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On the formation of imines in water—a comparison

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ABSTRACT

The reaction of aniline with aryl aldehydes in water has been investigated in the past, but contradictory results have been published. While only small amounts of imines **3** were detected by NMR analysis, isolation afforded high imine yields. A reinvestigation of the reaction of benzaldehyde (**1a**) and salicylaldehyde (**1b**) with aniline (**2**) revealed two important factors which explain the putative contradiction: (i) NMR only reveals the fraction of products which is soluble in water, and (ii) imines **3** form during or after workup.

1. Introduction

The reaction of primary amines with carbonyl compounds to give imines—also called Schiff bases or azomethines—is a reaction which is well known.[1] In nature it serves to interconvert amino acids and α-ketoacids into one another with the help of vitamin B6 (pyridoxamine–pyridoxal as coenzyme in transaminases[2]), but it has also been widely used in organic chemistry for numerous purposes since the 1800s. Due to its reversibility, the formation of imines has gained increasing interest in recent years as it is one of the reactions widely used in dynamic combinatorial chemistry.[3] When an imine is formed from an aldehyde and a primary amine, one molecule of water is liberated per molecule of imine. Consequently, the formation of imines is facilitated when water is removed from the reaction mixture. In many experimental procedures, water-removing techniques or reagents are employed.[4] The synthetic chemist therefore hesitates to have water present when he tries to synthesize an imine, although water would be the environmentally most benign solvent.[5]

2. Results and discussion

In dynamic combinatorial chemistry (DCC), water which is produced by an imine formation will stay in the reaction mixture, and the question arises to which extent water can be tolerated. Literature studies reveal surprising answers. While we discovered that in a specific dynamic combinatorial library, water can even be used as the solvent,[6] other researchers have found less promising results. A recent study of Lehn and co-workers[7] shows that only small amounts of imines can be detected in water. Among many other substrates, they investigated the reaction of benzaldehyde (**1a**) or salicylaldehyde (**1b**) with aniline (**2**) (Fig. 1).

In contrast to these results, Tashiro and co-workers[8] reported excellent yields of imines **3** when they reacted aldehyde **1a** or **1b** with aniline (**2**) in water—a remarkable putative contradiction. Due to the high relevance for DCC, we reproduced these experiments in our laboratory to understand this discrepancy (see Table 1).

First, the NMR experiment of Lehn's group (**A1**)[7] was repeated in our laboratory. The literature experiment was carried out using a molar ratio of aldehyde **1a** to amine **2** of 1:3. A 16.5 mM solution of aldehyde **1a** in D_2O at pD 7.5 gave 5.4% of imine **3a**. This yield had been determined by simply integrating the signals for aldehyde **1a** and imine **3a** in D_2O.

When repeating this experiment, we did not use a buffer to allow for a comparison to the Tashiro experiments.[8] With a molar

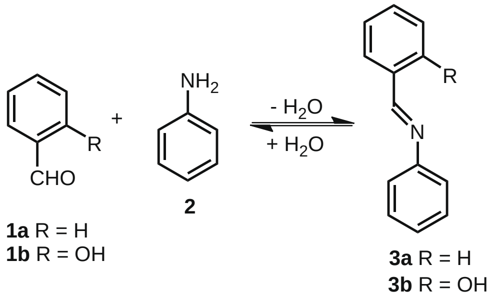

Figure 1. The reaction of aldehydes **1** with an amine such as aniline (**2**) to give imines **3** is a reversible process.

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Table 1
Reaction conditions, analysis conditions, and product ratios for the imine formation between aldehydes **1a**–**b** and aniline (**2**)

Experiment	Aldehyde	Reaction condition	Analysis	Ratio **1**:**3**
A1	**1a**	D_2O	NMR	96:4
A2	**1a**	H_2O	NMR after workup and vacuum	5:95
A3	**1a**	No solvent, vacuum	NMR	5:95
B1	**1b**	D_2O	NMR	88:12
B2	**1b**	H_2O	NMR after workup and vacuum	3:97[a]
B3	**1b**	No solvent, vacuum	NMR	3:97[b]

[a] Yield after recrystallization: 85%.
[b] Yield after recrystallization: 83%.

ratio of aldehyde **1a** to amine **2** of 1:1 at 10 mM for each starting material in D_2O, it became obvious that both starting materials which are liquids were not soluble in deuterated water, and the resulting mixture was non-homogeneous. Also pure aldehyde **1a** and pure amine **2** form two layers with water, showing that the solubility of these compounds is low in water. Neither heating of the NMR tube nor application of ultrasound resulted in the formation of a single layer. Either the solution remained biphasic or it became emulsion like. When a ^{1}H NMR was recorded, it resulted in the same ratio of imine **3a** to aldehyde **1a** as reported by Lehn.[7]

It must be noted that when analyzing the water layer alone by recording its NMR spectrum, only a small amount of the starting material was analyzed. The major part of the material is in the other layer and the NMR does not analyze it. The experiment was repeated with 3 equiv of aniline (**2**) without any improvement of the solubility or the percentage of imine **3a** dissolved in water. When calcium chloride ($CaCl_2$) or hydrochloric acid (HCl) was added to the emulsion, everything dissolved completely and the solution finally was clear. However the Lewis acid and the Brønsted acid simply solubilized aldehyde **1a** and amine **2** but their addition had no effect on the formation of imine **3a**, whose concentration remained low. No imine could be detected when HCl was used, and when $CaCl_2$ was used the amount of imine **3a** was less than 5%.

