

# Process optimization of a catalyzed bleach oxidation for the production of functionalized aldehydes using microreaction technology

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## Abstract

This paper presents results of a parameter study on the homogeneously catalyzed oxidation of 2-butoxyethanol to 2-butoxyacetaldehyde. The original recipe, developed for a batch process, was successfully transferred to a continuous microreaction process to provide a better control on the suppression of the unwanted subsequent oxidation to 2-butoxyacetic acid. For the investigation of the global reaction kinetics a new type of passive mixing microreactor was developed that allows variation of the internal hold-up and thus residence time. A systematic screening of process parameters showed a combined impact of residence time and introduced mixing energy on the reaction progress. By improving mixing quality in the microreactor the macroscopic reaction rate was increased compared to the lab-scale batch process.

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## 1. Introduction

Microreaction technology is a promising tool for optimization of continuous processes. Improved mass transport and heat exchange characteristics allow the investigation of fast and strong exothermic reactions in a very controlled way [1]. Furthermore, it is possible to adjust process parameters immediately. Because of the small hold-up and the continuous operation mode the optimum performance can be found rapidly, e.g. by applying a statistical DoE (design of experiments) procedure. That allows a systematic variation of process parameters such as temperature, residence time, and stoichiometry of different reactants. By controlling these parameters the time-resolved course of product concentration can be analyzed to determine the global reaction kinetics at isothermal conditions.

Here we report on the process optimization of a homogeneously catalyzed reaction [2–4] using microreaction technology. The reaction is based on a versatile biphasic selective oxidation method for the synthesis of functionalized aldehydes from the corresponding alcohols. As a catalyst

2,2,6,6-tetramethyl-piperidine-1-oxyl (“TEMPO”) is used. The functionalized aldehydes obtained are important intermediates for different types of organic reactions such as enantioselective Aldol condensations [5], Reformatsky reactions [6], or Wittig reactions [7]. Furthermore, aldehydes are also used as starting materials for synthesis of cyanohydrins, used as intermediates for the asymmetric Strecker synthesis of amino acids [8].

In our case the oxidation of 2-butoxyethanol to 2-butoxyacetaldehyde was investigated (Fig. 1). The organic catalyst TEMPO that is required for the reaction is continuously activated by hypochlorite solution (bleach) and bromide as co-catalyst (Fig. 2). In case of  $\beta$ -functionalized activated alcohols the formation of the corresponding carboxylic acid via overoxidation is the major side reaction increasing with longer reaction times [9], particularly in batch or even in *semi*-batch setups where back mixing causes a broad residence time distribution. Selective oxidation of 2-butoxyethanol thus yields significant amounts of 2-butoxyacetic acid as undesired side product.

To avoid broad residence time distribution a continuous process with a preferably narrow residence time distribution is desirable. This approach was generally confirmed in a recent study, where an appropriate preparative continuous process was set-up for bleach oxidation and tested successfully for a wide variety of different activated alcohols [9].

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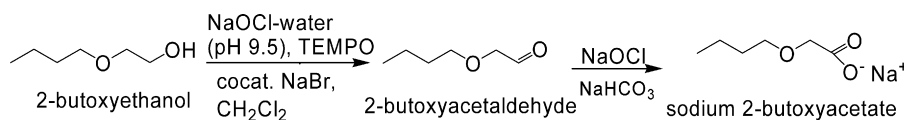


Fig. 1. Reaction scheme of the investigated oxidation process. In order to obtain maximum yield of the desired aldehyde, the formation of 2-butoxyacetic acid has to be suppressed.

The objective of this study was the analysis of the kinetic of a continuous biphasic microreaction process at isothermal conditions in order to identify appropriate process conditions for aldehyde formation, which was not the objective of the previous study [10]. It is important here to note the biphasic nature of the reaction mixture in conjunction with the importance of intense mixing for kinetic and selectivity of the reaction studied. The results obtained were compared with batch experiments at lab-scale.

