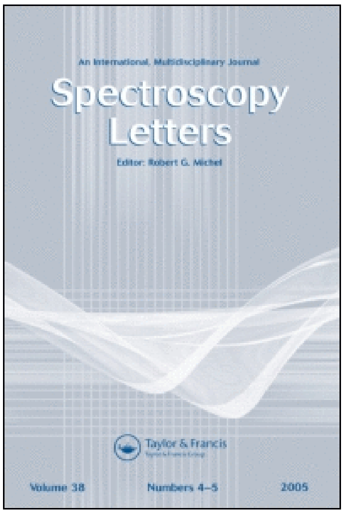

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Monitoring the pH-Dependent Oximation of Methyl Ethyl Ketone and Benzaldehyde by *in situ* Fourier Transform IR Spectroscopy in a Heterogeneous Liquid-Liquid Two-Phase System

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Monitoring the pH-Dependent Oximation of Methyl Ethyl Ketone and Benzaldehyde by *in situ* Fourier Transform IR Spectroscopy in a Heterogeneous Liquid–Liquid Two-Phase System

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ABSTRACT *In situ* Fourier transform IR spectroscopy was a useful tool in monitoring the pH-dependent and two-step oximation of methyl ethyl ketone and benzaldehyde in a liquid–liquid two-phase system, one phase of which was water. Carrying out the oximations at pH 8, the oximation was complete within 45 min and the corresponding carbonyl compound–hydroxylamine adduct (**2**) could be detected as an intermediate, but at pH 10, the corresponding oxime (**3**) was formed faster, practically without the appearance of the intermediate. At pH ~ 2.5 using methyl ethyl ketone, the protonated form of the corresponding oxime (**3'a**) developed gradually without the transient appearance of the intermediate (**2**). pH dependence of the **3a** → **3'a** and **3'a** → **3a** interconversions were studied in separate experiments.

KEYWORDS Heterogeneous phase reaction, *in situ* Fourier transform IR, intermediate, monitoring, oximation, pH dependence

INTRODUCTION

In situ Fourier transform IR spectroscopy is a suitable method for monitoring different organic chemical reactions.[1–6] The time-dependent IR spectra reveal the concentration profile of the components, which allows formal kinetic measurements, determination of equilibrium constants, and optimization of the reaction studied. This latter is important from the point of view of green chemistry. It is also possible to identify intermediates in the mixture and hence evaluate reaction mechanisms. *In situ* Fourier transform IR spectroscopy is a suitable tool to study organic chemical reactions over a wide range of temperatures (–80°C to 250°C), and even under pressure. The spectrometer is supplied with an attenuated total reflection (ATR) probe that is in contact with the reaction mixture. *In situ* Fourier transform IR currently

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is becoming a routine method in the fine chemical, pharmaceutical, and even plastics industries. It is a question, however, if heterogeneous phase reactions can also be monitored by *in situ* Fourier transform IR spectroscopy. The signal–noise ratio may depend on the given situation. In this article, we study the oximation of selected carbonyl compounds by an *in situ* Fourier transform IR spectrometer in aqueous–organic two-phase system under different conditions. In the current study, our primary purpose was to investigate if heterogeneous oximations can be monitored by the *in situ* Fourier transform IR and under what conditions the intermediates can be seen. The calculation of rate constants was not the goal in the given stage. In earlier cases, the oximation of oxo-compounds was followed by spectrophotometry using a cuvette, which is not so practical and is less informative as only a single reaction component can be monitored at the same time.[7] Although the oximation of acetone is a basic example in organic chemistry textbooks, only a limited number of data can be found in the literature on the course of the reaction under discussion.[7–10] Cocivera et al. made considerable progress by studying the oximation of acetone by flow ^{1}H nuclear magnetic resonance (NMR) spectroscopy.[11,12] Rate constants for the addition and dehydration steps were determined, and the appearance of the aminocarbinol intermediate was investigated as a function of the pH value. The oximation of acetoaldehyde was also monitored by flow NMR spectroscopy.[13] It is worth mentioning that the oximation of the keto carbonyl of ethyl acetoacetate is followed by a spontaneous cyclization to 3-methylisoxazole-5-one.[14] In the analogous reaction of acetylacetone, no oxime intermediate could, however, be pointed out by flow NMR spectroscopy.[15,16] In another study, secondary isotope effects were used in the evaluation of the mechanism for the formation of imines.[17] We have contributed to this field recently and studied the pH dependence of the two-step oximation of acetone by *in situ* Fourier transform IR in aqueous solutions. It was found that by carrying out the oximation at 5°C, the intermediate carbonyl adduct could be observed only at pH 8.5. pH adjustment affected strongly the reaction times; at pH 10, 8.5, and ~2.5, completion of the oximation required <1, 60, and 30 min, respectively. At low pH, the oxime was formed in its protonated form. The pH-dependent interconversions were also explored.[18] Our findings were in accord with earlier experiences that around pH 7, the dehydration of the acetone–hydroxylamine adduct is the rate-determining step, where as at low pH, the formation of the carbinolamine itself is the slower step.[7]

