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Effect of segmented fluid flow, sonication and phase transfer catalysis on biphasic reactions in capillary microreactors

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Abstract

The contact between immiscible liquids in a microfluidic system creating segmented flow offers great potential in the study of biphasic reactions in organic chemistry with significant advantages with respect to conventional flask techniques.

For a simple biphasic hydrolysis, we show that the application of various reaction conditions in microreactors using segmented flow can dramatically increase the reaction rate, especially when sonication and phase transfer catalysis are combined with segmentation.

Keywords: Microreactors; Phase transfer catalysis; Segmented flow; Sonochemistry

1. Introduction

Microreaction technology can offer significant advantages in chemical synthesis over existing conventional techniques. In reactions involving liquids a high surface-to-volume ratio can be easily achieved in microreactor systems. This offers a fast and efficient heat and mass transfer which can lead, together with short diffusion distances, to increased reaction rates. As a result, there is a growing interest in microreactor applications in organic chemistry [1].

In fluidic biphasic systems, an efficient mixing between the two immiscible phases is a challenge because of the interfacial tension caused by differences in the physical properties of both phases. Reactions in such systems can either occur at the interface or in one of the phases in which one reactant must be transferred from one phase into the other [2].

Depending on the microchannel's geometry and material as well as the physical properties of solvents along with other parameters, the contact between two immiscible liquids can create different flow patterns. The most common form of biphasic flow pattern is known as *parallel flow* in which the respective fluid phases align side-by-side as shown in Fig. 2. Another biphasic form, known as *segmented flow*, is a flow system characterized by a series of regular liquid segments of one phase separated by the segments of the other phase. High interfacial tension between the phases and a T-shaped geometry of the inlet junction is required to cause the segmented flow as shown in Fig. 1. Once these fluid segments are formed, an internal fluid vortex is generated because of the interaction of the liquid with the channel wall, causing rapid mixing within each segment while continuously refreshing the interface. In the last few years, an increasing interest has emerged in the utilization of multiphase flow microreactors for the development of chemical systems, especially when it comes to segmented flow [3].

2. Results and discussion

Following on previous results, we now report new results to further increase the rate of hydrolysis of *p*-nitrophenyl acetate in the microreactor under a variety of new conditions. We investigated the hydrolysis of *p*-nitrophenyl acetate **1** in toluene with 0.5 M aqueous sodium hydroxide as a biphasic system [4]. Under these conditions, the hydrolysis of *p*-nitrophenyl acetate involves a nucleophilic attack by the hydroxide at the carbonyl carbon atom to displace the *p*-nitrophenyl moiety. Once the acetate is hydrolysed, the *p*-nitrophenolate **2** transfers into the aqueous phase resulting in a colour change from colourless to yellow. The reaction progress was monitored by the UV–vis absorption of phenolate **2** at $\lambda_{max} = 400$ nm in the aqueous layer.

This is a fast reaction and the rate is controlled by diffusion. Thus, the mass transfer can be enhanced through segmentation

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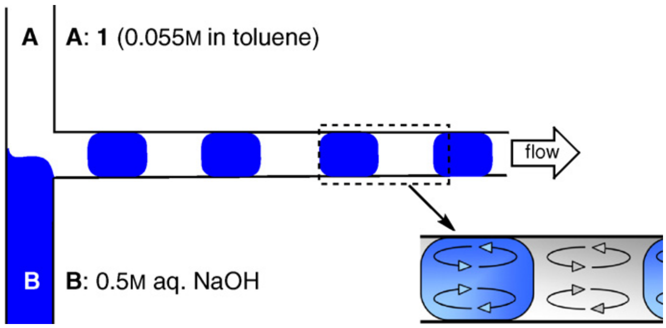
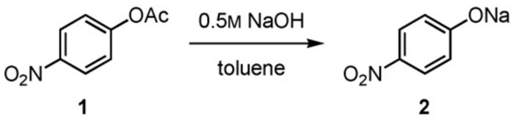


Fig. 1. Hydrolysis of *p*-nitrophenyl acetate **1** using segmented flow with T-inlet junction.