## 2. Materials and methods

For the reaction, the following two solutions were prepared:

- Solution 1 (methylene chloride phase): 2.46 g (20.6 mmol) 2-butoxyacetic acid, 177 mg (1.13 mmol) 2,2,6,6-tetramethylpiperidine-1-oxyl (“TEMPO”), and 182 mg (1.14 mmol) bromine dissolved in 2 mL  $\text{CH}_2\text{Cl}_2$  were added to 40 mL  $\text{CH}_2\text{Cl}_2$ .
- Solution 2 (water phase): By addition of 20% sulphuric acid, 11 g bleach (approximate concentration between 2.0 and 2.4 M) are adjusted to pH 9.5. To neutralize the carboxylic acid formed during the reaction, 1 g  $\text{KHCO}_3$  in 6 mL water is added to this solution. The hypochlorite concentration is determined by iodometric titration. *Note:* This solution is unstable and must be used within an appropriate time. To prolong its stability, it should be stored at  $0^\circ\text{C}$ .

### 2.1. Microreaction experiments

The microreaction set-up of a first series of experiments is schematically shown in Fig. 3. Each of the two corrosion resistant syringe pumps (S 1610, Sykam GmbH, Germany) consists of two alternately pumping 1 mL syringes. The volume flows of

solution 1 and solution 2 were adjusted to a stoichiometric ratio of 1.2 for bleach and 2-butoxyethanol.

Intensive mixing was achieved by using a split-and-recombine micromixer consisting of G-shaped mixing elements along one channel; a detailed description of the micromixer is given elsewhere [10]. Since this type of micromixer comprises only an internal volume of approximately  $4\ \mu\text{L}$ , a PTFE capillary (ID = 0.8 mm) was connected subsequent to the mixer to provide additional residence time. The global reaction time was varied systematically by changing the total flow rate (1–8 mL/min) and by using capillaries of different length as residence time units, respectively (volumes of residence time units were approximately 0.07, 0.13, 0.33, 0.51, and 1.01 mL). The temperature of the cooling bath was adjusted to  $10^\circ\text{C}$ .

A controlled termination of the reaction mixture was carried out in a microstructured quench reactor made of silicon at the end of the residence time unit by using a 10% aqueous solution of sodium thiosulfate as quenching agent. The quench reactor consisted also of a G-shaped split-and-recombine mixing structure with 11 microchannels in parallel for reduction of pressure drop [10]. Quenched reaction mixtures were analyzed by NMR providing a “snapshot” of the reaction progress after the corresponding reaction times.

In a second set of experiments another setup was realized by replacing the combination of split-and-recombine micromixer and subsequent residence time unit (PTFE capillary) by a new in-house designed monolithic microreactor device made of glass (Fig. 4).

The meander-shaped reaction channel of the microreactor ( $150\ \text{mm} \times 55\ \text{mm} \times 5\ \text{mm}$ ) comprises a chaotic mixing structure over its full length. It was fabricated by using the micro-sandblasting technique. After structuring of the four necessary glass layers, they were sandwiched between a top and a bottom layer and bonded. The structure ensures intensified emulsification of the two phases over nearly the entire reaction

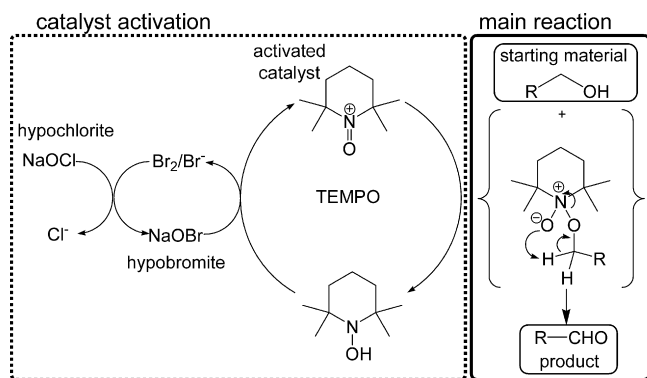


Fig. 2. The proposed reaction mechanism can be separated into two regimes. The first regime is used for the activation of the TEMPO catalyst by using bleach and bromide as co-catalyst. The second regime is the reaction to form the aldehyde.