MATERIALS AND METHODS

The oxime of ethyl methyl ketone **3a** was prepared on the basis of analogies.[12] According to this, 6.0 g (0.150 mol) sodium hydroxide in 30 mL water was added to 10.0 g (0.144 mol) hydroxylamine hydrochloride in 30 mL water. Then, 12.9 mL (0.144 mol) ethyl methyl ketone was added at 26°C, and the mixture was stirred for 5 h. After completion of the reaction, the two phases were separated, and the organic phase was dried (Na_2SO_4) and distilled in vacuum to afford 7.5 g (60%) of the oxime (**3a**) as an oil. Boiling point (BP) 54–6°C/20 mmHg; IR (neat) (from data base) 930 (935), 976 (980), 1073 (1075), 1096 (1100), 1219 (1220), 1241 (1245), 1272 (1273), 1328 (1328), 1370 (1370), 1457 (1460), 1665 (1664), 2883 (2880), 2919 (2919), 2939 (2939), 2973 (2973) cm^{-1}.

Benzaldehyde oxime **3b** was prepared in a similar way, but hydroxylamine hydrochloride was added to a mixture of aqueous sodium hydroxide and benzaldehyde. Distillation of the organic phase led after drying to a single (presumably *syn*) isomer of the benzaldoxyme (BP: 100–102°C/11 mmHg, BP[19]: 122–124°C/12 mmHg for the *syn* oxime) in 59% yield. ^{13}C NMR ($CDCl_3$) δ 127.3 (C_3), 129.0 (C_4), 130.3 (C_4), 131.9 (C_1), 150.6 (>C = N); On standing, the product solidified. IR (neat) (from data base) 946 (950), 1027 (1020), 1073 (1075), 1123 (1098), 1177 (1180), 1212 (1210), 1289, 1319* (1320), 1451 (1445), 1498 (1495), 1583, 1602 (1590), 2987 (2970), 3030 (3040), 3064 (3080) cm^{-1} (*a shoulder).

In situ measurements were carried out using ReactIR 1000 equipment (Mettler–Toledo Autochem, Inc, Columbia, USA) working on the principle of attenuated total reflection (ATR) Fourier transform infrared spectroscopy. The DiComp (diamond) measuring head was placed in a 250-mL 4-necked flask equipped with a dropping funnel, a condenser, a thermometer, and a magnetic stirrer. The temperature was maintained by using an appropriately adjusted water bath.

Experiment 1: Oximation of Ethyl Methyl Ketone at pH 8

To 10.0 g (0.144 mol) hydroxylamine hydrochloride in 20 mL water was slowly added 5.8 g (0.144 mol) sodium hydroxide in 20 mL water. A pH of 8 was obtained with some drops of 0.1 M aqueous sodium hydroxide. Adjusting the temperature to 5°C, 12.9 mL (0.144 mol) ethyl methyl ketone was added over a 4-min period, and the two-phase mixture was stirred further (Fig. 1).

Experiment 2: Oximation of Ethyl Methyl Ketone at pH 10

The reaction was carried out as above, but only on one-third scale, and 2.1 g (0.053 mol) sodium hydroxide was used (Fig. 2).

Experiment 3: Oximation of Ethyl Methyl Ketone at pH ~ 2.5

To 10.0 g (0.144 mol) hydroxylamine hydrochloride in 40 mL water was added 12.9 mL (0.144 mol) ethyl methyl ketone at 5°C within 4 min. In the meantime, the pH was changed from 3.5 to 1.5 (Fig. 3). At the end of reaction, the mixture became almost homogeneous.

