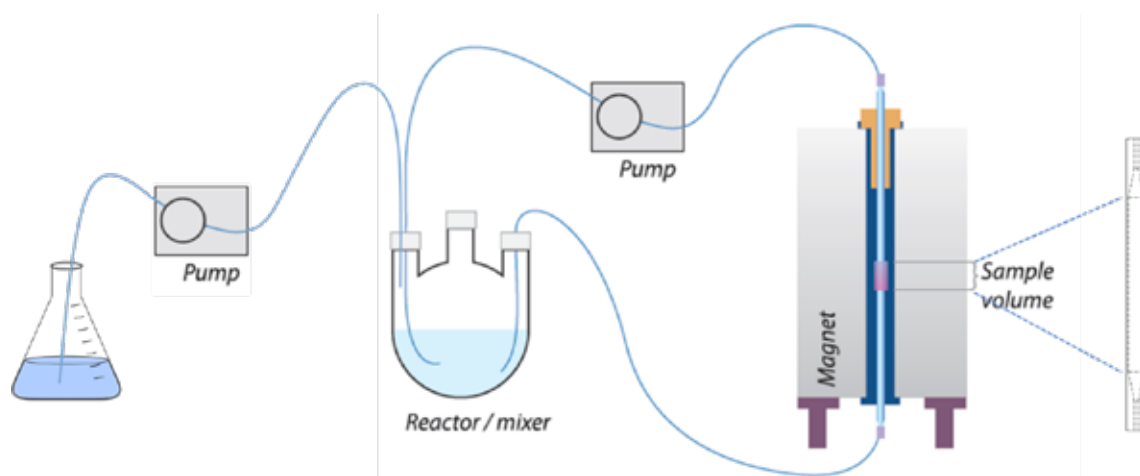

Fig. 2: Schematic representation of the experimental setup (RM kit 2) for online reaction monitoring.

Results

After the reaction was completed, the 1H 1D spectra of the starting materials were compared with the first and last point of the reaction. Figure 3 shows a stack plot where the characteristic peaks of each species (Figure 1) can be easily identified. The spectrum of isobutyraldehyde (Fig. 3a) possesses characteristic peaks around 9.6 ppm (aldehyde), around 2.3 ppm (CH) and a doublet at about 1.1 ppm which corresponds to the two methyl groups. Figure 3b shows the spectrum of diamine, where the singlet corresponding to the four aromatic protons can be seen at a chemical shift of 6.5 ppm, and the amine proton generates a broad peak at 3.5 ppm. In the spectrum collected at the beginning of the reaction (Fig. 3c), we can clearly see the appearance of the characteristic monoimine peaks at 7.8 ppm (imine), 6.7 ppm (aromatic), 2.3 ppm (CH), and 1.1 ppm (methyl). Finally, Figure 3d shows the spectrum at the end of the reaction, where the signals of diimine can be identified. In comparison with the signals of monoimine, the imine and methyl signals appear slightly shifted in the spectrum and can be differentiated (see also Fig. 5). The aromatic protons generate a singlet like diamine, but in this case at 7.1 ppm (see Fig. 4).

As it can be seen in the spectra, the evolution of the reaction can actually be monitored by integrating any of these different chemical groups in the spectrum. The aromatic region, however, is the one showing the least overlap between signals. In contrast, the characteristic peaks of the methyl groups show partial overlapping.

