


carbohydrates. With the particles adsorbed onto the liquid–liquid interface, water-in-oil (w/o) or oil-in-water (o/w) emulsions are formed, depending on the solid’s affinity for one of the two phases. In Pickering emulsions (PEs), emulsions stabilized by solid particles, significant research has been directed towards developing an approach for flow PE (FPE) catalysis, further expanding the possibilities for catalysis beyond standard batch PE reactions. This microreactor allowed for the inline analysis of the catalytic process with in situ Raman spectroscopy, as demonstrated for the acid-catalyzed deacetalization of benzaldehyde dimethyl acetal to form benzaldehyde. Furthermore, the use of the FPE system showed a ninefold improvement in yield compared to the simple biphasic flow system (FBS), highlighting the advantage of emulsification. Finally, FPE allowed an antagonistic set of reactions, the deacetalization–Knoevenagel condensation, which proved less efficient in FBS due to rapid acid-base quenching. The droplet microfluidic system thus offers a versatile new extension of PE catalysis.

Biphasic catalysis has shown to be a great tool for efficient chemical transformations, for example, enabling facile product separation[1,2] and extraction of reactive species to reduce side product formation.[3] A major drawback of classical biphasic systems, however, is the low interfacial area between the two phases. Increasing the interfacial area, and thus reactivity and extraction,[4,5] of a biphasic system can be accomplished by adding emulsifying agents, such as surfactants or amphiphilic solid particles. Emulsions stabilized by the latter are called Pickering emulsions (PEs). With the particles adsorbed onto the liquid–liquid interface, water-in-oil (w/o) or oil-in-water (o/w) emulsions are formed, depending on the solid’s affinity for one of the two phases. While with surfactant-stabilized emulsions, surfactants recovery and phase separation is difficult, with PEs this can be easily done. PEs can therefore be considered reversible reaction media. Such de-emulsification can be achieved by centrifugation or, when responsive particles are used, changing the pH[8] or applying a magnetic field.[9]

Previous research has mainly focused on the formation and stability of PEs[10–12] to replace surfactant-stabilized emulsions for pharmaceutical and cosmetic applications.[13] More recently, the use of batch PEs as reaction media for catalysis[14–16] has drawn attention, an approach that comes with considerable potential but also with experimental challenges. Batch PEs are prepared by vigorous stirring and as a result show broad droplet size distributions, making it difficult to measure kinetics, for example. Furthermore, the opacity and intimate phase mixing in batch PE make in situ investigations impossible, with analysis necessitating sampling, de-emulsification and further work-up.

To deal with these analytical complexities and to make a more industrially relevant reaction system, continuous flow (w/o) PEs were developed by Yang et al. as liquid equivalent of a packed bed reactor.[17] In this system, the flow is determined by gravity and droplet size, which is not trivial to control with the PE being prepared by vigorous stirring. Analysis of reaction products was done ex-situ by collection of the oil phase at the end of the reactor, leaving little room for changing parameters or measuring kinetics during reaction. While reaction kinetics could possibly be measured spectroscopically at different column heights, this is generally impossible to measure in a PE using spectroscopy due to scattering at the solid particles and droplet surface. The use of a continuous flow droplet microreactor could overcome this challenge. In addition, droplet microfluidics provide a way to gain control over the droplet size, for example, to create a more homogeneous system.[18]

The rapidly growing microfluidics field uses small channel systems in the micrometer range that allow for increased temperature control, homogeneity of the droplets and enhanced mixing due to convective flow in- and outside the droplets. Droplets in a microchannel are more stable compared to bulk biphasic systems and can exist without the use of surfactants due to regular spacing, but surfactants still improve stability and prevent droplet coalescence when two droplets do collide. Solids have been used less as stabilizing agents in microfluidics...
and most reported examples focus solely on stability or applicability for the food and biomedical industry. One of the difficulties in preparing in-flow PEs is the lack of shear, causing particle adsorption at the interface to be very slow requiring sufficient time to fully cover the droplets with particles before they encounter each other. 

