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Flow Processing of Microwave-Assisted (Heterogeneous) Organic Reactions

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Abstract:

A commercially available continuous-flow reactor was adapted to run three organic reactions, e.g. two heterogeneous and one homogeneous mixture under microwave heating. The setup was operated either as a batch-loop reactor for running a biocatalyzed esterification of (*R,S*)-1-phenylethanol with vinyl acetate and the esterification of (*S*)-pyroglutamic acid with *n*-decanol (i.e., Laurydone process) or in a single pass for the aspirin synthesis as a homogeneous mixture. The tubular reactor has been characterized to perform a series of three equally sized, continuously operated stirred tank reactors on average. Although the (operational) costs of the microwave-heated tubular reactor are higher than conventionally heated processes in fine chemical operations, it was demonstrated that the experimental data can be used for process design. Plugging remains an important obstacle to be dealt with. However, benefits with respect to safety and scalability are expected to enable a fair compensation for the costs when implementing this novel technique.

1. Introduction

Today, much effort is being invested in an increasingly competitive world to meet the requirements of the fine chemical and pharmaceutical industry with respect to “first-time-right” performance, a short-time-to-market, and avoidance of surprises during process scale-up. A demand for larger quantities does not imply replacing “mg” with “kg” in the recipe of the chemical process.

Process intensification based on, e.g., microreactor technology and microwave heating is actively pursued to achieve a better position in the industrial scene. Increase of reaction rates and improved selectivity, combined with the automation of repetitive procedures, demonstrate the advantageous application of these enabling techniques. One of the major weaknesses of microwave-assisted chemistry is scaling-up. Since the penetration depth of microwaves is limited, the best chances for increased production volumes lie in relatively small-scale continuous operations, somewhat uncommon in the fine chemical industry.[1−3]

Figure 1. **FlowSynth of Milestone srl, Italy.**

To make microwave heating feasible on a larger scale this technique should perform better than operation with conventional heating. Besides aspects like productivity, selectivity, safety, and the investment costs in equipment, any supplementary costs of applying microwave technology have to be compensated by the added value of improved reaction conditions (e.g., microwave effect)[4] or more effective downstream processing.

In this study we demonstrate that, with our selected setup (utilizing the FlowSynth tubular reactor of Milestone), a proper starting point for direct comparison of microwave with conventional heating has been created, allowing prediction of the potential upscaling of microwave-assisted chemistry in continuous operation. Three chemical reactions were selected to illustrate how much effort and adaptation are required, particularly with heterogeneous systems, to make continuous-flow operations under microwave irradiation conditions viable.

2. Experimental Characterization of the FlowSynth Reactor

Characterization of the flow reactor was necessary to allow a comparison with standardized equipment, especially to clarify the limitations of the flow reactor and to define the operational window. A selection of reactor type and peripheral equipment (for example, type of pump) had to be made on the basis of the specification of the reaction conditions. At the start of our study one type of microwave equipment, i.e. the FlowSynth of Milestone srl, Italy (Figure 1),[5,6] was commercially available that involves a combination of a membrane pump, a tubular reactor, and a microwave oven, all controlled by one computer.

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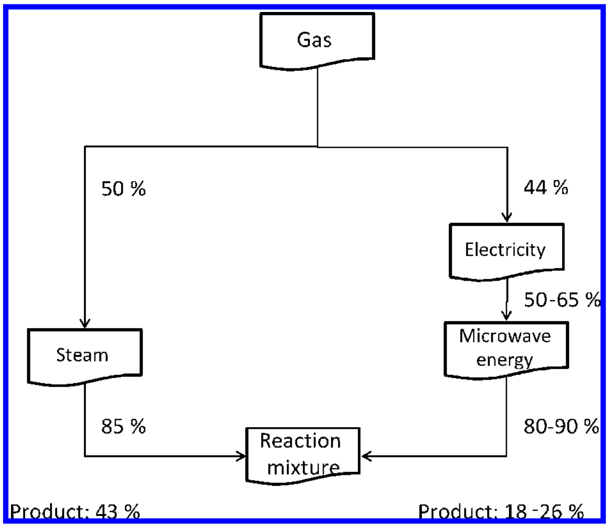