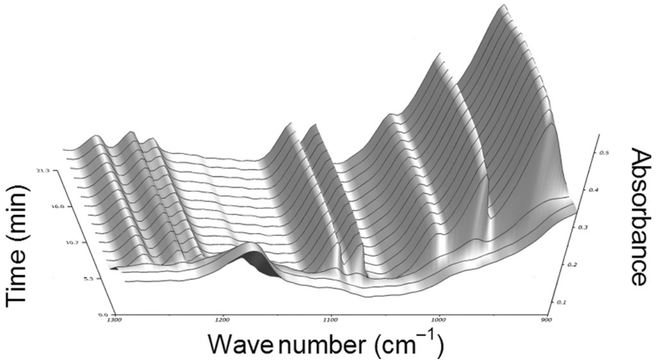


FIGURE 2 A segment of the time-dependent IR spectrum for the formation of 3a from 1a at pH 10 and 5°C.

Experiment 4: Oximation of Ethyl Methyl Ketone at pH 8 Followed by Change in the pH

An additional variation was based on Experiment 1 by changing the pH according to an 8 → 2.5 → 8

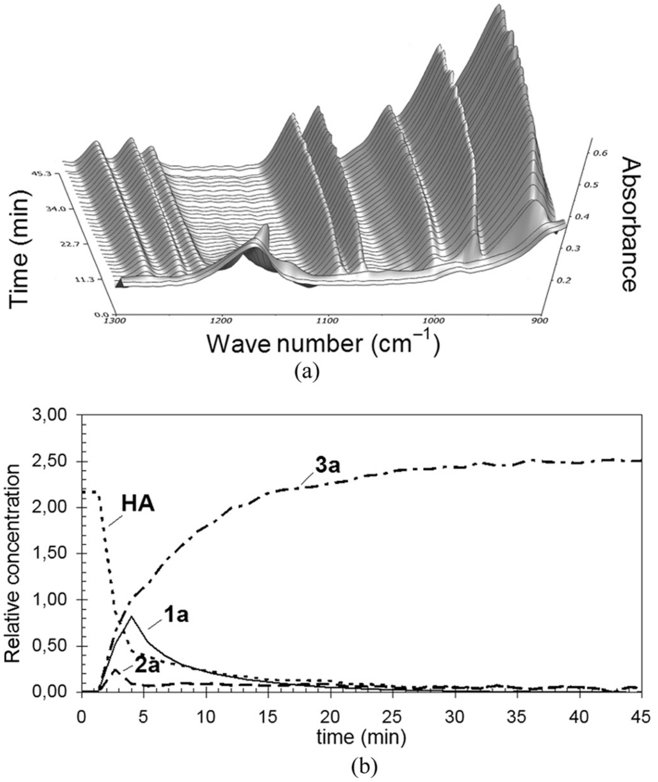


FIGURE 1 A segment of the time-dependent IR spectrum (a) and the concentration profile (b) for the 1a → 2a → 3a transformation at pH 8 and 5°C.

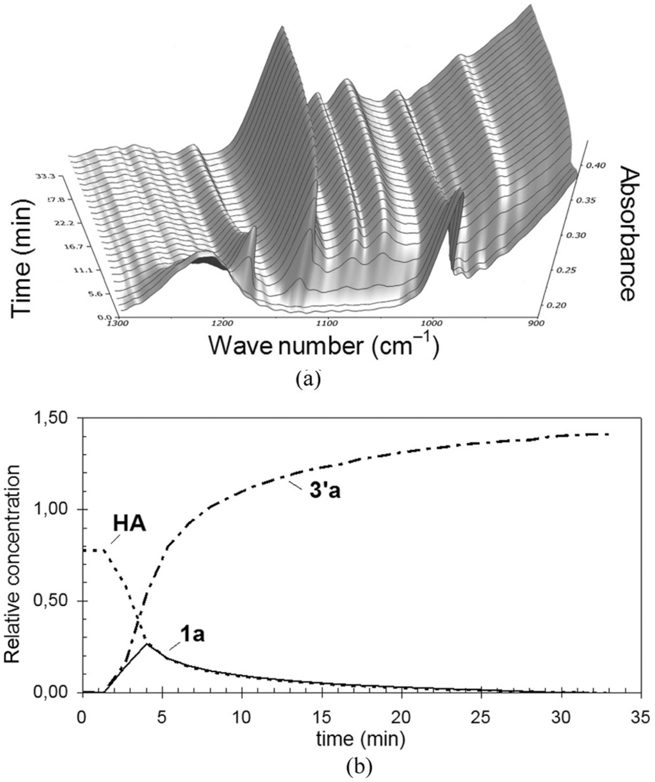


FIGURE 3 A segment of the time-dependent IR spectrum (a) and the concentration profile (b) for the formation of 3’a from 1a at pH 2.5 and 5°C.