Here, we developed, as outlined in Figure 1, a tube-in-tube co-flow microreactor for the production of droplets to prepare FPEs. The use of hydrophobic FEP outer tubing with hydrophilic fused silica inner tubing led to the formation of w/o droplets, as schematically shown in the Supporting Information (Figure S1). The chemically resistant and optically transparent polymer tubing allows for observation of the formation and stability of droplets over the whole tubing, enabling in situ Raman spectroscopy. By measuring spectra at different positions in the flow channel, the reaction mixture can be monitored at various reaction times for kinetic profiling of reactants and products. The reaction time can be easily controlled by changing the total flow rate or the tube length. Furthermore, the advantage of automatic phase separation after the tubing’s outlet simplifies post-analysis of both phases.

This microreactor was used to demonstrate the advantage of Pickering stabilized droplets over non-stabilized droplets for biphasic flow catalysis, using the acid–base catalyzed deacetalization–Knoevenagel condensation of benzaldehyde dimethyl acetal as probe reaction. We previously showed PEs to positively influence this reaction in batch. In this microreactor, the progress of the acid-catalyzed deacetalization reaction, could be followed with in situ Raman spectroscopy, at various temperatures with both stabilized and non-stabilized droplets. Secondly, a positive effect of Pickering stabilization of a microfluidic flow system is shown for the deacetalization–Knoevenagel tandem reaction, now using ex situ GC analysis.

Droplets were created using an acidic, aqueous phase and 4-propylguaiaicol (PG) as oil phase. The w/o droplets formed with a homogeneous size distribution, with and without the addition of solid stabilizing particles. Although addition of silica for PE formation increased the viscosity of the continuous phase, it did not change the droplet size significantly. The spherical droplets were of similar size to the inner diameter of the FEP tubing. However, without solid stabilization droplet coalescence was observed during reaction, possibly due to product formation changing the viscosity. In contrast, the droplets remained stable in the PE system and no coalescence was observed.

The FPE system was uniformly heated by coiling the tubing around a cylindrical heating device. The temperature accuracy of the heating device was tested with luminescence thermometry as described earlier, using Yb-Er doped NaYF₄ particles. The temperature inside the tubing showed a maximum deviation of 2.2 °C from the temperature setpoint (Supporting Information). The flow rates of the continuous organic and dispersed aqueous phase were set at 20 μL min⁻¹ and 5 μL min⁻¹, respectively, leading to a 25 mol% catalyst ratio with respect to the substrate.

The acid-catalyzed deacetalization of the acetal to benzaldehyde was probed inside the tubing with a 532 nm in situ Raman laser; a full spectrum with assignments of the most important peaks is given in the Supporting Information (Figure S2); the silica in the FPE did not influence the Raman measurements. The spectra were taken at different positions in the tubing, each loop equating to approximately 2 min of reaction time (Figure 2a). The first measurement at loop 0, almost directly after droplet formation, corresponds to 5 s of reaction. The Raman spectra as function of position in the tubing and temperature are shown in Figure 2b. In the Raman spectra at 60 and 90 °C, a shoulder originating from benzaldehyde can be observed at the 460 cm⁻¹ peak, growing in concomitantly with the peak at 1700 cm⁻¹.

The kinetic profiles of benzaldehyde formation at all temperatures and with and without silica are shown in Figure 3. At room temperature without any silica present, the reaction pro-

Figure 1. Droplet microfluidic approach for in-flow PE catalysis with 4-propylguaiaicol as continuous phase (CP) and water as dispersed phase (DP). Top inset: The deacetalization reaction can be monitored in situ using Raman spectroscopy. Bottom inset: Scheme of the deacetalization–Knoevenagel reaction inside the tubing, including a depiction of the particles on the droplet surface.
ceeds slowly, yielding only 10% of benzaldehyde after 22 min. Full conversion was reached after \( \approx 18 \) min at a reaction temperature of 60 °C, and after 2 min at 90 °C. Addition of silica had a clear positive effect on the reaction at room temperature and at 60 °C. At room temperature, silica addition resulted in a jump in activity, increasing the yield from 10% in the normal flow biphasic system (FBS) to 90% in the PE after 22 min. At 60 °C full conversion was reached within 2 min, whereas the FBS gave only 10% yield at that time. At 90 °C, the reaction was too fast to measure any differences between the FBS and FPE. A control experiment, with only silica and no HCl, showed no significant benzaldehyde formation, indicating that the higher droplet stability and therefore higher interfacial area in the PE are causing the enhanced reactivity.