Figure 2. **Energy efficiency of conventional heating (steam) and microwave heating.**[10–13]

The precommercial version of the FlowSynth was described by the group of Ondruschka.[7] This novelty has been patented.[8,9]

Energy efficiencies, operation, the flow and mixing characteristics, and heat transfer were investigated.

2.1. Energy Efficiencies. To make a fair comparison between energy efficiencies of conventional and microwave heating the starting point needs to be identical, being gas as a natural source of energy. Figure 2 illustrates the energy efficiency for each transformation step. Different energy sources (gas or electricity) imply different prices, based on the technology necessary to generate this power.[10−13] In short, microwave heating loses at least 2 times more energy (43% over 22%, see Figure 2) in its fore track, and at the end the energy bill is at least a factor of 8 higher (0.088 € over 0.011 €)[10] compared to condensing steam heating for industrial applications. The efficiency values given in Figure 2 are based on different literature sources and experimental results.[10–13] Altogether, the energy costs for microwave heating will be higher than those for conventional (steam) heating.

The efficiency of the transition from microwave energy to the reaction mixtures is a rather uncertain value, depending on scale, equipment type, and loss tangent. Hoogenboom et al. reported that the losses on small scale are much higher than for larger scales.[14] Predominantly this is due to heat losses to the environment, based on a relatively high surface-to-volume ratio for small equipment. Thermal insulation of the reaction vessel with microwave-transparent material is a simple solution to improve the energy efficiency. Fortunately, a low heat conductivity is also a good material property of polymer materials such as Teflon or PEEK (poly(ether ether ketone)) which are commonly used to construct microwave-heated reactors with a high chemical resistance or high mechanical strength (e.g., for pressure), respectively.

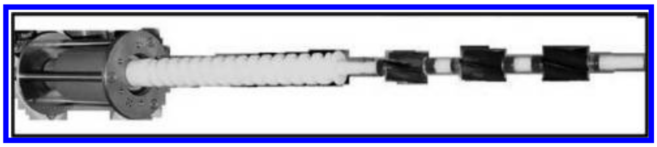

Figure 3. **Stirring shaft with three Weflon[15] blades for the tubular reactor of the FlowSynth.**

The efficiencies of transferring microwave energy into heat were measured in the FlowSynth reactor for three solvents (*p*-xylene, demineralized water, and ethylene glycol) under different conditions. The Milestone FlowSynth was equipped with a typical stirrer shown in Figure 3. The efficiency (η) was defined by the ratio of the thermal energy required to heat up the solvent (see eq 1) and the amount of electromagnetic energy delivered by the microwave oven.

$$\eta = \frac{\phi_m \cdot c_p \cdot (\Delta T)_{\text{observed}}}{\text{microwave power used}}$$

$$\begin{aligned} \phi_m &= \text{mass flow rate } [\text{kg} \cdot \text{s}^{-1}] \\ c_p &= \text{heat capacity } [\text{J} \cdot \text{kg}^{-1} \cdot \text{K}^{-1}] \\ \Delta T &= \text{difference in temperature, outlet} - \text{inlet } [K] \\ \eta &= \text{efficiency } [\%] \end{aligned} \tag{1}$$

The experimental results demonstrate that the absorption of microwaves increases in the order *p*-xylene < water < ethylene glycol.[16] This could be expected from the loss tangents for ethylene glycol, water, and *p*-xylene at 20 °C being 1.35, 0.127, and 0.0011, respectively.[17] Operating in a turbulent flow regime would improve the efficiency. Each solvent appears to have an average maximum of η, which is not influenced by the operational conditions. The error margin of the measured values is in the range of 5−10%.