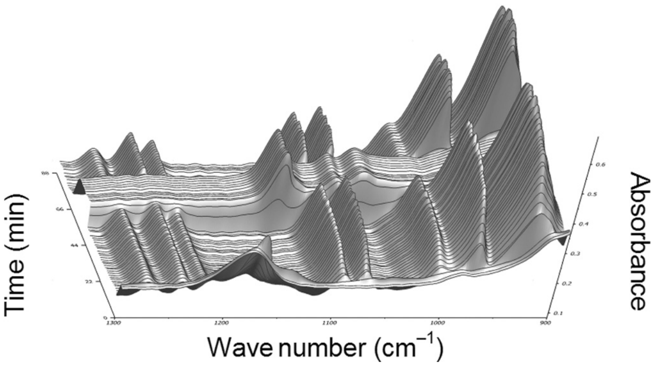


FIGURE 4 A segment of the time-dependent IR spectrum for the 1a → 2a → 3a → 3'a and 3'a → 3a transformations achieved by the change of pH.

sequence by adding 12.4 g 37% hydrochloric acid after 47 min and 5.8 g sodium hydroxide in 10 mL water after 65 min, respectively (Fig. 4).

Experiment 5: Oximation of Benzaldehyde at pH 8

To 10.0 g (0.144 mol) hydroxylamine hydrochloride in 30 mL water was slowly added 5.9 g (0.148 mol) sodium hydroxide in 30 mL water. Adjusting the pH to 8 and the temperature to 20°C, 14.6 mL (0.144 mol) benzaldehyde was added over a 1-min period, and the two-phase mixture was stirred further (Fig. 5).

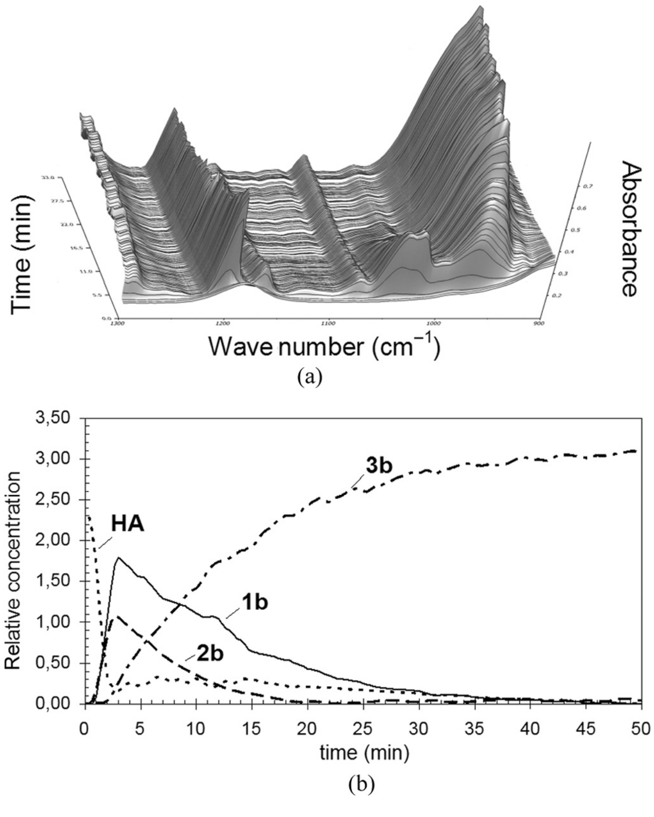


FIGURE 5 A segment of the time-dependent IR spectrum (a) and the concentration profile (b) for the 1b → 2b → 3b transformation at pH 8 and 20°C.

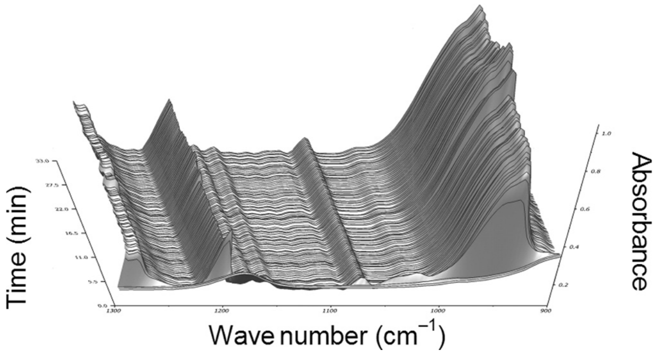


FIGURE 6 A segment of the time-dependent IR spectrum for the formation of 3b from 1b at pH 10 and 20°C.