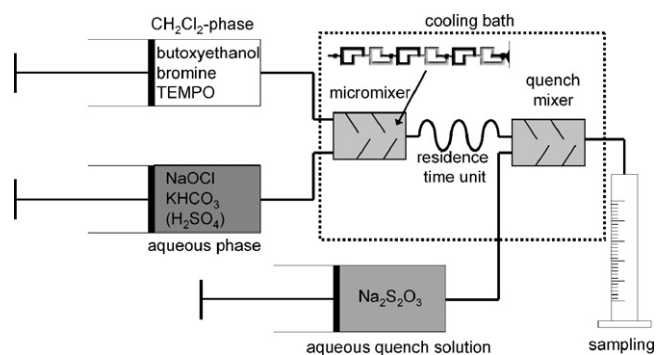


Fig. 3. Schematic set-up of the microreaction process. The simple reaction unit consisting of split-and-recombine micromixer and a subsequent PTFE capillary was later replaced by a monolithic microreactor as shown in Fig. 4.

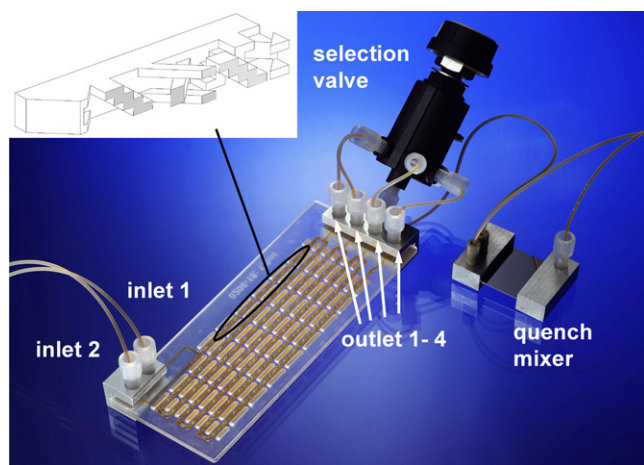


Fig. 4. Monolithic microreactor that ensures constant mixing of the two-phase system during the entire reaction time (reactor design: Fraunhofer ICT, design of mixing elements and fabrication: Little Things Factory, Ilmenau, Germany). The passive mixing structure in the microchannel is shown in top left. A selection valve allows the adjustment of channel length and volume. The reaction is terminated in a microstructured quench mixer.

time—including most of the residence time unit. The average cross-section of the channel was approximately  $1.25 \text{ mm}^2$ . The microreactor has four individual outlet fluid-ports along the main reaction channel. Therefore, by using an appropriate selection valve four different hold-ups can be realized with the same device (Fig. 5). The adjustable hold-ups are 0.11, 0.45, 0.76, and 1.08 mL which correspond to a channel length of 0.11, 0.37, 0.62, and 0.88 m. An additional unmixed residence volume of 0.08 mL is provided by the capillaries for the interconnection between the microreactor outlet and the quench reactor, including the intercostal selection valve (Upchurch Scientific, USA).

