OPOLE UNIVERSITY

FACULTY OF CHEMISTRY

Investigation of Multiphase Oxidation Reactions with Oxygen and Hydrogen peroxide in Microstructured Reactors for Pharmaceutical and Fine-Chemical Production

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PhD dissertation

Summary/Autoreferat

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Introduction and Objectives

In recent years, the demand on more sustainable oxidation methods has generated much interest in the use of oxygen and hydrogen peroxide as oxidizing agents.[1-3] Without doubt, molecular oxygen is the most sustainable oxidizing agent, counting for its potential to perform oxidations with an atom efficiency of 100%.[4] Besides molecular oxygen, hydrogen peroxide is a very attractive oxidizing agent for sustainable oxidation reactions. Hydrogen peroxide has the potential to oxidize organic compounds with an atom efficiency of 47%, whilst generating water as the only theoretical by-product.[2] However, in the area of pharmaceutical and fine-chemical production other, often toxic, oxidants like manganates, sodium hypochlorite, and chromates are applied.[5,6] For most reasons, use of oxygen is not considered due to safety aspects. Most crucial fact is the possibility of oxygen and the organic reactant/solvent to form explosive mixtures.[7] A further reason why, oxygen is not often considered in pharmaceutical and fine chemical production is associated with the low selectivity of aerobic oxidations. The resulting complex molecules possess several reactive sites and therefore, various products/by-products can be formed during the oxidation process.[7] Hydrogen peroxide is a highly reactive species, which can lead to combustions in combination with organic solvents in liquid-phase oxidation processes. Therefore, hydrogen peroxide is normally utilized in batch processes only in low concentrations and under mild reaction conditions.[7,8] By use of microstructured reactors, the described limitations in safety can be overcome and harsher reaction conditions can be accomplished.

A microstructured reactor, or microreactor, is a device in which chemical transformations take place in a compartment with a lateral dimension below one millimeter. Most common form of such compartments are microchannels.[9] Devices with lateral dimension above one millimeter are commonly described as millireactors.[10] In the presented work, the used devices apply capillaries with lateral dimensions between 0.5 mm and 3 mm and are referred as microreactors or microstructured reactors. Microstructured reactors are typically operated in a continuous flow process.[11] General concept of flow chemistry whilst using microreaction technology is displayed in Figure 1. To conduct continuous experiments peripheral equipment is needed in addition to the microstructured reactor. In order to maintain a continuous feed stream of the liquid or gaseous reactants pumps and flow meters are necessary. Reactants can be combined in mixing units at precisely specified points along the reactor. Depending on the microreactor design, it is possible to heat, cool or apply UV/Vis radiation to the reaction mixture in the reaction zone.

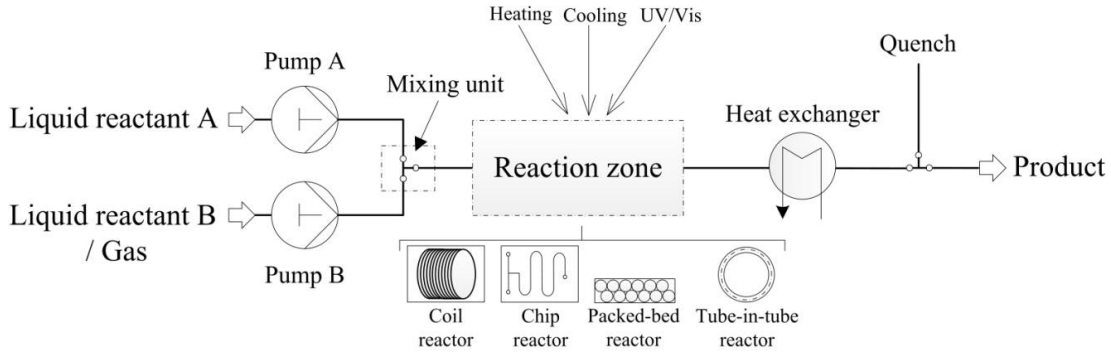


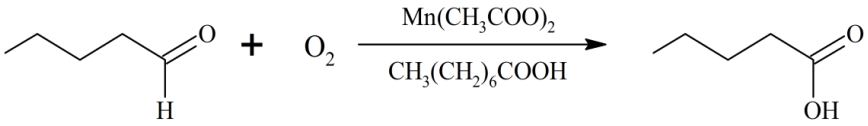
Fig. 1: General concept of flow chemistry using microreaction technology [11]

To stop the reaction under precise conditions the reaction mixture can be quenched. This can be done, for example, by addition of a continuous stream of additional reactant along the reactor which reacts rapidly (e.g. acid-base reaction) with one of the substrates.[12] The product solution is typically collected at the outlet of the microreactor and can be analyzed by post-run analytical methods. In addition to off-line analysis, the microreactor process can be coupled with in-line or on-line analytical measurements. For instance, in-line Raman spectroscopy,[13] on-line UV spectroscopy,[14] on-line electrospray ionization mass spectrometry (ESI-MS),[15] or on-line NMR spectroscopy are common methods enabling real-time reaction tracking.[16]

The potential of microreaction technology to intensify chemical transformations from laboratory to production scale is widely promoted in the extant literature.[11,17-23] Commonly cited advantages are increased mass and heat transfer properties. Combined with small reactor volumes, the overall safety of processes, in particular on the formation of hot spots and thermal runaways, can be significantly improved. This enables process conditions far from conventional practices including high temperatures and pressures, high concentrations up to solvent free conditions, and control of highly exothermic reactions or unstable intermediates. This work discusses the use of microreaction technology for intensification of chemical transformations with oxygen and hydrogen peroxide in the area of pharmaceutical and fine chemical preparation.

The described potential of microreaction technology for conducting continuous oxidation reactions with oxygen and hydrogen peroxide is demonstrated by three example reactions. The first example describes the investigation on transition metal catalyzed oxidation of valeraldehyde with molecular oxygen to valeric acid (Fig. 2). The liquid-phase oxidation proceeds via free-radical reaction, which is catalyzed by manganese(II) acetate.

Free-radical reactions with oxygen as oxidizing agent generally tend to an increased by-product formation.[24,25] To increase selectivity of valeric acid, the reaction is carried out with addition of octanoic acid. Selectivity increase through addition of octanoic acid is described by Lehtinen et al. for the synthesis of 2-ethylhexanoic acid from 2-ethylhexanal with molecular oxygen.[25,26]

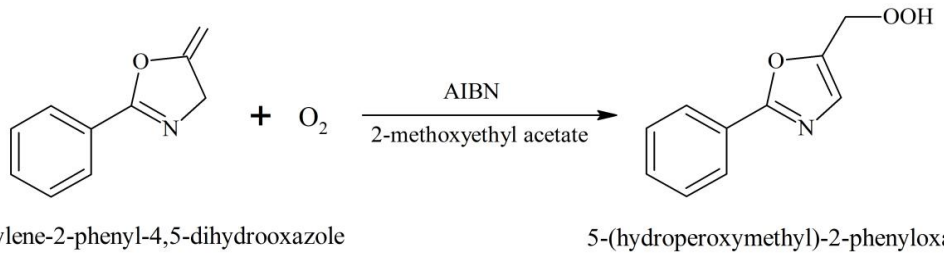


valeraldehyde valeric acid

Fig. 2: Manganese(II) acetate catalyzed oxidation of valeraldehyde to valeric acid

In addition to exothermic conditions (ΔH_R = - 269.32 kJ mol^{-1}) with an adiabatic temperature rise of around 1300 K, synthesis of valeric acid was chosen as an example reaction due to the possibility to increase mass transport of oxygen into the liquid phase, since the oxidation process is described with a mass transport limitation.[27] Valeric acid has a broad application and is mainly produced for preparation of its salts and esters. For example, sodium and calcium salts are used as rodenticides and fungicides. Salts formed with organic compounds find application as pharmaceuticals and cosmetics. Its esters are used because of their good odor in perfumery.[28]