Experiment 6: Oximation of Benzaldehyde at pH 10

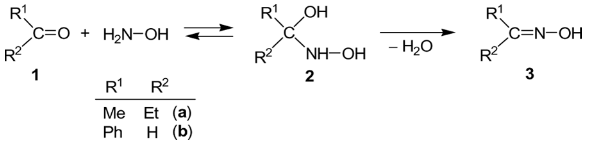
The reaction was carried out as above, but 6.3 g (0.157 mol) sodium hydroxide was used (Fig. 6).

RESULTS AND DISCUSSION

The oximation of ethyl methyl ketone (**1a**) and of benzaldehyde (**1b**) were chosen as the model reactions. The reaction sequence involving the adduct of the carbonyl compound and hydroxylamine (**2**) as an intermediate is shown in Scheme 1.

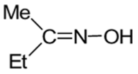
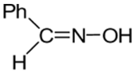
Before the *in situ* Fourier transform measurements, the IR spectra of the reaction components and the products (**3a** and **3b**) prepared in separate experiments were studied. The data are summarized in Table 1.

The range of 900–1300 cm^{-1} seemed to be the most appropriate for monitoring the oximation of ethyl methyl ketone and benzaldehyde. The range of 1650–1700 cm^{-1} would be informative mainly for the carbonyl group. In water solution, decrease of the relative quantity of the oxo-components **1a** and



SCHEME 1 The oximation of carbonyl compounds.

TABLE 1 **IR Absorptions of the Oxo-components (1a, 1b) and Oximes (3a, 3b) in the Range 900–1300 cm^{-1} Determined by ReactIR 1000**

Ethyl methyl ketone (**1a**)		Benzaldehyde (**1b**)		 (**3a**)		 (**3b**)	
Neat	In water mixture	Neat	In water mixture	Neat	In water mixture	Neat	In water mixture
945		924		930	923		
998	1000 (weak)	1003	1004	976	977	946	950
		1023	1023			1027	1027
1086	1089	1071	1073	1073	1073	1073	1077
		1110	1116	1096	1096	1123	1123
1171	1185	1165	1166			1177	1177
1206	1216 (shoulder)	1204	1204	1219	1220	1212	1212
		1288		1241	1243		
				1272	1270		

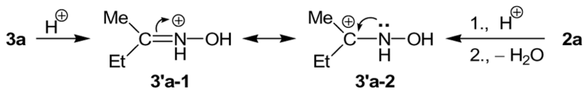
1b may be followed on the basis of the absorption at 1185 and 1166/1204 cm^{-1}, respectively. Increase of the proportion of oxime **3a** may be shown by the bands at 923, 977, 1073, 1096, 1220, 1243, and 1270 cm^{-1}, and the similar numbers for oxime **3b** are 950, 1027, 1077, 1123, 1177 and 1212 cm^{-1}. The absorptions at 923 (**3a**) and 950 (**3b**) are due to the $\nu_{N\text{–}O}$ vibration, and that at 1073 and 1077 (for **3a** and **3b**) corresponds with the $\nu_{N\text{–}O\text{–}H}$ vibration.[18] The signal at 1212 cm^{-1} for **3b** is the consequence of the $\delta_{O\text{–}H}$ vibration. On the basis of analogies, absorption bands for the oxo-compound–hydroxylamine adducts (aminocarbinols) (**2**) can be expected at around 1200 and 1070 cm^{-1} due to the $\delta_{C\text{–}O\text{–}H}$ and $\nu_{C\text{–}N}$ vibrations, respectively.[18]

In the first experiment, hydroxylamine (HA) was liberated from HA · HCl by an equivalent amount of sodium hydroxide in aqueous solution and then reacted with methyl ethyl ketone at pH 8 at 5°C. The ketone was added dropwise in 4 min. At the adjusted pH, the ethyl methyl ketone–HA adduct (**2a**) was formed as an intermediate with a maximum concentration at around 3 min. A characteristic band of adduct **2a** appeared at 1175 cm^{-1}. Species **2a** was converted fast to oxime **3a** by dehydration. Product **3a** revealed absorptions at 930, 977, 1073, and 1096 cm^{-1}. The latter two signals suppressed an absorption of the intermediate (**2b**) expected in a similar region. The reaction was complete after 40 min (Scheme 1; Fig. 1). The rate of the reaction is also effected by the transfer between the two liquid phases. This is the second case[18] where the relative concentration of all three reaction components (**1**–**3**) was simultaneously monitored.