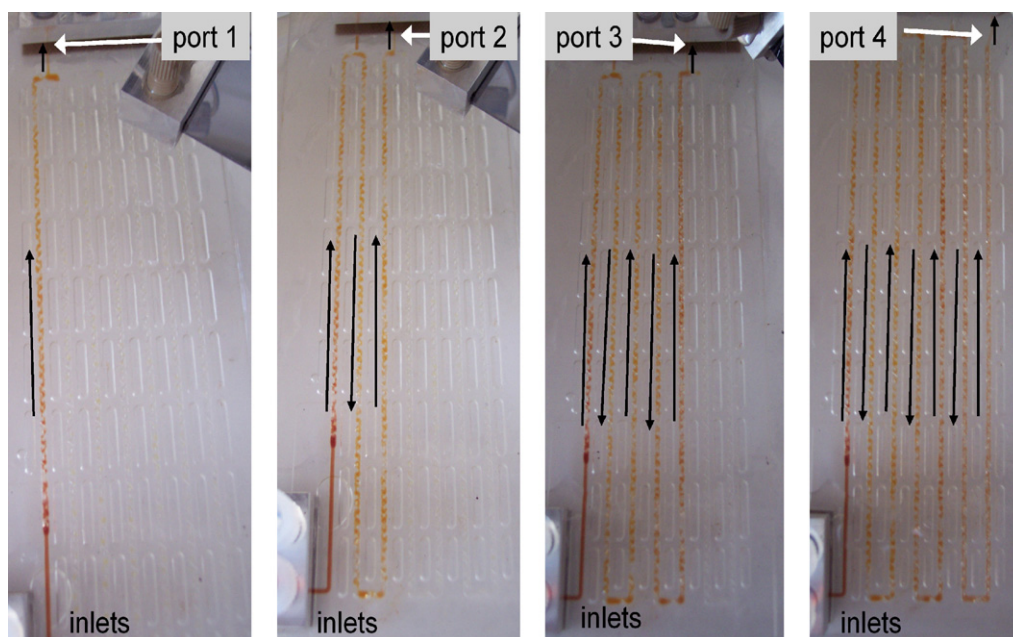


Fig. 5. By turning the selection valve to one of the four different fluidic outlet ports the internal volume of the microreactor can be varied. The brownish parts of the reaction channel contain the reaction mixture. The transparent parts are filled with water.

According to the former setup a microstructured quench mixer made of silicon was used again for a controlled termination of the reaction once the reaction mixture has left the monolithic reactor.

The results obtained in the continuous microprocess experiments were compared with batch experiments. In the latter case the same stoichiometric ratio (bleach:butoxyethanol = 1.2:1) was adjusted as in the continuous process. Solution 1 was provided in a flask and cooled down to  $-10^\circ\text{C}$ . While stirred at 700 rpm, solution 2 was added within 3 s. During bleach addition, temperature rises up to ca.  $10^\circ\text{C}$ . For determination of the reaction progress the mixture was quenched after 3, 6, 15, and 30 s, respectively, by flushing the reaction vessel with a 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  solution, which was previously cooled down to approximately  $0^\circ\text{C}$ .

After reaction, the organic phase containing both starting material (2-butoxyethanol) and product (2-butoxyacetaldehyde) was analyzed by  $^1\text{H}$  NMR using naphthalene as an internal standard. 2-Butoxyacetic acid which remains in the aqueous phase as sodium or potassium salt was not further considered for analysis.

### 3. Results and discussion

A comparison of the experimental results obtained in the first continuous microreactor setup with those from the batch experiments is shown in Fig. 6. The results indicate that product formation was obtained more slowly in the microreaction setup than in the batch process. In the continuous process 50% conversion was achieved after approximately 8 s at flow rates between 1 and 8 mL/min compared to ca. 3 s in the batch process. Uncertainties in reaction time of the batch process result from the dosage time of the bleach, which was about 3 s.