The simple microreactor thus enabled a facile real-time analysis of the deacetalization of benzaldehyde dimethyl acetal in FBS and PEs, again demonstrating the advantage of using PEs for biphasic catalysis. The use of in situ Raman spectroscopy eliminates the need for the work-up procedures normally used for batch BS and PEs, offering new analytical opportunities for PE catalysis characterization, for example, access to more accurate kinetic profiles.

The FPE also proved beneficial for antagonistic tandem catalysis in flow, in this case by coupling deacetalization to an additional Knoevenagel condensation. Addition of a base catalyst (2-(1-ethylpropyl)piperidine) and malononitrile as second substrate to the mixture used before, resulted in a slight increase of the viscosity of the organic phase. To retain stable droplets, the flow rates were adjusted to 10 \( \mu \text{L min}^{-1} \) for both the organic and the aqueous phase, resulting in a total reaction time of 34 min. The reaction was executed at 90 °C, as the Knoevenagel condensation is much slower than the deacetalization, with 20 mol% acid and 10 mol% base and analyzed ex situ by GC, as strong malononitrile fluorescence unfortunately precluded in situ Raman spectroscopy in this particular case. In the FBS, benzaldehyde dimethyl acetal conversion was only 34%, yielding 10% and 17% of the intermediate benzaldehyde and the final product benzyldiene malononitrile, respectively (Figure 4). The low conversion and yields were attributed to rapid acid–base quenching in the FBS. The use of an FPE system considerably improved the reaction, giving full conversion of benzaldehyde dimethyl acetal under identical conditions, with 69% benzaldehyde and 25% of final product. The acid-base quenching was slower in this system, attributed to the physical boundary present at the interface between the two phases. The yield of final product is limited in this case by the available short reaction time, dictated by the number of loops that could be coiled around the heating device. Residence time of the reactants in the microchannel can, however, in principle be extended by simply extending the tube length.

In conclusion, we report the first use of a tube-in-tube co-flow microfluidic setup for continuous flow BS and PE reactions. Residence time can simply be tuned by changing the tubing length or the flow rate, a clear benefit of this system.

Figure 2. a) Schematic drawing of the measurement positions, b) CCl\(_4\) peak (460 cm\(^{-1}\)) and benzaldehyde peak (1700 cm\(^{-1}\)) in the Raman spectra at different positions in the tubing at room temperature (1, 2), 60 °C (3, 4) and 90 °C (5, 6) without silica (1, 3, 5) and with 2 wt% silica (2, 4, 6) in the continuous phase monitoring of the deacetalization reaction.

Figure 3. Concentration of benzaldehyde during the acid-catalyzed deacetalization reaction of benzaldehyde dimethyl acetal followed over time by in situ Raman spectroscopy at RT (a), 60 °C (b) and 90 °C (c). Reaction conditions: 1.0 \( \mu \text{M} \) benzaldehyde dimethyl acetal and 0.5 \( \mu \text{M} \) CCl\(_4\) in 4-propylguaiacol (and 2 wt% silica), 0.1 \( \mu \text{M} \) HCl in water, total flow 25 \( \mu \text{L min}^{-1} \).
The transparent tubing enabled reaction monitoring by in situ Raman spectroscopy. The formation of an FPE by silica addition, led to an increase in stability of the w/o droplets, which proved to be beneficial for catalytic performance. The acid-catalyzed decatation reaction performed much better in an FPE than in the FBS, showing a ninefold increase in yield. The higher reactivity of the FPE was attributed to high droplet stability as this is correlated to the high interfacial area which is required for this reaction. The FPE system also showed much improved performance in the antagonistic deacetalization–Knoevenagel condensation tandem reaction, with Pickering stabilization limiting mutual destruction of the acid and base catalyst. The continuous flow microfluidic PE reactor thus proved to be a very versatile system to further the possibilities and understanding of PE catalysis.

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Conflict of interest

The authors declare no conflict of interest.

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