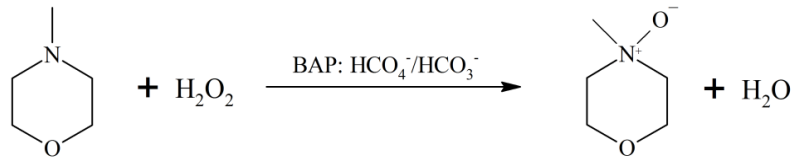
The second example is the synthesis of functionalized oxazoles with molecular oxygen. In particular, synthesis of (hydroperoxymethyl)-2-phenyloxazole (oxazole-hydroperoxide) through oxidation of 5-methylene-2-phenyl-4,5-dihydrooxazole (oxazoline) with molecular oxygen is chosen as example reaction (Fig. 3). The liquid-phase oxidation proceeds via a free-radical reaction and is accelerated by use of radical starting reagent AIBN. The synthesis is implemented in a microstructured reactor to increase process safety and to evaluate the scale-up potential of the multiphase oxidation process. Functionalized oxazoles are of great interest in organic synthesis due to their biological and pharmaceutical activity.[29-33] Pharmaceuticals containing the oxazole motif can be found in different areas. Examples are antibacterial drugs,[34] anti-inflammatory and immunosuppressive drugs,[35] and antidepressants.[36]



5-methylene-2-phenyl-4,5-dihydrooxazole 5-(hydroperoxymethyl)-2-phenyloxazole

Fig. 3: AIBN accelerated oxidation of 5-methylene-2-phenyl-4,5-dihydrooxazole with molecular oxygen to 5-(hydroperoxymethyl)-2-phenyloxazole

The third example describes hydrogen peroxide as oxidizing agent in the BAP-catalyzed synthesis of *N*-methylmorpholine *N*-oxide (NMMO) from *N*-methylmorpholine (Fig. 4). The catalytic oxidation proceeds via active oxidant species peroxymonocarbonate (HCO_4^-), which is formed in situ through equilibrium reaction of hydrogen peroxide and bicarbonate (HCO_3^-) (BAP).[37] In addition to a safe environment, which can be provided by the microstructured reactor since a exothermic *N*-oxidation (ΔH_R = - 68 kJ mol^{-1}) with an adiabatic temperature rise of around 330 K occurs, fast heat removal leads to nearly isothermal conditions. This is favorable as by-product formation of the carcinogenic N-nitrosomorpholine is encouraged at higher temperatures.[38]



N-methylmorpholine *N*-methylmorpholine *N*-oxide

Fig. 4: BAP-catalyzed *N*-oxidation of *N*-methylmorpholine with hydrogen peroxide to *N*-methylmorpholine *N*-oxide

Current major application of NMMO is the direct dissolution of cellulose from wood in commercial fibre production (Lyocell process).[39] Furthermore, NMMO is used as oxidant in various synthetic reactions. Examples are direct oxidation of organic halides to the corresponding aldehydes,[40,41] and catalyzed reactions such as oxidation of alcohols[42,43] and the cis-dihydroxylation of olefins.[44]

Further important fundamentals which are necessary for the conducted work are described in the dissertation. This includes the fundamentals of gas-liquid reactions in microstructured reactors, different two-phase flow patterns, which depend on gas- and liquid-flow rates, geometry of the microstructured reactor, viscosity, and surface tension. Furthermore, the influence of mass transfer from the gas into the liquid phase on the overall reaction rate and the properties of the used oxidizing agents oxygen and hydrogen peroxide are discussed.

Materials and Methods

Synthesis of valeric acid from valeraldehyde with molecular oxygen

The experimental set-up for the liquid phase oxidation of valeraldehyde with molecular oxygen is displayed in Figure 5. The used microstructured reactor can be applied from laboratory studies to small-scale commercial production. Due to the modular design, the reactor could be used for all conducted experiments (reactor volume: 4.76 – 5.30 mL, internal diameter: 1 – 3 mL, capillary length: 0.75 – 6 m, capillary material: Hastelloy C-22).

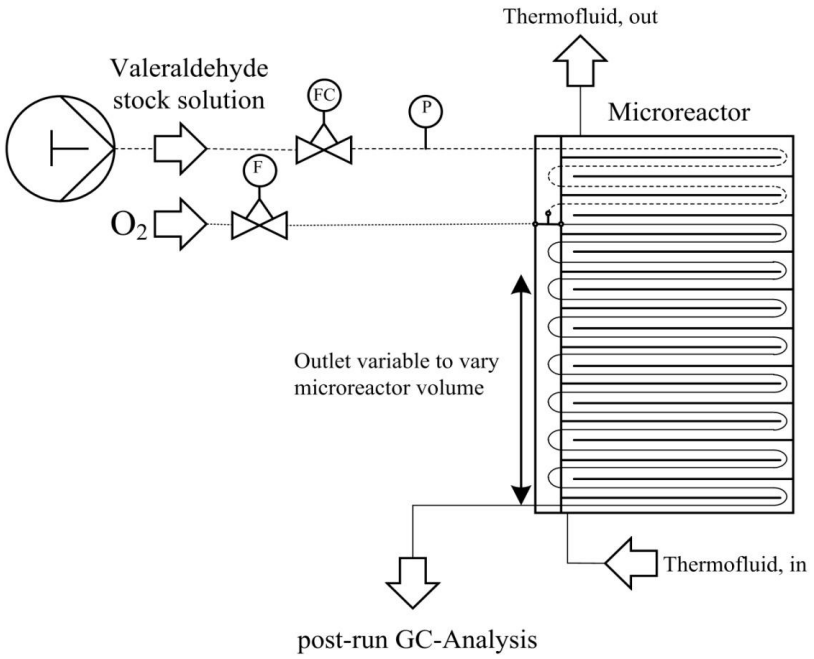


Fig. 5: Experimental set-up for the continuous oxidation of valeraldehyde with molecular oxygen including a syringe pump with a continuous operating mode (SyrDos 2, Hitec Zang GmbH, Germany) equipped with two 1 mL glass syringes, a piezoresistive pressure transmitter (0-100 bar, S-11, WIKA, Germany), a rotameter (Model E: 0.1-0.8 L min-1, VAF Fluid-Technik GmbH, Germany) and the microstructured reactor (MRM 1026-0261-2014, one-A Engineering Austria GmbH, Austria).

Quantitative analyses of the conducted experiments were carried out by GC (7820A with a flame ionization detector (FID), Agilent Technologies Inc., United States of America) applying a HP5 column (length: 30 m; diameter: 0.320 mm; film thickness: 0.25 µm). Samples to analyze the reaction process were collected at the reactor outlet, diluted with methanol (ratio of 10:1 (V/V)) and analyzed immediately by post-run GC-FID. The method was calibrated for the substrate valeraldehyde and the product valeric acid. Different amounts of the analytes were dissolved in 10 mL of methanol to obtain standard solutions. The

corresponding peak areas were plotted against the amount of analyte (Fig. 6). The respectively obtained gradients from the linear regression were used for the determination of the conversion of valeraldehyde and the yield of valeric acid for the samples of the reaction process.