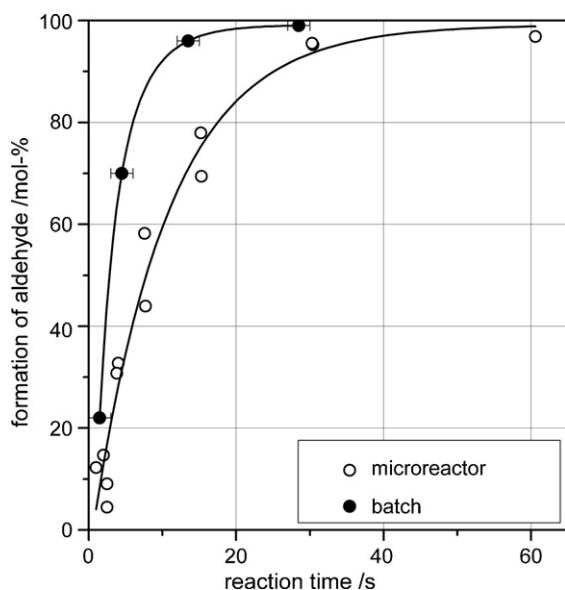


Fig. 6. Formation of aldehyde with reaction time for the first microreaction setup at flow rates between 1 and 8 mL/min and for the batch experiments. Error bars in the batch process arise from uncertainties caused by the dosing period of bleach (3 s).

A more detailed analysis of the microreactor experiments showed that the observed deviations of the course of aldehyde formation are mainly caused by the flow rate variations.

A visual inspection of the flow pattern in the PTFE capillary that was used as a residence time shows that at low flow rates (1 mL/min) a well-defined segmented plug-flow occurs [11] (Fig. 7). Since mass transport between the two phases is necessary, the macroscopic reaction rate is limited by the size of the interface. Moreover, internal circulations within one phase are necessary for a fast transport of the reactants to the interface [12]. The higher reaction rate in the batch process indicates that these transport processes are slower in the first microreactor experiments.

However, by increasing the flow from 1 to 2 mL/min the observed plugs in the capillary become unsteady and at 4 mL/min the segmented plug-flow passes into a churn flow

[13] showing cloudy and thus larger interfaces that accelerate the reaction to a certain degree (Fig. 7).

Generally, the retardation of aldehyde formation observed in the first microreaction setup is a potential drawback for the entire process. The retardation may cause an increase of the undesired 2-butoxyacetic acid and therefore diminishes the aldehyde yield. In order to obtain a more detailed understanding of the influence of the total flow and hold-up on the rate of aldehyde formation the new and more versatile monolithic microreactor was integrated into the process setup.

In this microreactor, a variation of the reaction volume by switching the valve allows investigating the course of aldehyde formation at different residence times under constant flow conditions. Moreover, by changing flow rates and with it pressure drops, different energy inputs for mixing and also different residence times can be realized in combination with different reaction channel hold-ups.

Fig. 8 shows the formation of aldehyde at the four different outlets of the monolithic microreactor at various flow rates. As expected, switching from outlet 1 to outlet 4 provides increased aldehyde formation due to longer reaction channels and thus longer reaction times. Once the flow is increased the aldehyde formation decreases again at a certain outlet due to reduced residence and reaction time. However, by using outlet 4 which provides the largest internal volume of 1.15 mL, the formation of aldehyde remains nearly constant since reaction is already finished even at higher flow rates (10 mL/min). At outlet 3 (0.84 mL internal volume), outlet 2 (0.52 mL internal volume), and to a minor extent at outlet 1 a minimum in aldehyde formation is observed in each case showing clearly the two contrary effects that influence the amount of aldehyde formed. An increase in total flow leads on the one hand to a reduced residence and reaction time, but on the other hand it provides an increase in pressure drop and in mixing energy introduced into the microreaction system [14]. As a consequence, better mixing and thus improved conversion and selectivity is achieved.

For example, at outlet 2 the highest formation of aldehyde of 79% was obtained for the highest flow rate despite of a short reaction time  $t_R$  of approximately 3 s. A decrease of the flow rate results in a drastic decrease of mixing quality, which leads to a