Scheme 1. Hydrolysis of *p*-nitrophenyl acetate **1**.

by providing a large specific interfacial area and small molecular diffusion distance. In addition, by changing parameters such as temperature, sonication, and phase transfer catalysis (PTC), the rate of reaction can be enhanced (Scheme 1).

Initially, we conducted a comparison studies between parallel and segmented flow in the microreactor to investigate the effect of increasing the mass-transfer rate with and without the internal vortex mixing caused by the segmented flow. In order to generate segmented flow within a microchannel, a T-inlet junction was used (dimensions of both inlet tubes and reaction channel are identical) as described previously [4] and is schematically shown in Fig. 1. For the creation of parallel flow (Fig. 2) we had to consider, as for segmented flow, the properties of the solvents used and the geometry of the microreactor inlet. To generate parallel flow, using toluene and water as the solvent system was extremely difficult due to the high interfacial forces. To weaken such forces, a mixture of 1:1 toluene and acetonitrile as the organic solvent was used. Furthermore, a combination of high flow rates and straight microchannel design with a V-inlet junction having an angle of the inlet tubes of about 61°, in which the width of the microchannel doubles after the V-inlet junction, were required in order to give the most stable flow. The solubility of water in toluene (and vice versa) is very low (0.03–0.05%), but the partial miscibility between the organic (toluene:acetonitrile) and aqueous phase means a better mass transfer and therefore a faster reaction rate. In addition, the presence of dissolved sodium hydroxide in the aqueous phase affects the solvent–solvent interactions, which means the solubility of water in the acetonitrile:toluene organic phase is lower than usual.

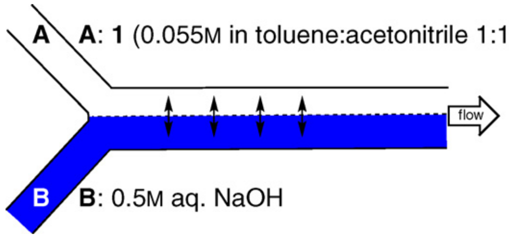


Fig. 2. Hydrolysis of *p*-nitrophenyl acetate **1** using parallel flow with V-inlet junction.

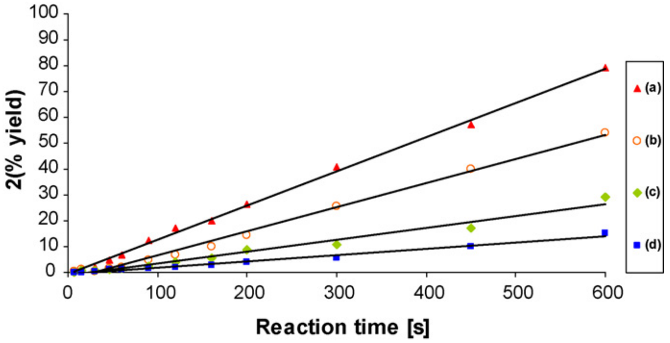


Fig. 3. Hydrolysis of **1** with aqueous NaOH and different organic phases in a flask at 20 °C: (a) hydrolysis reaction in acetonitrile:toluene (1:1) with stirring; (b) hydrolysis reaction in toluene with stirring; (c) hydrolysis reaction in acetonitrile:toluene (1:1) without stirring; (d) hydrolysis reaction in toluene without stirring.

Flask reactions using toluene, or toluene:acetonitrile as the organic solvent were conducted and, as expected, an increase in the reaction rate is seen when the mixture of toluene:acetonitrile as organic phase was used with stirring (Fig. 3). However, when making the same comparison in a microreactor (Fig. 4), the contrary was observed in reactions (a) and (b). The use of toluene as the organic phase (a) was superior to toluene:acetonitrile (b), but different flow regimes were operating here. Clearly, the effect of segmentation is stronger than the parallel flow even when the interfacial tension is weaker, because of the formation of higher interfacial area and the internal vortex mixing. The comparison in a flask would be between the reaction with stirring using toluene (b) and reaction (c) without stirring using acetonitrile:toluene (Fig. 3).

We have shown the effect of segmented flow on a biphasic system and its advantage in improving ester hydrolysis. By combining the segmented flow technique with other methods used in conventional bench chemistry to enhance the diffusion rate of the biphasic reaction system, we were able to further increase the reaction rate. We have investigated the effect of phase transfer catalysis and sonochemistry in the hydrolysis of **1** under segmented flow conditions and these results are shown in Fig. 5.