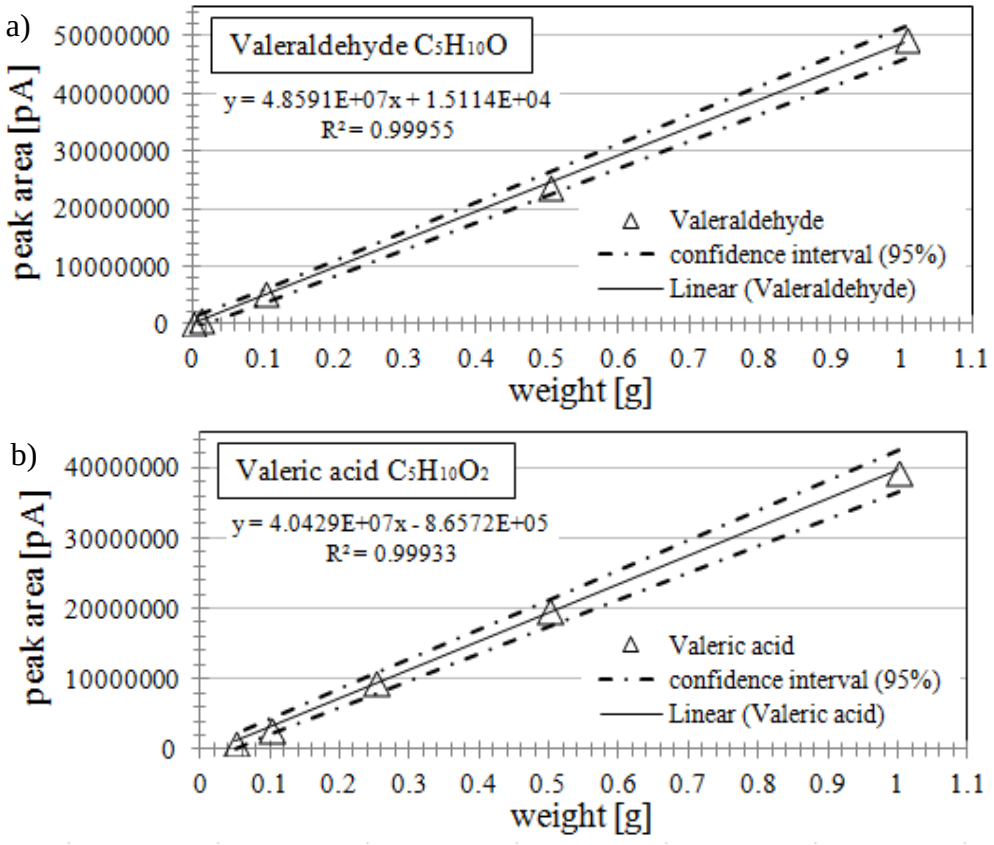


Fig. 6: Calibration curves for the determination of the concentration of valeraldehyde (a) and valeric acid (b) from the peak areas of the GC-FID chromatograms

The synthesis of valeric acid with molecular oxygen was carried out under flow conditions in the described experimental set-up. In general, the reaction proceeds with an oxidation of valeraldehyde by molecular oxygen in the liquid phase. The reaction was carried out in a temperature range from 0 °C to 40 °C. The metal catalyst manganese(II) acetate and the additional solvent octanoic acid were homogeneously mixed prior to the reaction with the valeraldehyde stock solution. The homogeneous valeraldehyde solution was continuously fed into the reactor, preheated and mixed in a T-Mixer with the gaseous molecular oxygen. Samples to analyze the reaction process were collected at the reactor outlet. The used operating parameters are displayed in Table 1

.

Table 1: Operating parameters for the liquid phase oxidation of valeraldehyde (VA)

Parameter	Laboratory-Conditions	Scale-up-Conditions
Oxygen flow rate	100 – 500 mL min^{-1}	200 mL min^{-1}
Flow rate VA stock solution	0.21 – 3.29 mL min^{-1}	0.29 – 1.01 mL min^{-1}
Molar ratio of VA to octanoic acid	1:0.15	1:0.15
Molar VA flow rate	0.0019 – 0.0309 mol min^{-1}	0.0027 – 0.0095 mol min^{-1}
Molar oxygen flow rate	0.0058 – 0.0928 mol min^{-1}	0.0109 mol min^{-1}
Molar oxygen excess	2 (relative to VA)	3 – 0.15 (relative to VA)
Manganese(II) acetate	1000 ppm (relative to VA)	100 ppm (relative to VA)
Temperature	0 °C, 20 °C and 40 °C	60 °C
Pressure	0.5 – 3.2 bar	0.5 bar

Synthesis of functionalized oxazoles with molecular oxygen

The experimental set-up for the liquid phase oxidation of oxazoline with molecular oxygen is displayed in Figure 7. The liquid-phase oxidation was performed in a microstructured reactor, consisting of a PTFE-T-Mixer (id: 0.5 mm) and a 3.175 mm PTFE residence time capillary (id: 1.58 mm, length: 5500 mm) (scale-up experiments: (id: 2.40 mm, length: 7650 mm).

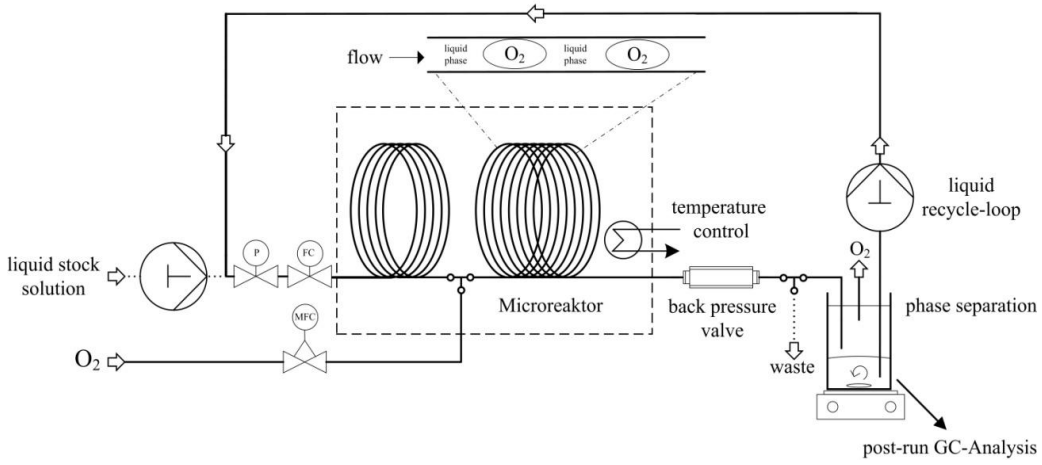


Fig. 7: Experimental set-up for the continuous synthesis of oxazoles-hydroperoxide from oxazoline. The dotted lines symbolize the starting condition. Once a stable operating state has been reached, the liquid stream is conducted in a recycle loop (solid lines) including a syringe pump with a continuous operating mode (SyrDos 2, Hitec Zang GmbH, Germany) equipped with two 1 mL glass syringes, a thermal mass flow controller (EL-FLOW Select, Bronkhorst High-Tech, Netherlands), a piezoresistive pressure transmitter (0-100 bar, S-11, WIKA, Germany), a back pressure regulator (P-764, IDEX, United States of America), a bath thermostat (eco silver RE415, Lauda Dr. R. Wobser GmbH & Co. KG, Germany) and the microstructured reactor made from PTFE.

Quantitative analyses of the conducted experiments were carried out by GC (7820A with a flame ionization detector (FID), Agilent Technologies Inc., United States of America) applying a HP5 column (length: 30 m; diameter: 0.320 mm; film thickness: 0.25 µm). Samples to analyze the reaction process were collected from the liquid reservoir (headspace-vial) (Fig. 7). The method was calibrated for the substrate 5-methylene-2-phenyl-4,5-dihydrooxazole (oxazoline) and the product 5-(hydroperoxymethyl)-2-phenyloxazole (oxazole-hydroperoxide) of the liquid-phase oxidation. To quantify the molar concentrations of oxazoline and oxazole-hydroperoxide, the response factors with the analytical standard n-dodecane were determined. For determination of the response factors, defined amounts of oxazoline, oxazole-hydroperoxide, and n-dodecane were dissolved in 5 ml of 2-methoxyethyl acetate respectively to obtain standard solutions. Different volumes of each standard solution of oxazoline and oxazole-hydroperoxide were mixed with variant volumes of the standard solution of n-dodecane. The obtained samples were analyzed according to the GC-FID method and the corresponding peak areas were determined. By plotting the ratio of the amounts of substance against the ratio of the integral areas a straight line is obtained and its gradient is the response factor (Fig. 8).