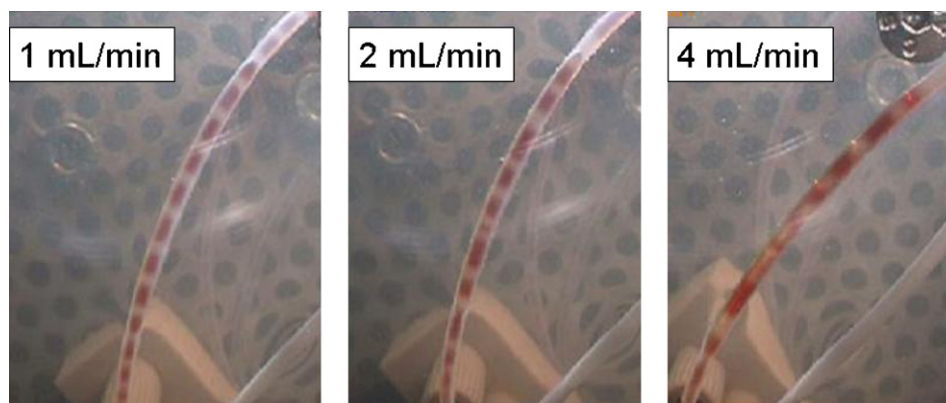


Fig. 7. Flow pattern in the residence time unit (PTFE capillary) at different flow rates (the dark phase is the  $\text{CH}_2\text{Cl}_2$  phase with alcohol and aldehyde, the transparent phase contains aqueous NaOCl). At low flow rates a segmented plug flow (Taylor flow) can be observed. With increasing flow the interfaces become blurred.

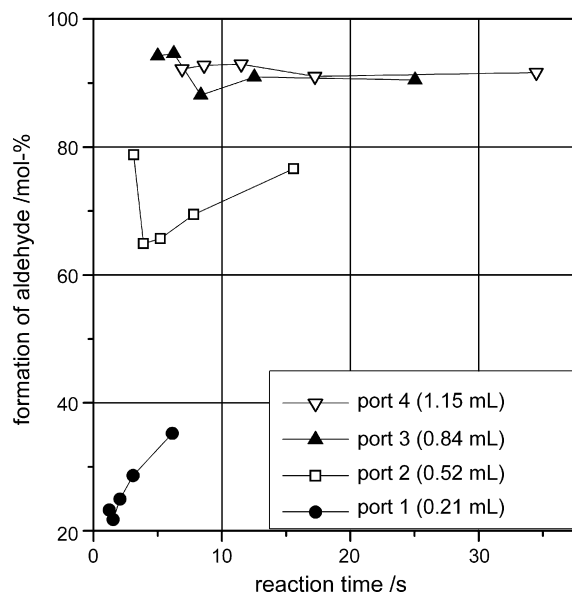


Fig. 8. Time-resolved course of aldehyde formation at different reaction times adjusted by different flow rates (applied flow rates for each curve were 2, 4, 6, 8, and 10 mL/min, respectively). The internal volume of the microreactor is varied by directing the reaction mixture to different outlet ports 1–4.

strong reduction of aldehyde formation down to 65% ( $t_R \approx 4$  s). A further increase of reaction time due to lower flow rates leads then again to a slight rise of aldehyde formation ( $t_R \approx 5$  s: 66%;  $t_R \approx 8$  s: 69%,  $t_R \approx 16$  s: 77%).

Obviously, the two factors “residence time” and “mixing quality” determine the conversion at a certain point of the oxidation reaction. Since changes in flow rate always affect both factors, a process optimum can be only achieved in accordance with the microreactor design and its internal hold-up.

For a better estimation of the course of aldehyde formation it is helpful to keep one of the two factors in the experimental series constant. By varying reactor hold-up at a constant flow rate it is possible to keep the mixing quality for the two-phase system approximately constant. Fig. 9 reveals the influence of the mixing quality on the formation of aldehyde. The enhanced mixing quality is a result of an increased pressure drop. The pressure drop range was between 0.22 bar (port 1, 4 mL/min), and 3 bar (port 4, 10 mL/min).

The time-resolved course of reaction at constant flow rate indicates very coherent changes in formation of aldehyde. The dependence of these changes on mixing quality becomes clear by looking at the trends for different flow rates. By increasing the flow rate from 4 to 10 mL/min, the half-life of reaction can be shifted from approximately 5–2 s. The strong changes of the reaction rates when flow rate is increased from 8 to 10 mL/min reveals that an additional improvement of mass transport due to higher mixing quality results in a further increase of reaction rate. This means that even at the maximum flow rate investigated in this study the kinetics is still restricted by macroscopic reaction parameters. It is very likely that the intrinsic micro-kinetics (i.e., molecular kinetics) is even faster.

