Biphasic reactions in microreactors

B. Ahmed-Omer\textsuperscript{a,b}, D. Barrow\textsuperscript{b}, T. Wirth\textsuperscript{a}

\textsuperscript{a} Cardiff School of Chemistry, Cardiff University, Cardiff, CF10 3AT, UK
\textsuperscript{b} Laboratory for Applied Microsystems, Cardiff School of Engineering, Cardiff University, Cardiff, CF24 3TF, UK

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. As organic solvents play a key role in many chemical processes within the pharmaceutical and chemical industry, there are many applications of biphasic reactions in different areas of chemistry. For a simple biphasic reactions, we show that the application of various reaction conditions in microreactors using segmented flow can dramatically increase the reaction rate, especially when microwave irradiation, sonication or phase transfer catalysis are combined with segmentation.

Keywords: microreactors, phase transfer catalysis, segmented flow

1. Introduction

The miniaturisation of chemical processes using chip-based microreactors can exhibit significant advantages over existing conventional techniques. The properties and reaction conditions in such microreactors are different to large-scale systems. A high surface-to-volume ratio, short diffusion distances, fast and efficient heat dissipation and mass transfer enable novel and diverse applications.\textsuperscript{[1]} These properties have been advantageously used in organic synthesis.\textsuperscript{[2]}

2. Results and Discussion

A microchip system applied in synthetic chemistry usually consists of an arrangement of microstructures such as capillary scale ducts, sensors and actuators. A combination of such microcomponents and a chip-to-world interface of fluidic, electrical, optical and other interconnects may form a microreactor which can be fabricated in different geometries and from a variety of materials. The majority of chemical reactions in solution carried out in microreactors involve homogeneous reactions at room temperature. Recently, an interest in applying microreactors utilizing multiphase flow (gas/liquid or liquid/liquid biphasic systems) has emerged.\textsuperscript{[3]} In a microchannel, the contact interface between immiscible liquids can follow various flow patterns, due to the forces at the interface generated from the different physical properties of both phases such as viscosity and surface tension. The most common mode of multiphase interface is known as parallel flow in which the respective fluid phases align side-by-side and mixing between them occurs principally via diffusion. Another multiphase mode, segmented flow, can be created in a microchannel when two (or more) fluid phases form serial trains of fluid packets, each phase being separated by the other. Once these fluid packets or segments are formed, an internal fluid vortex is generated which causes rapid mixing within a given segment by continuously refreshing the diffusion interface as shown in Figure 1. The area of this interface is approximately proportional to the cross-sectional area of the microchannel. The cross-section must be smaller than the length of the segments, otherwise emulsions are formed.\textsuperscript{[4]} Furthermore, the constructional material of the microchannel plays a significant role in the formation of segments and influences their shape due to the effects of interfacial tension and surface energies.\textsuperscript{[5]} The comparison of microreactors with conventional processing has become of interest recently\textsuperscript{[6]} as exploitation of their industrial usage is increasing.

![Figure 1. Schematic representation of segmented flow in a microchannel: Rapid mixing within a given fluid segment is caused by the internal vortex fluid flow; mass transfer between contiguous fluid segments is enabled by the continuously refreshing interface.](image)

We investigated the hydrolysis of \( p \)-nitrophenyl acetate \( 1 \) in toluene with 0.5 M aqueous sodium hydroxide as a biphasic system.\textsuperscript{[7]} 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 \( \lambda_{\text{max}} = 400 \) nm in the aqueous layer.

![Scheme 1. Hydrolysis of \( p \)-nitrophenyl acetate \( 1 \).](image)
The yield of the reaction is dependent upon reaction time which is inversely proportional to the flow rate. Additionally, the size of the segments will also have an effect on the reaction rate as the ratio of volume: interfacial area increases with increasing size of the segments.

Figure 2. Hydrolysis of 1 using different flow types and reaction times: (a) Short segmented flow (approx. 2 mm) under microwave irradiation at 50 ºC; (b) Long segmented flow (approx. 10 mm) under microwave irradiation at 50 ºC; (c) Segmented flow in PTFE tubing heated in an oil bath at 50 ºC; (d) Segmented flow at room temperature in PMMA reactor; (e) Segmented flow at room temperature in PTFE tubing; (f) Hydrolysis reaction at 50 ºC in flask with stirring; (g) Hydrolysis reaction at room temperature in flask with stirring.

A solution of substrate 1 in toluene (0.05 m) and an aqueous solution of sodium hydroxide (0.5 m) were passed through the two inlets of the micro-reactor or into T-junction of PTFE tubes using a dual syringe pump.

The hydrolysis of p-nitrophenyl acetate 1 was carried out under different reaction conditions in different reactors. It is possible to deduce a number of trends from the results shown in Figure 2. A comparison of the results of reactions labelled (f) and (g) in Figure 2 with the other results is obvious. The reaction rate of the hydrolysis using a conventional flask is much lower than using microreactors and the difference between hydrolysis at room temperature (g) and at 50 ºC (h) is not significant at that timescale.

Reactions labelled (d) and (e) were both carried out under similar reaction conditions, but in different reactors. These results show that the reaction in the PMMA (polymethyl methacrylate) microreactor (d) performs slightly better than in the PTFE tubing (e). The better performance in the PMMA microreactor is probably due to the visually slightly shorter segments and their higher regularity. The different T-junctions for creating the segmented flow might also play a role. As the PMMA microreactor with its metal housing cannot be inserted in the microwave, the experiments at elevated temperature (a, b, c) have been performed using PTFE tubing.

An increase of the reaction rate by heating can be seen by comparison of (e) and (c). A further increase is observed by microwave irradiation of the microreactor in a water bath (b) instead of heating with a conventional oil bath (c). By microwave irradiation of the microreactor without a surrounding fluid, insufficient energy is absorbed to cause significant heating. This is due to the low loss microwave materials (PMMA, PTFE) used in construction and the low absorption characteristics of the fluidic duct geometry. Those are known properties and microwave heating of microreactors with outside deposition of gold metal to increase microwave absorbance are known. Macro scale flow reactors suitable for microwave irradiation have also recently been reported.

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 Figure 3.

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. When 10 mol% tetrabutylammonium hydrogen sulfate (Bu4NHSO4) was used as the phase transfer catalyst (PTC) at room temperature 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).

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. In the sonochemical technique, the microchannel tubing was immersed in the ultrasonic bath during the reaction time. As a reasonable amount of heat is generated during sonication, the temperature of the sonicating bath was maintained constant at 25 ºC 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. Conclusions

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 microwave irradiation, 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.

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References