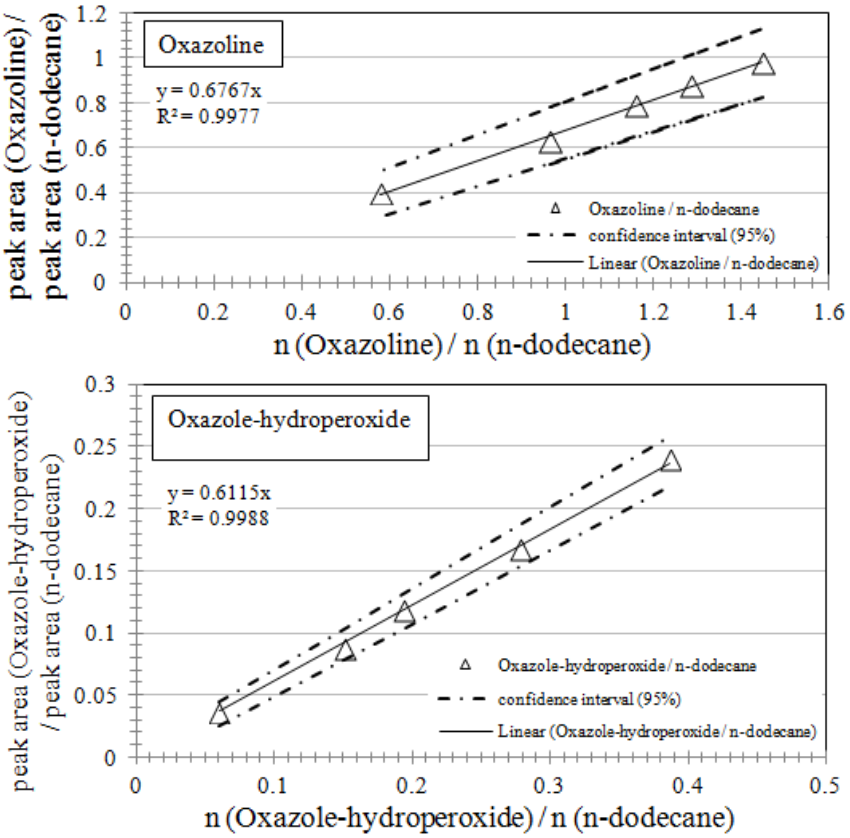


Fig. 8: Calibration curves for the determination of the response factors (RF) of oxazoline (a) (RF = 0.6767) and oxazole-hydroperoxide (b) (RF = 0.6115) from the peak areas of the GC-FID chromatograms

The obtained response factors were used for the determination of the conversion of oxazoline and the yield of oxazole-hydroperoxide from the samples of the reaction process.

Subsequently, the general procedure for the continuous synthesis of 5-(hydroperoxymethyl)-2-phenyloxazole (oxazole-hydroperoxide) from 5-methylene-2-phenyl-4,5-dihydrooxazole (oxazoline) by oxidation with molecular oxygen is described. The synthesis is carried out under flow conditions in the described experimental set-up. In general, the reaction proceeds with an oxidation of oxazoline by molecular oxygen in the liquid phase. Prior to the reaction, the substrate oxazoline (0.2 M) was homogeneously mixed with the radical starting reagent AIBN (10 mol %), the internal analytical standard n-dodecane (0.2 M) and the used solvent 2-methoxyethyl acetate. The reaction is carried out in a temperature range from 70 to 100 °C at two different pressures (1 bar(a) and 18 bar(a)). The homogeneous oxazoline solution is continuously added into the reactor, preheated and mixed in a T-Mixer with the gaseous molecular oxygen. Because of the relatively long reaction time of about four hours for a chemical conversion in a microstructured reactor, a process set-up with a recycle-loop of the liquid stream was chosen (Fig. 7). As soon as a stable operating state was obtained, the liquid phase was collected in a headspace-vial at the outlet of the microreactor, while the oxygen was separated. After a total volume of five milliliters had been collected, the pump inlet was switched into the headspace-vial to receive a liquid recycle loop. Samples to analyze the reaction process were collected from the headspace-vial. The used operating parameters are displayed in Table 2.

Table 2: Operating parameters for the conducted experiments and the scale-up of the liquid phase oxidation of valeraldehyde

Parameter	Conditions	Scale-up
Oxygen flow rate	0.28 – 5 mL min^{-1}	0.97 mL min^{-1}
Oxygen feed rate	0.161 – 3.065 mmol min^{-1}	0.033 mmol min^{-1}
Flow rate oxazoline stock solution	0.25 mL min^{-1}	0.86 mL min^{-1}
Start concentration of oxazoline	0.2 mol L^{-1}	0.2 mol L^{-1}
Initial feed rate of oxazoline	0.05 mol min^{-1}	0.173 mol min^{-1}
Concentration of AIBN	10 mol %	10 mol %
Concentration of the analytical standard n-dodecane	0.2 mol L^{-1}	0.2 mol L^{-1}
Temperature	70 °C, 80 °C and 100 °C	80 °C
Pressure	1 and 18 bar(a)	1 bar(a)

Synthesis of N-methylmorpholine N-oxide with hydrogen peroxide

The experimental set-up for the synthesis of N-methylmorpholine N-oxide with hydrogen peroxide is displayed in Figure 9. The used microreactor (MRM 1026-0261-2014, one-A Engineering Austria GmbH, Austria) can be utilized for laboratory studies and also for small-scale commercial production. Due to its modular design, the reactor is applicable to for all conducted experiments (reactor volume: 3.75 – 14.96 mL, internal diameter: 1 – 3 mL, capillary length: 1.5 – 4.5 m, capillary material: stainless steel (type: 1.4404)).

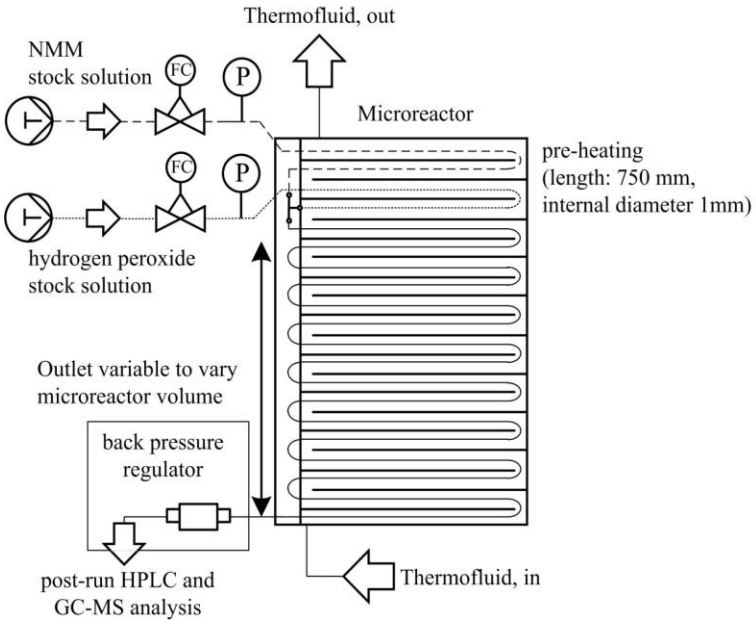


Fig. 9: Experimental set-up for the continuous oxidation of NMM with hydrogen peroxide including two syringe pumps with a continuous operating mode (SyrDos 2, Hitec Zang GmbH, Germany), each equipped with two 1 mL glass syringes, two piezoresistive pressure transmitter (0-100 bar, S-11, WIKA, Germany), a back pressure regulator (17 bar, P-764, IDEX, United States of America) and the microstructured reactor (MRM 1026-0261-2014, one-A Engineering Austria GmbH, Austria).

Quantitative analyses of the conducted experiments were carried out by HPLC (1100, Agilent Technologies, Inc., United States of America) applying a VA 150/4.6 Nucleogel RP 100-8 column (150 x 4 mm) (Macherey-Nagel, Germany). Samples to analyze the reaction process were collected at the reactor outlet, diluted with purified water (ratio of 10:1 (V/V)) and analyzed by post-run HPLC. The method is calibrated for the substrate (NMM) the product (NMMO), and the by-product (morpholine). Different amounts of the analytes were dissolved in 10 mL of purified water to obtain standard solutions. The corresponding peak areas where plotted against the amount of analyte (Fig. 10). The obtained gradients when performing a linear regression, are used for determination of conversion of NMM and yield of NMMO.