2.2. Reactor Type. At first sight the reactor in the FlowSynth looks like a tubular reactor, and the presence of stirrers (Figure 3) may induce (additional) residence time distribution. Measurement of the residence time distribution (RTD) allows for characterization of the reactor.[18] The theory of RTD was first proposed by MacMullin and Weber,[19] and worked out in more detail by Danckwerts[20] some years later. A tracer is

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Table 1. **Number of equally sized tanks in series for various flow rates and stirrer speeds in the Milestone FlowSynth**

entry	flow rate ($mL \cdot min^{-1}$)	stirrer speed (rpm)	reactors in series (number)[a]	remark
1	191	0	*3.0*	–
2	191	140	*4.9*	–
3	191	215	*5.3*	–
4	191	285	*2.4*	split peak
5	191	327	*1.8*	shoulder
6	191	380	*2.3*	–
7	214	0	*3.7*	–
8	214	140	*3.6*	split peak
9	214	215	*2.5*	split peak
10	214	327	*4.2*	shoulder
11	232	0	*3.5*	split peak
12	232	140	*3.9*	shoulder
13	232	215	*2.9*	shoulder

[a] n calculated from tracer response curves using eqs 4a–4c.

injected in the reactor feed. Detection of the tracer is performed at the outlet. A pulse or a step injection can be chosen to introduce the tracer. In our setup the response on a tracer pulse has been measured. These measurements give access to the exit-age function $E(t)$ which characterizes RTD. $E(t)$ quantifies the time-dependent fraction of the tracer. Equation 2 shows how $E(t)$ can be calculated from the response of a tracer pulse. The flow rate (ϕ_v) is constant, the concentration $C(t)$ of the tracer is measured, and the exact amount of tracer (N_0) is not directly known. $E(t)$ dt stands for the fraction tracer leaving the system between t and $t + dt$ after the injection. Note that for $t \rightarrow \infty$ all the tracer should have left the reactor, see eq 3.

$$E(t) = \frac{\phi_v . C(t)}{N_0} = \frac{C(t)}{\int_0^\infty C(t)\, dt} \tag{2}$$

$$\int_0^\infty E(t)\, dt = 1 \tag{3}$$

Benzyl alcohol, as tracer in a stream of toluene, has been measured by GC-FID. In this way there is a linear relation between the measured GC-peak area and the actual concentration ($C(t)$). The exit-age function $E(t)$ is used in a one-parameter model for nonideal reactors implying the number of equally sized CSTRs in series (n) which gives the same $E(t)$ as measured for the reactor considered, see eq 4a. The number of tanks (n) is calculated from the dimensionless variance. The variance itself is the square of the standard deviation (σ), and the mean residence time is $\langle\tau\rangle$ see eqs 4b and 4c.[18]

The RTD results are influenced when the reactor setup is operated under different conditions. Table 1 summarizes the number of equally sized tanks and the operational conditions (i.e., flow rates and stirrer speeds) for the Milestone FlowSynth.

$$E(t) = \frac{n^n \cdot t^{n-1} \cdot e^{-n \cdot t/\langle\tau\rangle}}{\langle\tau\rangle^n \cdot (n-1)!} \tag{4a}$$

$$\sigma^2 = \int_0^\infty (t - \langle\tau\rangle)^2 \cdot E(t)\, dt \tag{4b}$$

$$n = \frac{\langle\tau\rangle^2}{\sigma^2} \tag{4c}$$

On average the FlowSynth is equivalent to approximately three equally sized CSTRs in series. If the flow inside the reactor is synchronized with the stirrer speed, the residence time distribution is small. Then, the stirred tubular reactor tends to perform more like a plug-flow reactor.