In comparison with the batch process a significant acceleration of the aldehyde formation can be achieved at flow rates of

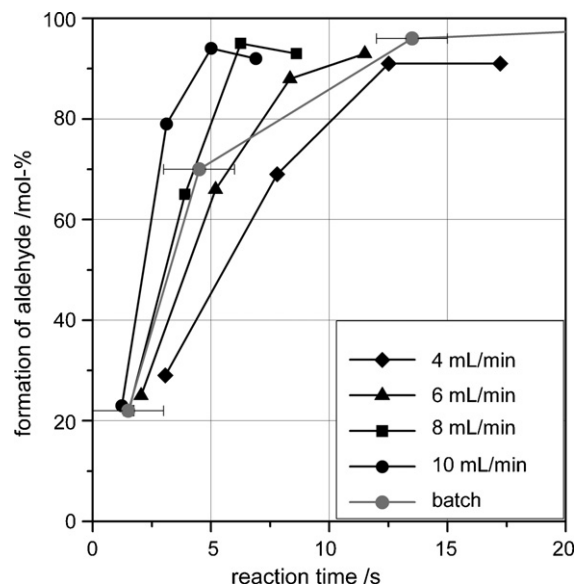


Fig. 9. Time-resolved course of aldehyde formation at different reaction times obtained by changing the internal reactor volume at different flow rates (error bars in the batch process arise from uncertainties caused by the bleach dosing time of 3 s).

8 mL/min and higher in the microreaction process. Whereas the initial slope of aldehyde formation is quite comparable in both processes the maximum amount of aldehyde is obtained significantly faster in the microreaction process. For example, the microreaction process provides 94% aldehyde after 5 s which is up to 15% more than in the batch process at the same time where approximately 10 s are needed to achieve the same amount of aldehyde.

However, the maximum formation achieved in the microreaction unit (95%, 8 mL/min and 6 s at outlet 3) is lower than that in the batch reactor (99%, 28.5 s). This fact is attributed to macroscopic flow inhomogeneities, caused by the pumps during the switching from one syringe to the other. An abrupt reduction of the existing pressure drop results in a backflow to the inlets. This changes the adjusted and necessary stoichiometry for a short time and that way reduces formation of aldehyde. This undesired effect increases with higher pressure drops. Hence, the formation even decreases at outlet 4 compared to outlet 3 for a flow rate of 8 mL/min (from 94 mol% at 5 s to 92 mol% at 6.9 s) and 10 mL/min (from 95 mol% at 6.3 s to 93 mol% at 8.6 s).

Nevertheless, the very fast formation of aldehyde is required to suppress the undesired reaction to 2-butoxyacetic acid [9]. In addition to that, a significant optimization of conversion is expected for the catalyzed bleach oxidation process as soon as pulsation-free pumps avoid macroscopic inhomogeneities within the microreaction unit.

#### 4. Conclusions

A new monolithic microreactor was developed that provides permanent mixing along the entire microreaction channel while it allows the variation of the internal microreactor volume.

The microreactor was successfully used for the analysis of the course of reaction of the homogeneously catalyzed oxidation of 2-butoxyethanol to 2-butoxyacetaldehyde. A systematic variation of internal reactor volume and flow rate of the reactants showed clearly the combined influence of available residence time and mixing quality on the rate of aldehyde formation.

Moreover, the reaction kinetics of this two-phase reaction system could be additionally enhanced by passive mixing structures inside of the microreaction channels. Such continuous passive mixing prevents the coagulation of an unstable emulsion and helps to avoid the formation of depletion zones between the two phases.

Finally, a process optimization was achieved on basis of an appropriate combination of reactor hold-up and flow rate that provides a significantly accelerated aldehyde formation in comparison to batch processes.

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