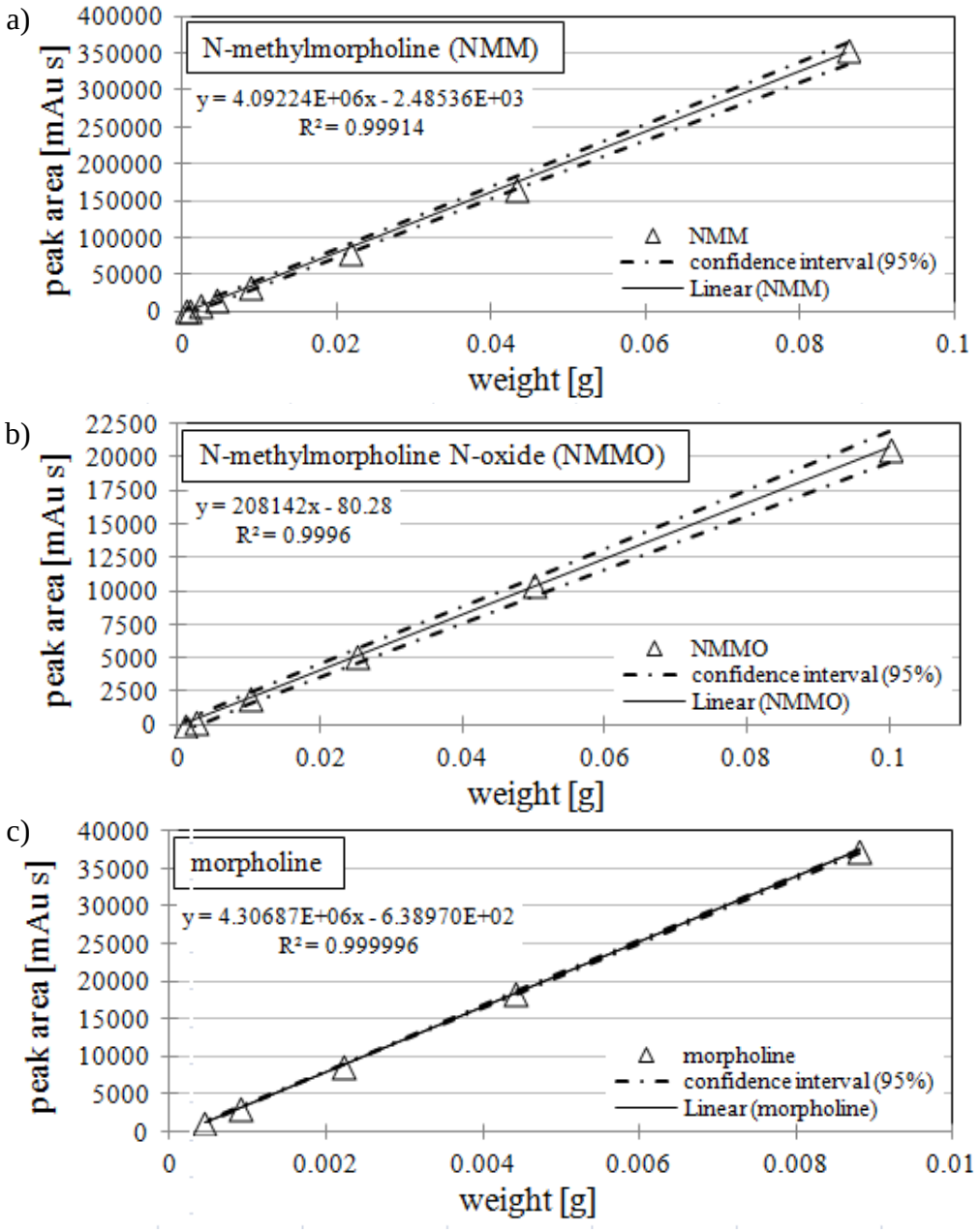


Fig. 10: Calibration curves for the determination of the concentration of N-methylmorpholine (a), N-methylmorpholine N-oxide (b) and morpholine (c) from the peak areas of the HPLC chromatograms

Synthesis of NMM with hydrogen peroxide is carried out under flow conditions in the experimental set-up described above. In general, the reaction proceeds with NMM (8.5 M) through oxidation with hydrogen peroxide (30 wt % – 50 wt %) in a temperature range of 40 °C to 70 °C and at a pressure of 17 bar(a). Carbon dioxide (0.5 wt % – 1 wt % relative to NMM) is dissolved prior to the continuous reaction in the NMM stock solution. Phosphoric acid (0.1 wt % relative to hydrogen peroxide) is homogeneously mixed prior to the reaction with the hydrogen peroxide stock solution. Samples to analyze the reaction process, were collected at the reactor outlet.

Results and Discussion

Synthesis of valeric acid from valeraldehyde with molecular oxygen

The microreactor experiments are based on a catalyst screening which was carried out by Hollmann in 2014[45] and the work of Lehtinen et al.[25,26] on the influence of different solvents in the metal catalyzed oxidation of aldehydes. Based on the results manganese(II) acetate is chosen as catalyst and octanoic acid is applied as additional solvent in the conducted experiments in the microstructured reactor.

The microreactor experiments are carried out with a large molar excess of oxygen (2 equivalents). Because of this excess and the low density of oxygen, compared to the liquid, the dominant phase in the capillary is the gas phase. Therefore, an annular flow pattern can be assumed. Due to the large excess of oxygen, the phase ratio is nearly constant over the entire reaction process. These process parameters were selected to achieve a high mass transfer rate, since the oxidation process is described with a mass transfer limitation.[24,28] Annular flow is characterized by the presence of a liquid film flowing on the channel wall and with the gas flowing in the channel core. In contrast to plug flow, the gas and the liquid phase have not the same velocity inside the microreactor channel. To characterize the results, the superficial liquid flow residence time is chosen. This needs the assumption that solely the liquid flows through the capillary. Calculation of the resulting superficial liquid flow residence time is displayed in Equation 1.

$$\tau_{sf} = \frac{Vr}{\dot{V}_{lq}} \tag{1}$$

The conversion of valeraldehyde at 0 °C, 20 °C and 40 °C with addition of octanoic acid and manganese(II) acetate (1000 ppm relative to valeraldehyde) is displayed in Figure 11 a). A rapid conversion of valeraldehyde is achieved with the applied reaction conditions (superficial liquid flow residence time: 82 s, conversion: 95%). The corresponding yields of the experiments are shown in Figure 11 b). The reaction can be accelerated by an increase of the reaction temperature. A rough calculation of the activation energy (E_A = 9.5 kJ mol^{-1}) is performed by using the initial reaction rates. An activation energy below 20 kJ mol^{-1} indicates a mass transport limitation of the reaction process.[46] It is supposed that the reaction takes place in the liquid boundary layer due to fast reaction rate and the low solubility of oxygen in valeraldehyde. Typical by-products formed in the oxidation of aldehydes are ketones, alcohols, formate, and carbon dioxide. In the presented reaction, these are butan-2-on,

butan-2-ol and carbon dioxide. The formation of formate is not straightforward due to the missing α-alkyl group in valeraldehyde. By analyzing the mass balance of valeraldehyde and valeric acid, a selectivity of 80 to 85% is observed.

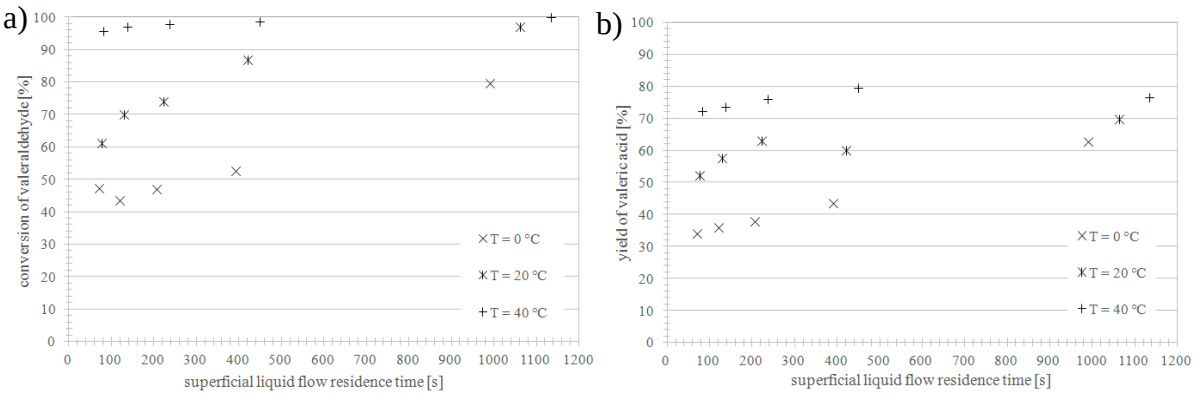


Fig. 11: a) Valeraldehyde conversion and b) yield of valeric acid for the catalyzed liquid phase oxidation with molecular oxygen at three different reaction temperatures (0 °C, 20 °C and 40 °C) with the addition of 1000 ppm manganese(II) acetate and octanoic acid

The results are in a good accordance to the results of Lehtinen et al. for the oxidation of 2-ethylhexanal.[25] They reported a selectivity of 84% for 2-ethylhexanoic acid by the use of manganese(II) acetate and octanoic acid. However, the reaction time in the presented oxidation of valeraldehyde (superficial liquid flow residence time: 82 s, conversion: 95%) is significantly shorter compared to the reported reaction time of 2 hours by Lehtinen et al. in a flat-bottomed glass vessel. A scale-up to bigger microchannels (3 mm) is carried out, but it is not straightforward due to the change of hydrodynamic mass transfer. The results of the scale-up experiment are displayed in Figure 12. The scale-up experiments are carried out at a higher temperature to further increase the productivity of the oxidation process.