In contrast, Tashiro and co-workers were able to isolate imines **3** in good yields. The authors used a 0.6 M solution of aldehyde **1a** and amine **2**. The starting materials **1a** and **2** were stirred in water vigorously for 3 h. Then, the products were extracted with dichloromethane, dried, and analyzed by NMR. The yield of imine **3a** was found to be 97%.[8]

When this reaction was repeated (**A2**), again the low solubility of the starting materials in water could be observed. Vigorous stirring only provoked the reaction mixture to become emulsion like. Analogous to the reference, the reaction was stopped after 3 h, and the reaction mixture was extracted with dichloromethane, dried over $MgSO_4$, and the solvent was evaporated in vacuo. In order to record the NMR and to remove the remaining solvent traces, the vessel containing the oily product was evacuated using an oil pump. A few seconds after the vacuum was established, the oily product solidified and heat was developed. This was the first clue that the imine-forming reaction takes place when the two starting components are in concentrated contact with each other after the workup. Water does not play any role in the reaction as the starting aldehyde **1a** and amine **2** as well as the final product are only slightly soluble in water. Then after the workup, when the two reagents are concentrated, they react. The oil pump vacuum simply helps in the formation of imine **3a** by removing the water formed in the imine condensation.

To prove the latter hypothesis, aldehyde **1a** and amine **2** were mixed without any solvent in experiment **A3**.[9] After a few seconds, a solid formed and the reaction was exothermic. The crude product was kept in vacuo for 10 min. Subsequent NMR analysis afforded the same yield as experiment **A2** (95%).

A second imine-forming experiment has also been investigated in both references in water:[7,8] the reaction between salicylaldehyde (**1b**) and aniline (**2**). Also in this case, the yields reported for the formation of imine **3b** in water are completely different. In the NMR experiment of Lehn et al.,[7] the reported yield of imine **3b** was only 14% while in the experiment of Tashiro et al.,[8] the same imine **3b** was obtained in 87% yield. Suspecting the same effects during the reaction and workup as in experiments **A1**–**A3** [**1a** with aniline (**2**)], this reaction was also carried out in the three different ways as described above.

NMR experiment **B1** was carried out under the same conditions as experiment **A1**, and it did not show drastic changes in the ratio of final imine **3b** to aldehyde **1b** compared to the ratio reported by Lehn.[7] Although salicylaldehyde (**1b**) is a little bit more soluble in water than benzaldehyde (**1a**), the solution once more was biphasic, and, as in experiment **A1**, neither heating nor sonication improved the solubility of the starting materials. Experiment **B2** was repeated in the same way as experiment **A2** was carried out. In this particular case, after workup, when the crude oil was subjected to vacuum, only a small amount of solid appeared. But after 12 h in vacuo, the product was almost completely solid. Recrystallization from *n*-hexane gave pure imine **3b** as yellow needles in 85% yield.

In the last experiment (**B3**),[10] salicylaldehyde (**1b**) and aniline (**2**) were simply mixed together in a ratio of 1:1, and then the reaction was evacuated for 12 h. The result was the same as in experiment **B2**. After recrystallization from *n*-hexane, 83% of the final imine **3b** was recovered. Thus this experiment also shows that water as a solvent does not play any role during the formation of the imine. The liquid aldehyde and the liquid amine react with each other to give the respective imine **3b** in the absence of solvent.

3. Conclusion

The scope of this work was to elucidate the contradictory results presented in two different and recent papers. Both papers contain reproducible experiments and their goal is not focused on the synthesis of a single imine but on (a) a general imine synthesis in the presence of water[8] and (b) the relationship between the structure and stability of imine formation in aqueous solution.[7] However, when the same starting materials were used (**1a**, **1b**, and **2**), drastically varying yields were found for the respective imines **3a** and **3b**.

The putative contradiction in the two sets of experiments lies in the fact that the reaction only presumably takes place in water and that the 'water results' are compared. But on the contrary, the reaction takes place best in the absence of solvent.

The solubilities of the starting materials, and those of the final products, play an extremely important role in the dynamical combinatorial chemistry. Even if the starting building blocks are well soluble in water but the final product is not, this can drive a reaction to the latter product, into a thermodynamic trap. In order to have a good and reproducible distribution of products in a library, all the components should be soluble and, by this, be free to interact with one another.

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9. *Experiment* **A3**: 1.0 mL (10 mmol) of benzaldehyde (**1a**) and 910 μL (10 mmol) of aniline (**2**) were mixed in a 5 mL flask. The crude oil was left under vacuum (4×10^{-4} mbar) for 10 min, until all the oil became solid. Then, 10 mg of the crude product[11] was analyzed by ^{1}H NMR. Ratio imine **3a**/aldehyde **1a**: 95:5.
10. *Experiment* **B3**: 966 μL (10.0 mmol) of salicylaldehyde (**1b**) and 911 μL (10.0 mmol) of aniline (**2**) were mixed, and the reaction mixture was left under vacuum (4×10^{-4} mbar) for 12 h. Then, 10 mg of the crude product was analyzed by ^{1}H NMR. Ratio imine **3b**/aldehyde **1b**: 97:3. Recrystallization from *n*-hexane gave the final product[11] in 83% yield.
11. *N-Benzylideneaniline* (**3a**): SDBS No.: 2145, CAS No.: 538.51.2; *o*-(phenyliminomethyl)phenol (**3b**): SDBS No.: 7178, CAS No.: 779-84-0.