Any disturbance leads to more axial mixing, which has the tendency to be more equivalent to a continuous stirred-tank reactor (CSTR) for the flowing fluid. The presence of either a shoulder or split-peak points to two or multiple routes which lead to differences in the residence time (see Figure 4). Figure 5 illustrates the theoretically calculated residence time distributions (eq 4a) for a series of equally sized CSTRs with different values of n. Comparing Figures 4 and 5 shows that the residence time distribution in the Milestone FlowSynth is equivalent to that in a series of three equally sized CSTRs.

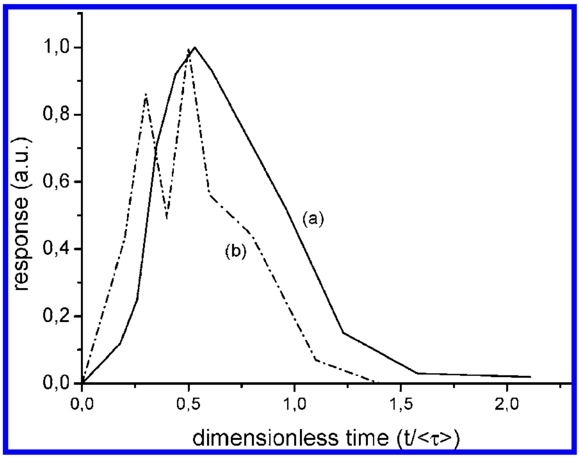


Figure 4. **Plot of response of a pulse injection measured by GC (in arbitrary units) changing in time (dimensionless; $\langle\tau\rangle$ is mean residence time in the whole system) for the FlowSynth with Weflon impeller blades (see Figure 2). (a) Typical plot with small disturbance [Table 1, entry 2]. (b) Large disturbance in tubular reactor leading to enhanced axial mixing [Table 1, entry 8].**

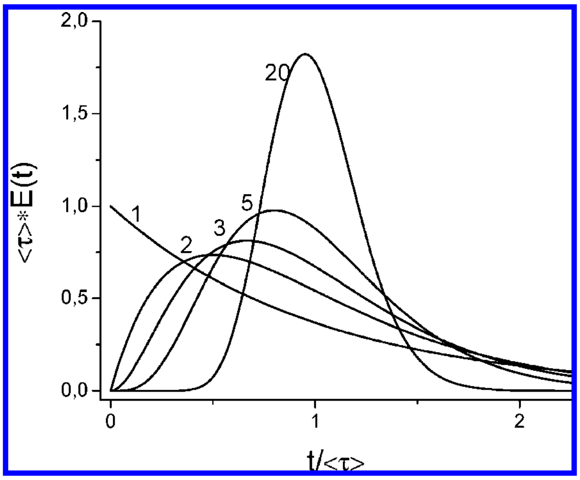


Figure 5. **Theoretically calculated residence time distribution with an increasing number of tanks (n = 1, 2, 3, 5 and 20).[21]**

Table 2. **Mixing regimes**[21]

entry	time constant (t_{reaction})	type of mixing
1	10 min·h	independent of mixing (intrinsic kinetics)
2	s·min	macromixing (i.e., circulation)
3	ms	micromixing (i.e., diffusion)

Table 3. **Relationship between flow rate and Reynolds number**[a] **in the reactor coil at four temperatures**

	flow rate (mL·min^{-1})				
temperature (°C)	53	115	167	214	250
25	31	69	100	128	149
50	40	89	128	165	192
75	50	110	158	204	238
100	60	132	191	245	286

[a] Reynolds number using eq 5; $d_t = 1.75 \times 10^{-2}$ m; *p*-xylene.

Table 4. **Relationship of stirring speed and Reynolds number**[a] **in the Milestone FlowSynth at four temperatures**

	stirrer speed (rpm)				
temperature (°C)	60	195	322	380	425
25	402	1306	2191	2546	2854
50	517	1680	2817	3273	3669
75	640	2080	3488	4054	4544
100	769	2501	4193	4873	5463

[a] Reynolds using eq 6; $d_{\mathrm{imp}} = 1.68 \cdot 10^{-2}$ m; *p*-xylene.