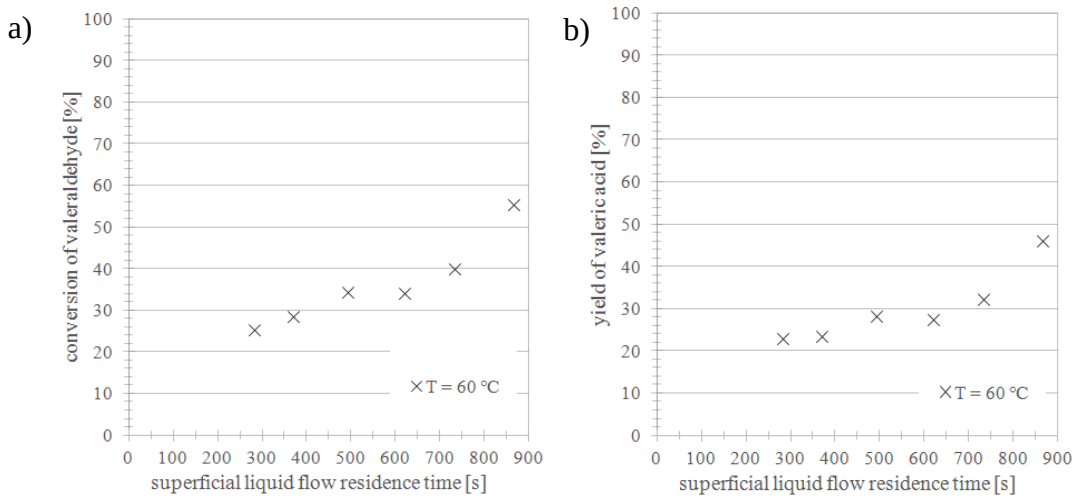


Fig. 12: a) Conversion of valeraldehyde and b) yield of valeric acid for the conducted scale-up experiments by oxidation with molecular oxygen and a reaction temperature of 60 °C

Synthesis of functionalized oxazoles with molecular oxygen

The microreactor experiments are based on batch experiments from Hashmi et al. from 2012.[47] The experiments on the synthesis of 5-(hydroperoxymethyl)-2-phenyloxazole are carried out in dry Schlenk flasks under oxygen atmosphere with a substrate (5-methylene-2-phenyl-4,5-dihydrooxazole) amount of 0.5 mmol (79.53 mg). The reaction was carried out for 48 h and a yield of 82% for the oxazole-hydroperoxide could be achieved. Hashmi et al. also described the possibility to accelerate the reaction by the addition of the radical starting reagent AIBN.[47]

The influence of different parameters for example the concentration of the radical starting reagent AIBN (Fig. 13), different phase ratios of gas and liquid phase and the temperature dependence (Fig. 14) are investigated in the continuous experiments in the described microreactor set-up. A kinetic model was established from the experimental data to describe the temperature-dependent observed reaction rate (described in the dissertation). From this model the observed activation energy was calculated. A scale-up of the reaction is performed to review the potential for large scale applications (Fig. 15). Furthermore, the capability of the microreactor set-up for follow-up transformations was investigated by a coupling of the oxidation reaction with an in situ reduction of the generated hydroperoxide (described in the dissertation).

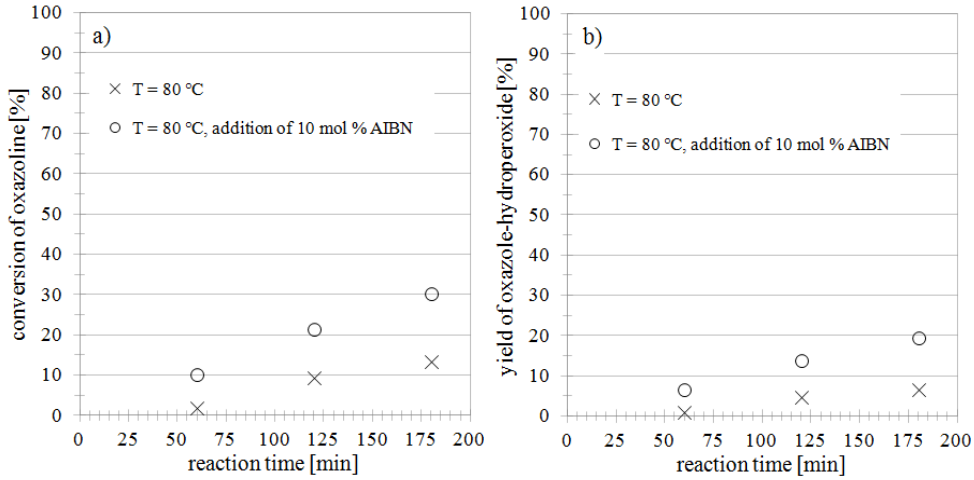


Fig. 13: Influence of AIBN (10 mol %) on the conversion of oxazoline (a) and the yield of oxazoles-hydroperoxide (b)

The results in Figure 13 show a significant increase of the reaction rate by the addition of 10 mol % AIBN. The conversion of oxazoline was increased from 13 to 31% within a total reaction time of 3 h. As an additional effect, the selectivity for the desired product oxazole-hydroperoxide relative to oxazoline was increased from 50% to 65%. For all following

experiments, AIBN was used to accelerate the oxidation of oxazoline. The influence of the reaction temperature on the oxidation of oxazoline is investigated at normal pressure and a gas-to-liquid phase ratio of 20:1. The reaction temperature varied from 70 °C to 80 °C and 100 °C, which is displayed in Figure 14. A temperature increase of 10 °C from 70 °C to 80 °C doubled the conversion to 39% after a reaction time of 4 h. Raising the temperature to 100 °C led to a conversion of 64% after 4 h, suggesting an approximately linear correlation of the conversion with the temperature. Simultaneously, the yield could be enhanced with an increase in the reaction temperature. At elevated temperatures a decrease in selectivity is going along with the formation of small amounts of a side product, 5-methyl-2-phenyl-1,3-oxazole.

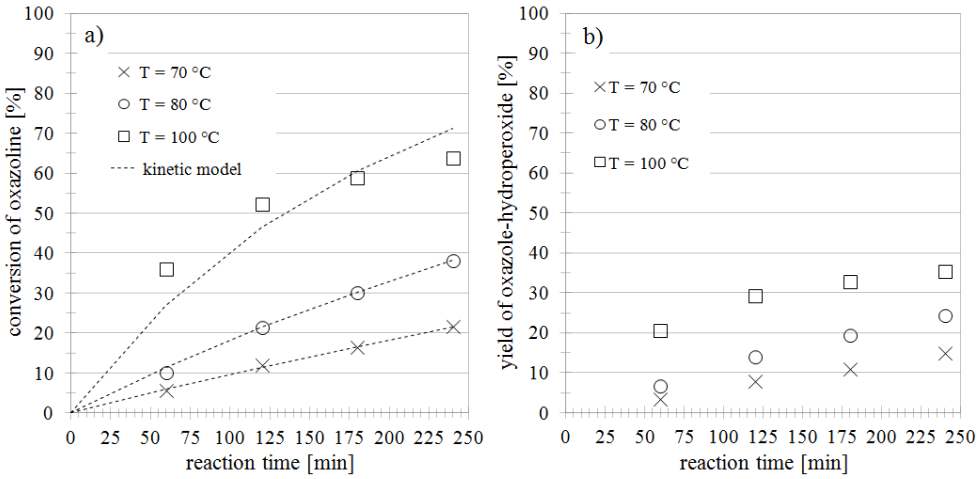


Fig. 14: Influence of different reaction temperatures 70 °C, 80 °C and 100 °C and a gas-to-liquid phase ratio of 20:1 on the conversion of oxazoline (a) and the yield of oxazoles-hydroperoxide (b)

A scale-up of the reaction was conducted using a residency time capillary with a larger inner diameter of 2.4 mm. To maintain a basis for comparison, the ratio of the inner diameter to capillary length was kept constant to the previous experiments. This leads to a scale-up factor of 3.46 for reactor volume (34.6 ml), liquid reservoir volume (17.3 ml), and the liquid and oxygen flow rates (0.86 and 0.97 ml min^{-1}). Based on this approach, the residence time in the microreactor was kept constant as in the previous experiment. The conversion of oxazoline and the yield of oxazole hydroperoxide could be reproduced in the scale-up experiment (Fig. 15). This leads to the conclusion that the scale-up was successful and a pilot plant process could be possible.