In this application note we show the results obtained from two regions in the spectrum, which make it possible to cross-check the mass balance of the different species. Region 1 (see Fig. 3) is simply the aromatic region and Region 2 shows the disappearance of the aldehyde proton (9.6 ppm) which is only present in the starting chemicals and during the reaction becomes part of the mono- and diimine.
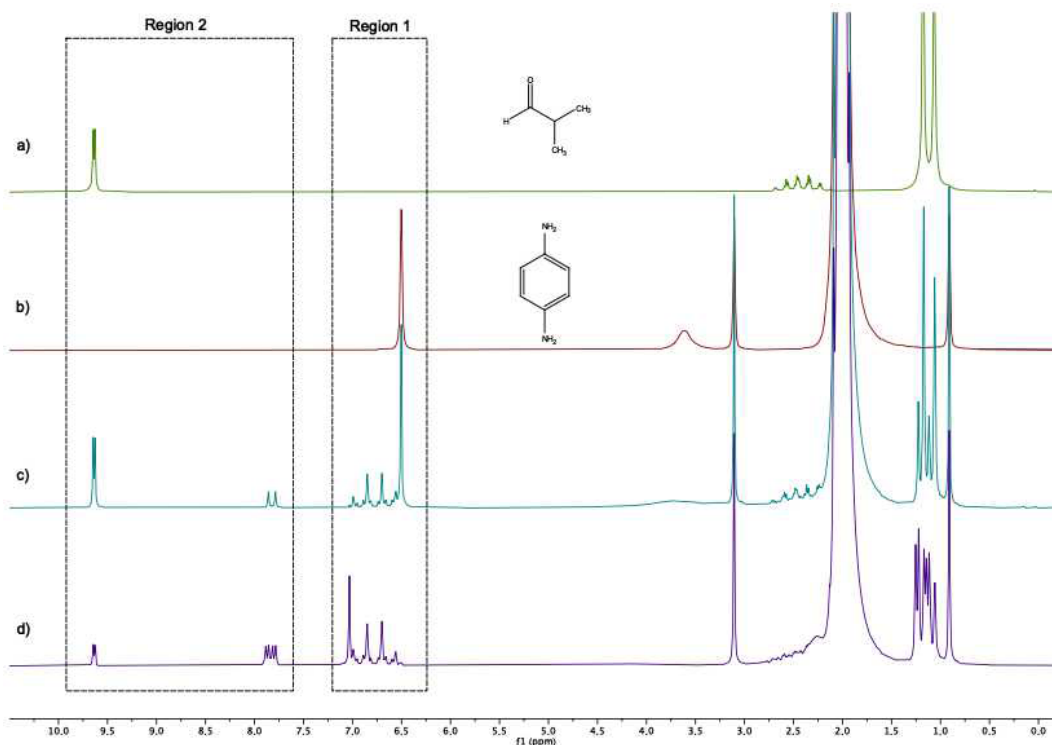
Fig. 3: 1D 1H spectra of: a) neat isobutyraldehyde; b) phenylenediamine (Down; C = 92 mM - 4 mg/400 µL - 1.26 wt%); c) after 20 min of reaction; d) after 15 hours (overnight).

Figure 4 shows a zoom of the spectra collected during the reaction where the aromatic region can be observed (Region 1 in Fig. 3). By integrating the signals corresponding to the different products we can see that the concentration of phenylenediamine (6.54 ppm) decreases with time, while the concentrations of mono- and diimine (at 6.80 ppm and 7.06, respectively) increase, showing the typical behaviour of a two step reaction. After approximatively 2 hours, the concentration of monoimine starts to decrease as phenylenediamine is almost completely consumed and the monoimine gets converted into diimine. After a few hours, it can be observed that almost all the starting materials disappeared (96.1%), but still the concentration of monoimine remains relatively high. This is the behaviour expected in a situation where the kinetic constant of the first step is much larger than the kinetic constant of the second step.
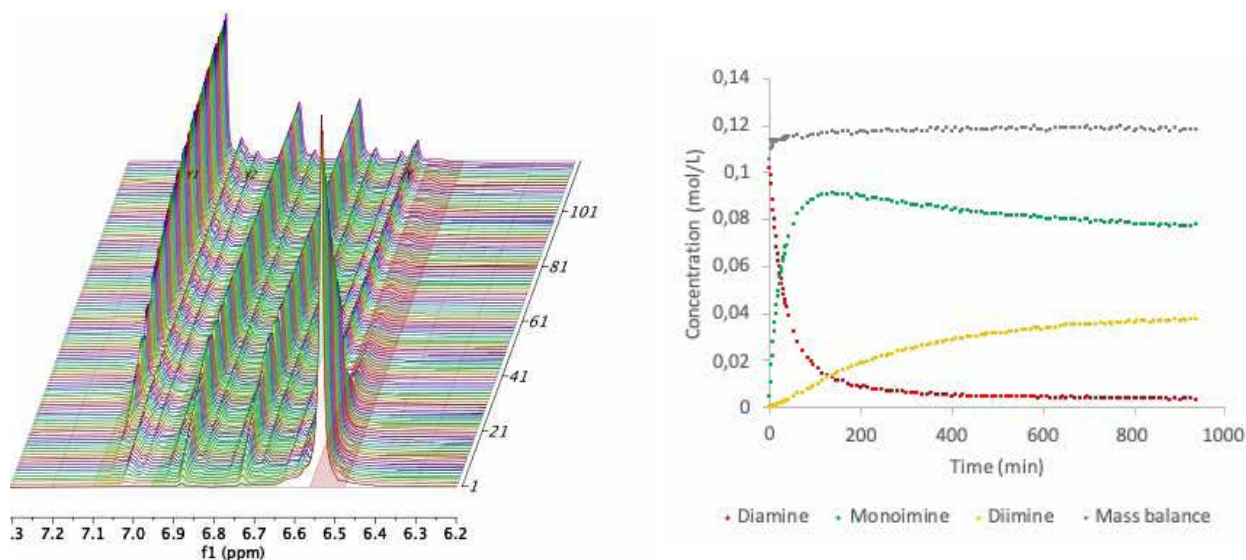

Fig. 4: Left: Zoom of the aromatic region showing the decrease of phenylene diamine (red) and the growth of mono- and diimine (green and yellow), respectively. Right: Integrals of the different signals plotted as a function of time converted to concentration of phenylene diamine (red), monoimine (green) and diimine (yellow).