Phase transfer catalysis is a common approach used to accelerate a biphasic reaction by ensuring a ready supply of necessary reagent to the phase in which the reaction occurs [5]. When 10 mol% tetrabutylammonium hydrogen sulfate (Bu_4NHSO_4) was used as the phase transfer catalyst (PTC) at 20 °C under segmented flow conditions (d), an increase in the reaction rate was observed compared to a reaction under segmented flow conditions without phase transfer catalyst (e).

We already have reported on the effect of microwave irradiation on segmented flow [4], here we investigate now the enhancement by sonication. Ultrasound irradiation is a transmission of a sound wave through a medium and is considered as a form of energy for the excitation of reactants hence increasing the rate of diffusion [6]. In the sonochemical technique, the microchannel tubing was immersed in the ultrasound bath [7]

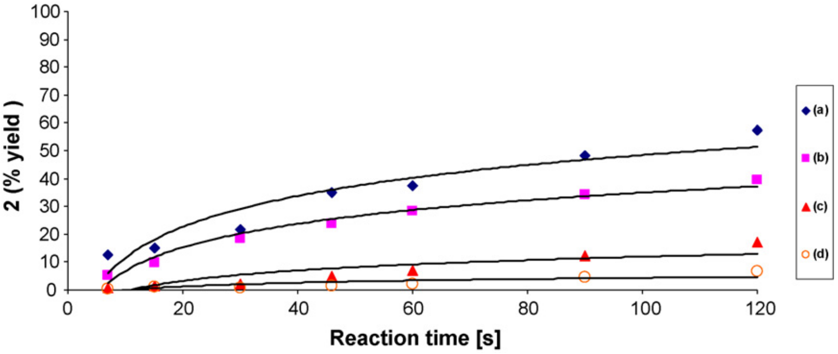


Fig. 4. Hydrolysis of **1** in a PMMA microreactor at 20 °C: (a) segmented flow (organic phase: toluene); (b) parallel flow (organic phase: acetonitrile:toluene, 1:1); (c) hydrolysis reaction in a flask with stirring (organic phase: acetonitrile:toluene, 1:1); (d) hydrolysis reaction in a flask with stirring (organic phase: toluene). Trend line equation and R^2 values: (a) $y = 16.026 \ln(x) - 25.363$, $R^2 = 0.9078$; (b) $y = 12.214 \ln(x) - 21.316$, $R^2 = 0.9743$; (c) $y = 5.362 \ln(x) - 12.813$, $R^2 = 0.7684$; (d) $y = 1.912 \ln(x) - 4.4663$, $R^2 = 0.6754$.

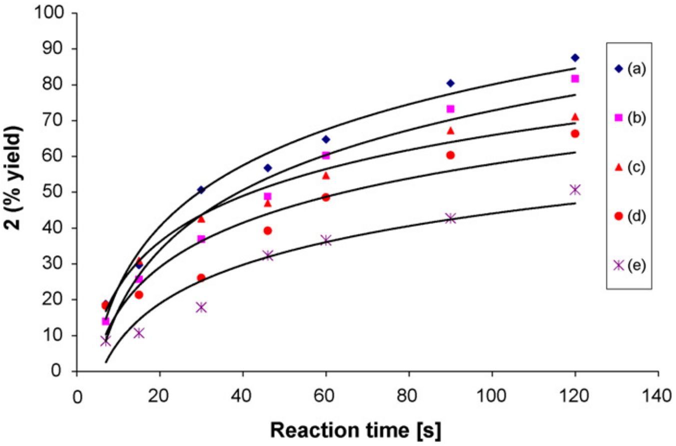


Fig. 5. Hydrolysis of **1** in polytetrafluoroethylene (PTFE) tubing (300 μm diameter microchannel, 400 mm length) using segmented flow conditions (organic phase: toluene): (a) 10 mol% Bu_4NHSO_4 and sonication; (b) sonication; (c) microwave irradiation at 50 °C; (d) 10 mol% Bu_4NHSO_4 at 20 °C; (e) 20 °C. Trend line equation and R^2 values: (a) $y = 24.618 \ln(x) - 33.32$, $R^2 = 0.9803$; (b) $y = 24.184 \ln(x) - 38.617$, $R^2 = 0.964$; (c) $y = 18.477 \ln(x) - 19.173$, $R^2 = 0.9796$; (d) $y = 17.876 \ln(x) - 24.463$, $R^2 = 0.8882$; (e) $y = 15.62 \ln(x) - 27.864$, $R^2 = 0.9257$.