The reaction under discussion was also carried out using some excess of sodium hydroxide at pH 10. In this case, the formation of the oxime (**3a**) was faster than that in the previous case ($t_r = 4$ vs. 40 min), and intermediate **2a** could not be detected (Fig. 2). The rate was somewhat limited by the transfer between the phases of the liquid–liquid system.

The rate dependence of the oximation observed above was in agreement with results of earlier reports,[9,10] according to which the rate of the oximation of the simplest analogue, acetone, is minimum at pH 8–9 and the reaction becomes faster at pH 10–12.

In the next experiment, HA · HCl was reacted with ethyl methyl ketone at pH 3.5 → 1.5 and at 5 °C. The aqueous solution of HA · HCl had a pH of 3.5. After adding the ketone (**1a**) to the mixture in 4 min, the pH was decreased gradually to pH 1.5 due to the liberation of hydrochloric acid formed along with the oxime. The average pH was ~2.5. Neither the intermediate (**2a**) nor the expected form of the oxime (**3a**) could be detected. Rather, a species with an 1131 cm^{-1} band appeared gradually. After 30 min, the conversion was complete. In accordance with our earlier experiences,[18] the new species formed was assigned as the protonated form of the oxime (**3'a**) (Scheme 2; Fig. 3). It is obvious that **3'a** may be formed both from adduct **2a** (by protonation followed by dehydration) and from oxime **3a** (by



SCHEME 2 **Formation of the protonated form of oxime 3a**

protonation). The compound **3'a** was isolated from the reaction mixture, and the IR spectrum of the product revealed an absorption at $1127\,\mathrm{cm}^{-1}$ in the solid phase and $1131\,\mathrm{cm}^{-1}$ in water that is due to the $\nu_{\mathrm{N-O}}$ vibration.

It can be concluded that appearance of the ethyl methyl ketone–hydroxylamine adduct (**2a**) at 5°C is pH dependent; the intermediate (**2a**) could be detected only at pH 8. The reaction time also depended on the pH; carrying out the oximation at pH 10, 8, and 2.5, the completion required 4, 40, and 30 min, respectively. In the third case, the oxime was formed in the protonated form.

To realize the **3a** → **3'a** conversion, a reaction was set at pH 8, and the mixture was acidified after 47 min by the addition of hydrochloric acid to pH 2.5. The relative quantity of **3a** decreased and at the same time that of **3'a** increased. To prove that the interconversion is reversible, the pH was set to 8. Compound **3'a** was instantly converted back to **3a** (Fig. 4).

In the second part of our study, the oximation of benzaldehyde (Scheme 1) was investigated at pH 8, 10, and ~2.5. At pH 8 at 20°C, the hydroxylamine–carbonyl adduct (**2b**) appeared again as an intermediate with a short lifetime at 1027 and $1042\,\mathrm{cm}^{-1}$ (Fig. 5). Completion of the reaction required 45 min.

We could not differentiate the theoretically possible two (*syn* and *anti*) isomers of the oxime of methyl ethyl ketone and benzaldehyde. Instead, overall signals were detected characteristic for both geometric isomers.

At the same time, the oximation was again faster at pH 10 than at pH 8 (Fig. 6). In this instance, the reaction time was 6 min.

In summary, *in situ* Fourier transform IR spectroscopy was found to be a useful tool for the monitoring of the liquid–liquid two-phase (heterogeneous phase) oximation of methyl ethyl ketone and benzaldehyde and to find the optimum reaction times. The oximations were found to be pH dependent. The rate of the reaction was the slowest at pH 8, but in this case the carbonyl adduct could be detected as an intermediate. At pH 10 or at pH ~ 2.5, the oximations were much faster.