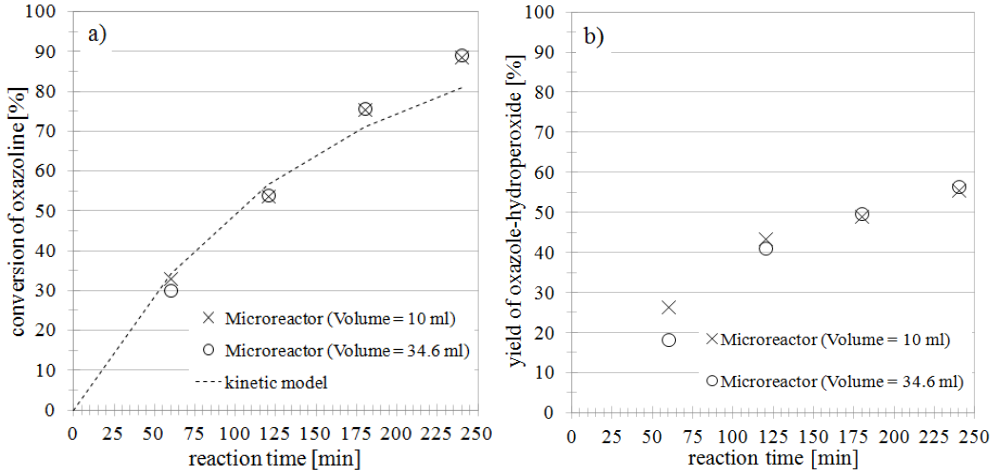


Fig. 15: Conversion of oxazoline (a) and the yield of oxazoles-hydroperoxide (b) for the conducted scale-up experiments at and a phase ratio of gas to liquid of 1.1:1

Synthesis of N-methylmorpholine N-oxide with hydrogen peroxide

The overall objective of presented investigation on the oxidation of NMM with hydrogen peroxide is to apply much higher concentrations and harsher reaction conditions, by using the benefits of microstructured reactors, i.e., high heat and mass transfer, and low hold-up of critical material during the reaction process. The influence of different parameters, for example hydrogen peroxide (Fig. 16) and catalyst concentration (Fig. 17), and temperature dependence are investigated (Fig. 18 and Fig. 19). A scale-up of the reaction is performed to demonstrate its potential use for large scale applications (described in the dissertation).

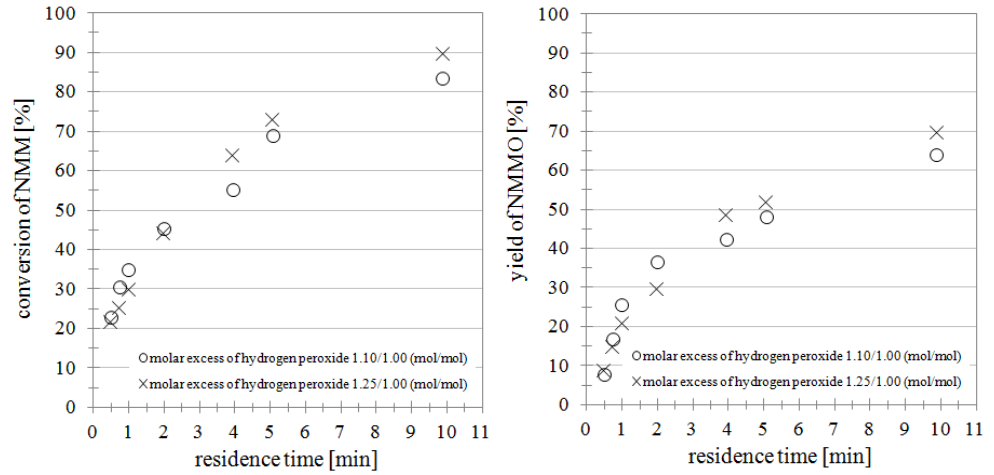


Fig. 16: Influence of molar excess of hydrogen peroxide on conversion of NMM (a) and yield of NMMO (b)

Two experiments were carried out with 10% and 25% molar excess of hydrogen peroxide. The results, presented in Figure 16, show no acceleration of the reaction process due to a higher excess of hydrogen peroxide.

The influence of carbon dioxide, respectively of the active oxidant peroxymonocarbonate HCO_4^- (bicarbonate activated hydrogen peroxide) on the reaction process, is illustrated in Figure 17. The results show a significant increase of reaction rate when adding 0.5 wt % to 1 wt % of carbon dioxide. Conversion of NMM is increased from 74% to 97.5% within a residence time of 13.90 minutes when providing a reaction temperature of 50 °C, while selectivity of NMMO relative to NMM is nearly constant at 93% and 94%. In comparison, without carbon dioxide, a conversion of 26%, respectively 59% for NMM, and a yield of 25%, respectively 55% for NMMO, at 40 °C and 60 °C is reached within a residence time of 14.81 minutes.

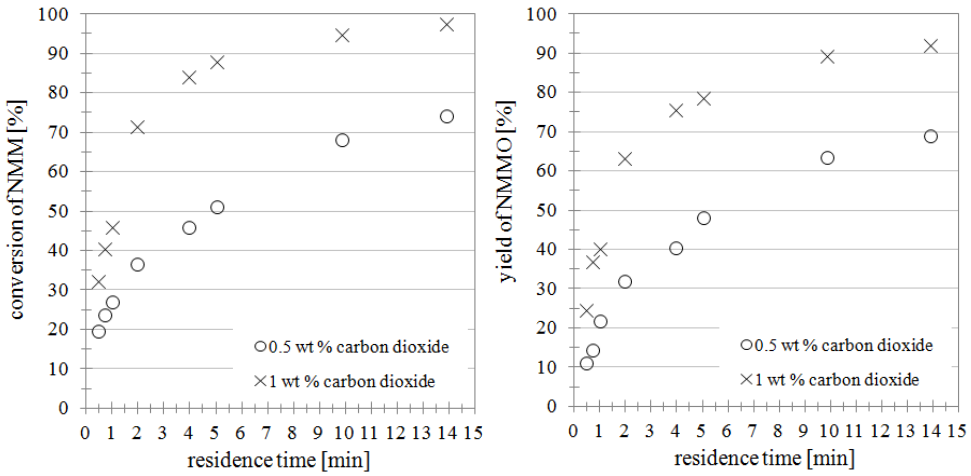


Fig. 17: Influence of carbon dioxide on conversion of NMM (a) and yield of NMMO (b)

The influence of reaction temperature on *N*-oxidation of NMM is investigated with two different concentrations of hydrogen peroxide. Reaction temperature was set to 40 °C, 50 °C, respectively 60 °C, at a hydrogen peroxide concentration of 29 wt %. The results are displayed in Figure 18. The corresponding results with a hydrogen peroxide concentration of 50.75 wt % are provided in Figure 19. The results show a moderate temperature dependence of the reaction process. Conversion of NMM and yield of NMMO nearly double when increasing temperature by 10 °C.