during the reaction time [8]. As a reasonable amount of heat is generated during sonication, the temperature of the sonicating bath was maintained constant at 25 °C during the reaction.

When sonication was used under segmented flow in microreactors, a higher conversion rate was observed in reaction (b) than in reactions (c), (d) and (e). During sonication, irregular sized segments (1–10 mm length) are formed together with some emulsions. Increasing the interfacial area during sonication with the help of segmentation led to an enhancement of the reaction rate. This indicates that the reaction rate is now controlled by diffusion. Further increase of the rate of hydrolysis of **1** was obtained (a) when sonication, phase transfer catalyst and segmentation methods were all combined together.

3. Conclusion

In conclusion, by utilizing the large specific interfacial area provided by the microreactor under segmented flow, the hydrolysis reaction of *p*-nitrophenyl acetate **1** was found to be much more efficient than parallel flow and flask method.

The combination of sonochemistry and segmented flow was found to enhance the rate more than just segmented flow and phase transfer catalyst combined. Further enhancement was obtained when segmented flow was combined with both, sonochemistry and phase transfer catalysis.

4. Experimental

- General method for the biphasic parallel flow using V-inlet junction (width 150 μm and depth 300 μm)/segmented flow using T-inlet junction (width 300 μm and depth 300 μm) hydrolysis of *p*-nitrophenyl acetate **1** in a PMMA microreactor at 20 °C (microchannel: 300 μm × 300 μm, 400 mm): a solution of *p*-nitrophenyl acetate **1** in a 1:1 mixture of toluene and acetonitrile (10 ml, 0.05 M) was loaded into syringe A and an aqueous solution of sodium hydroxide (10 ml, 0.5 M) loaded in syringe B. Syringes A and B were attached to a syringe pump (KD Scientific) and connected to the microreactor housing through PEEK tubing. The reagents were delivered in controlled flow rates. The reaction mixture was collected and analysed quantitatively.
- General method for the biphasic hydrolysis of *p*-nitrophenyl acetate **1** in PTFE tubing at 20 °C (300 μm diameter, 400 mm length): a solution of *p*-nitrophenyl acetate **1** in toluene (10 ml, 0.05 M) was loaded in syringe A and aqueous solution of sodium hydroxide (10 ml, 0.5 M) loaded in syringe B. Syringes A and B were attached to a syringe pump (KD Scientific) and connected to the PTFE tubing through PEEK tubing using a KEL-F Tee connector with 0.25 mm bore (Supelco), for use of tubing with ID (1/16) in. The reagents were delivered in controlled flow rates. The reaction mixture was collected and analysed quantitatively.
- General method for the biphasic hydrolysis of *p*-nitrophenyl acetate **1** in PTFE tubing (300 μm diameter, 400 mm length) at 20 °C using a phase transfer catalyst: similar to the general procedure for the hydrolysis reaction at 20 °C in PTFE tubing except that tetrabutylammonium hydrogen sulfate (10 mol%) was dissolved together with **1**.

- General method for the biphasic hydrolysis of *p*-nitrophenyl acetate **1** in PTFE tubing (300 μm diameter, 400 mm length) at 20 °C using sonication: similar to the general procedure for the hydrolysis reaction at 20 °C in PTFE tubing except that the tubing was immersed in sonication bath (water) and sonicated at 20 °C.
- General method for the biphasic hydrolysis of *p*-nitrophenyl acetate **1** in PTFE tubing (300 μm diameter, 400 mm length) at 50 °C using a microwave: similar to the general procedure for the hydrolysis reaction at 20 °C in PTFE tubing except that the tubing was irradiated with a focused microwave (CEM) at 50 °C (50 W).

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