Figure 5 (left) shows a zoom where the signal of the aldehyde (9.68 ppm) and the imine protons of mono- (7.85 ppm) and diimine (7.9 ppm) can be observed. The aldehyde signal corresponds to one of the starting materials and the imine signals account for the conversion of this molecule into mono- and di- imine that are the intermediate and final products, respectively. In the imine region we can clearly see the doublet corresponding to monoimine appearing first and the second doublet corresponding to diimine getting visible later. Figure 5 (right) shows the integral of the different signals in the spectra converted into concentration to allow one to directly quantify the concentration of each component. To quantify mono- and diimine we integrated the peaks of each doublet in an interleaved way and added them together. The time dependence of each component agrees with the one obtained from Region 1 showed in Fig. 4, and the mass balance stays nicely constant as expected. The speed of each reaction step is clearly different, and we can observe how monoimine is generated at a faster rate compared to diimine. For example, from the spectra collected at the end of the reaction we can conclude that 68% of monoimine and 32% of diimine have been formed after 15 hours of reaction.
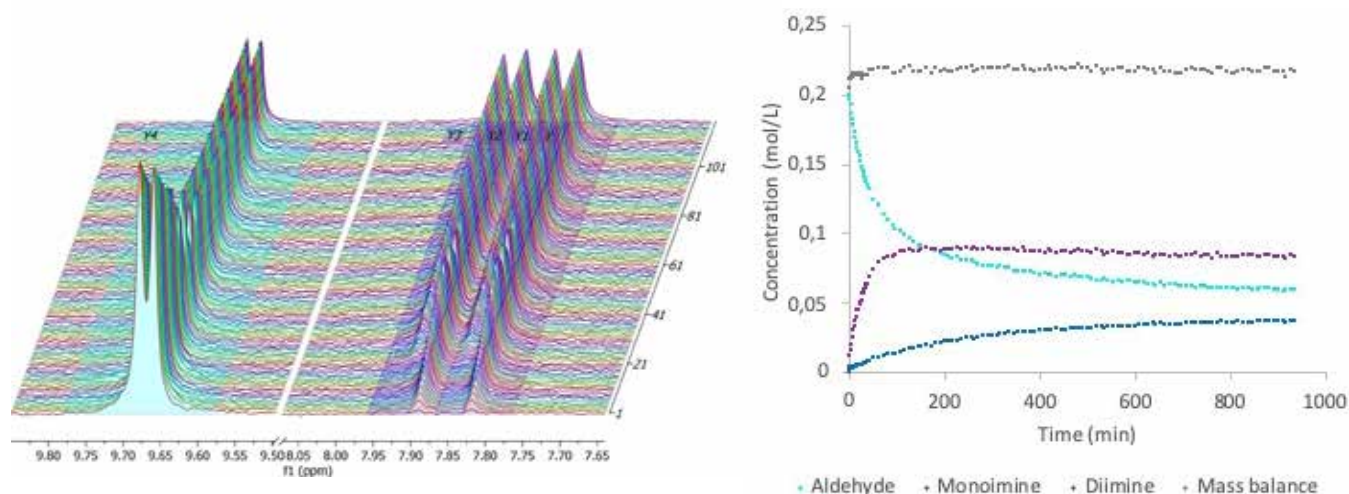

Fig. 5: Left: Zoom of the spectra showing the signals corresponding to the aldehyde and imine groups. While the doublet of the aldehyde is well separated from the rest of the signals in the spectrum, the doublets corresponding to the imine protons of mono- and diimine are interleaved and show some degree of overlapping. Right: Integrals of the different peaks showing the decrease in concentration of aldehyde (cyan) and the increase in concentration of mono- (violet) and diimine (blue). The mass balance in grey remains constant, as expected.

[1] Chem. Soc. Rev., 2004,33, 410-421
[2] International Journal of Organic Chemistry, 2014, 4, 7-15
[3] https://doi.org/10.1016/0143-7208(94)85012-7
[4] dyes-and-pigments; vol 130; 2016; 37-53
[5] Journal of Catalysts; Volume 2013 (2013), Article ID 893512, http://dx.doi.org/10.1155/2013/893512
[6] Anal. Chem., 2014, 86 (24), pp 12008–12013 - DOI: 10.1021/ac502300q

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