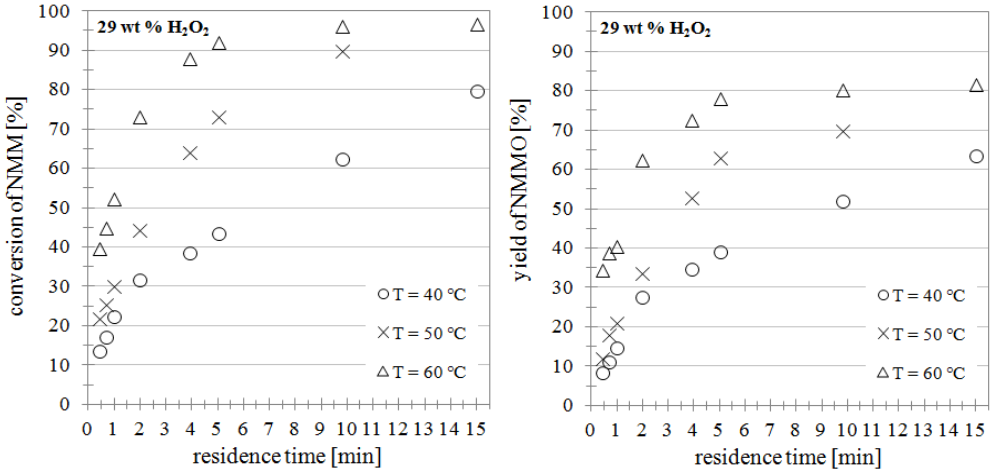


Fig. 18: Temperature dependence of conversion of NMM (a) and yield of NMMO (b) at a hydrogen peroxide concentration of 29 wt %

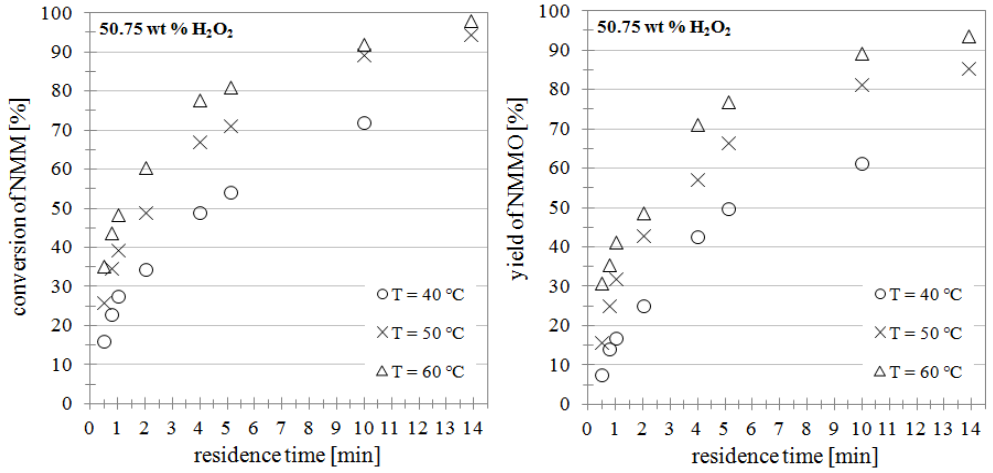


Fig. 19: Temperature dependence of conversion of NMM (a) and yield of NMMO (b) at a hydrogen peroxide concentration of 50.75 wt %

Conclusions

In recent years, the demand on more sustainable oxidation methods has generated much interest in the use of oxygen and hydrogen peroxide as oxidizing agents.[1-3] The application of microstructured reactors enables the use of oxygen and hydrogen peroxide in chemical reactions in a safe and beneficial manner. In the presented work, the use of oxygen and hydrogen peroxide as oxidizing agents by application of microstructured reactors was demonstrated by three examples from the field of fine chemical and pharmaceutical syntheses:

1. **Molecular oxygen** as oxidizing agent in the manganese(II) acetate catalyzed oxidation of valeraldehyde to valeric acid
2. **Molecular oxygen** as oxidizing agent in the synthesis of (hydroperoxymethyl)-2-phenyloxazole (oxazole-hydroperoxide) from 5-methylene-2-phenyl-4,5-dihydrooxazole (oxazoline)
3. **Hydrogen peroxide** as oxidizing agent in the BAP-catalyzed (bicarbonate activated hydrogen peroxide) synthesis of *N*-methylmorpholine *N*-oxide (NMMO) from *N*-methylmorpholine

Due to the benefits of microstructured reactors, it is possible to use molecular oxygen without dilution in solvent free chemical reactions. This could be demonstrated by the first example, the fast and exothermic synthesis of valeric acid from valeraldehyde. With temperatures up to 40 °C and a catalyst concentration of 1000 ppm manganese(II) acetate, conversions for valeraldehyde of 95% could be achieved within a reaction time of 82 s. In contrast, typical industrial processes for liquid-phase aldehyde oxidations, which are conducted for example in bubble column reactors or gas-liquid stirred tank reactors, often apply strongly diluted reaction mixtures for safety reasons.[48]

The second example, the synthesis of (hydroperoxymethyl)-2-phenyloxazole (oxazole-hydroperoxide) is comparatively slow for a continuous process in a microstructured reactor. To increase the efficiency of the process, a set-up with a liquid recycle loop was used. The reaction could be accelerated by the addition of the radical starting reagent AIBN. With a reaction temperature of 80 °C and an AIBN concentration of 10 mol %, a conversion of 89% and a yield of 56% within a reaction time of four hours could be achieved. It could be demonstrated that the microstructured reactor provided a safe environment for the reactions with molecular oxygen and the organic reactants at high temperatures and pressures.

The third example successfully applies hydrogen peroxide in the BAP catalyzed N-oxidation of NMM to NMMO. With temperatures up to 60 °C and catalyst concentrations of 1 wt % carbon dioxide, conversions of 98% and yields of 93.5% within residence times of 13.90 min could be achieved. Also the limitations, according to the mass and heat transfer properties, of the applied microreactor could be demonstrated for the synthesis of NMMO. Temperatures of the capillary wall from 40 °C to 60 °C led to nearly isothermal conditions inside the microstructured reactor during the oxidation process. In contrast, a capillary wall temperature of 70 °C resulted in a thermal runaway with a hot-spot temperature of 120 °C.

Apart from all positive aspects which are described in the presented work for oxidation reactions with oxygen and hydrogen peroxide in microstructured reactors, microreaction technology competes with well-established production technologies. An application of microreaction technology is expected only by significant advantages, for example on costs, environment and development time.

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Pre-published content

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[I] Baumeister, T.; Kitzler, H.; Obermaier, K.; Zikeli, S.; Röder, T.; Two-Phase Flow Oxidation of Valeraldehyde with O_2 in a Microstructured Reactor, Org. Process Res. Dev. 2015, 19, 1576-1579.

[II] Bay, S.; Baumeister, T.; Hashmi, A. S. K.; Röder, T.; Safe and Fast Flow Synthesis of Functionalized Oxazoles with Molecular Oxygen in a Microstructured Reactor, Org. Process Res. Dev. 2016, 20, 1297-1304.

[III] Baumeister, T.; Zikeli, S.; Kitzler, H.; Aigner, P.; Wieczorek, P. P.; Röder, T.; Continuous flow synthesis of amine oxides by oxidation of tertiary amines, React. Chem. Eng., 2019, Advance Article, DOI: 10.1039/C9RE00127A.

Patent

[I] Zikeli, S.; Kitzler, H.; Fosodeder, V.; Baumeister, T.; Production of an Amine Oxide by Oxidation of a Tertiary Amine, WO/2018/115443 A1, PCT/EP2017/084391, 2018.

Oral Presentations

[i] Baumeister, T.; Röder, T.; Continuous Multiphase Reactions with Oxygen in Microstructured Reactors for Sustainable Processes, The 10th National Eco-Energy Festival, 9.-12th October 2018, Opole, Poland.

Poster Presentations

[i] Baumeister, T.; Kitzler, H.; Obermaier, K.; Zikeli, S.; Röder, T.; Mehrphasen Oxidation von Valeraldehyde mit O_2 im Mikroreaktor, Jahrestreffen der Fachgruppe Mikroverfahrenstechnik, 14th September 2015, Frankfurt, Germany.

[ii] Baumeister, T.; Bay, S.; Hashmi, A. S. K.; Röder, T.; Safe and Fast Flow Synthesis of Functionalized Oxazoles with O_2 in a Microreactor, SCI/RSC Continuous Flow Technology III, 14.-16th March 2016, Cambridge, Great Britain.

[iii] Baumeister, T.; Bay, S.; Hashmi, A. S. K.; Röder, T.; Mehrphasensynthese von funktionalisierten Oxazolen mit molekularem Sauerstoff im Mikroreaktor, Jahrestreffen Reaktionstechnik zusammen mit der Fachgruppe Mischvorgänge, 2.-4th May 2016, Würzburg, Germany.