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REFERENCES

1. Ende, D. J.; Preigh, M. J. Process optimization with *in situ* technologies. *Curr. Opin. Drug Disc.* **2000**, *3*, 699–706.
2. Keglevich, Gy.; Csontos, I.; Novák, T.; Mucsi, Z.; Marosi, Gy.; Greiner, I. Monitoring of esterifications by *in situ* Fourier transformation spectroscopy. *Hung. Chem. J.* **2006**, *112*, 114–116.
3. Pintar, A.; Batista, J.; Levec, J. In situ Fourier transform infrared spectroscopy as an efficient tool for determination of reaction kinetics. *Analyst* **2002**, *127*, 1535–1540.
4. Mabon, T. J. Optically based methods for process analysis. 1992, Proceedings of SPIE Volume: 1681, Brittain, H; Farquharson, S.; Sohl, C.; Weyer, L; Lerner, J. M.; Bomse D. S.; Rein, A. J.; Todd, T. R. Editors, Somerset, NJ USA, pp. 190–195.
5. Sheridan, R. E.; Rein, A. J. FTIR system reveals secrets of chemical processes. *R&D Magazine* 1991, *33*, 100–102.
6. Yamagiwa, N.; Abiko, Y.; Sugita, M.; Tian, J.; Matsunaga, S.; Shibasaki, M. Catalytic asymmetric cyano-phosphorylation of aldehydes using a YLi(3)tris(binaphthoxide) complex (YLB). *Tetrahedron: Asymmetry* **2006**, *17*, 566–573.
7. Williams, A.; Bender, M. L. Studies on the mechanism of oxime and ketimine formation. *J. Am. Chem. Soc.* **1966**, *88*, 2508–2513.
8. Jencks, W. P. *Progress in Physical Organic Chemistry*, Vol. 2; Interscience Publishers: New York, 1965; 96, 98.
9. Hine, J.; Li, W. S. Internal catalysis in imine formation from acetone and acetone-d_6 and conformationally constrained derivatives of *N,N*-dimethyl-1,3-propanediamine. *J. Org. Chem.* **1975**, *40*, 2622–2626.
10. Hine, J.; Dempsey, R. C.; Evangelista, R. A.; Jarvi, E. T.; Wilson, J. M. Secondary amine catalysis of oximation of acetone. *J. Org. Chem.* **1977**, *42*, 1593–1599.
11. Cocivera, M.; Effio, A. Methyl-proton exchange involving transient species. Flow nuclear magnetic resonance study of the addition of hydroxylamine to acetone. *J. Chem. Soc. Chem. Commun.* **1976**, 393–394.
12. Cocivera, M.; Effio, A. Flow nuclear magnetic resonance study of the rapid addition of hydroxylamine to acetone and the rate-determining dehydration of the carbinolamine. *J. Am. Chem. Soc.* **1976**, *98*, 7371–7374.
13. Cocivera, M.; Fyfe, C. A.; Effio, A.; Vaish, S. P.; Chen, H. E. Flow nuclear magnetic resonance study of the dehydration of the tetrahedral intermediate resulting from the addition of hydroxylamine to acetaldehyde. *J. Am. Chem. Soc.* **1976**, *98*, 1573–1578.
14. Cocivera, M.; Effio, A.; Chen, H. E.; Vaish, S. Reaction of hydroxylamine with ethyl acetoacetate. Details of the addition and cyclization steps studied by flow nuclear magnetic resonance. *J. Am. Chem. Soc.* **1976**, *98*, 7362–7366.
15. Cocivera, M.; Woo, K. W. Flow NMR study of rapid cyclization following nucleophilic addition. Reaction of hydroxylamine with acetylacetone. *Tetrahedron Lett.* **1976**, 3109–3112.
16. Cocivera, M.; Woo, K. W. Flow nuclear magnetic resonance study of the addition, cyclization, and dehydration steps for the reaction of hydroxylamine with acetylacetone. *J. Am. Chem. Soc.* **1976**, *98*, 7366–7371.
17. Rossi, M. H.; Stachissini, A. S.; do Amaral, L. Secondary α-deuterium isotope effects in the formation of imines. *J. Org. Chem.* **1990**, *55*, 1300–1303.
18. Keglevich, Gy.; Csontos, I.; Szilágyi, N.; Greiner, I. A study of the pH dependence of the two-step oximation of acetone by *in situ* Fourier transform infrared spectroscopy. *Chem. Eng. Technol.* **2008**, *31*, 421–425.
19. Vogel, A. I. *A Text-book of Practical Organic Chemistry,* 5th ed.; Pearson: Harlow, England, 1989; 1048.