2.3. Flow and Mixing.

The Reynolds number, as a dimensionless number, represents the ratio of inertia forces and the viscous forces on the flowing fluid. The Reynolds number characterizes in this way the flow regime in the reactor for a certain experiment.

Mixing may be crucial not only to bring the reactants together (mass transport) but also to remove/supply the heat for temperature control during the reaction (heat transport). Table 2 gives an overview of the type of mixing relevant for various time constants of reaction.[22]

The tubing and the reactor have different diameters. Depending on the flow rate, a certain reaction mixture or solvent displays a laminar or turbulent pattern. If the Reynolds number (*Re*, see eq 5) is over 3500 in the tube, the flow will develop turbulence. In case of a turbulent flow the heat exchange from the Weflon blades of the semi-coil-shaped stirrer inside the reactor column towards the reaction mixture is much more efficient than for a laminar flow. Table 3 gives an overview of the conditions to convert a laminar flow in the reactor (without stirring) into a turbulent regime. The influence of stirring on the Reynolds number is summarized in Table 4 using eq 6.

$$\begin{aligned} Re_{\mathrm{tube}} &= \frac{d_t \cdot u \cdot \rho}{\mu} \\ d_t &= \text{tube diameter [m]} \\ u &= \text{mean velocity } [\mathrm{m \cdot s^{-1}}] \\ \rho &= \text{density } [\mathrm{kg \cdot m^{-3}}] \\ \mu &= \text{dynamic viscosity [Pa} \cdot \text{s]} \end{aligned} \tag{5}$$

$$\begin{aligned} Re_{\mathrm{imp}} &= \frac{\rho \cdot N \cdot d_{\mathrm{imp}}^2}{\mu} \\ d_{\mathrm{imp}} &= \text{impeller diameter [m]} \\ N &= \text{impeller speed } [\mathrm{s^{-1}}] \end{aligned} \tag{6}$$

2.4. Heat Transfer.

The Nusselt number (Nu) is the ratio of the convective heat transfer to the conductive heat transfer. Equations 7 and 8 give the definition of the Nusselt number and an empirical dimensionless correlation from heat transfer in stirred tanks, respectively.[22] The overall heat flow rate from the Weflon[15] blades (ϕ_q) to the fluid in the reactor is estimated by eq 9. Solvents with a small loss tangent can only absorb microwave energy indirectly via the Weflon blades mounted on the stirrer shaft in the tubular reactor. Efficient heat transport prevents high temperatures of the heating surface (A = 95 cm^2) of the Weflon blades (eq 9). With the assumption of direct and fast absorption of microwaves by the Weflon blades the temperature of these blades is at a constant value.

$$\begin{aligned} \langle Nu \rangle &= \frac{\langle h \rangle \cdot L}{\lambda} \\ \langle Nu \rangle &= \text{Nusselt number} \\ \langle h \rangle &= \text{heat transfer coefficient} \\ L &= \text{characteristic length (reactor diameter)} \\ \lambda &= \text{thermal conductivity} \end{aligned} \tag{7}$$

$$\begin{aligned} \langle Nu \rangle &= c_r \cdot Re^{2/3} \cdot Pr^{1/3} \cdot V_i^{0.14} \\ \langle Nu \rangle &= \text{Nusselt number} \\ c_r &= \text{stirrer constant} \\ Re &= \text{Reynolds number (rotation)} \\ Pr &= \text{Prandtl number} \\ V_i &= \text{viscosity constant } (\approx 1) \end{aligned} \tag{8}$$

$$\begin{aligned} \phi_q &= \langle h \rangle \cdot A \cdot (\Delta T)_{\ln} \\ \phi_q &= \text{heat supplied to the system } [\mathrm{J \cdot s^{-1}}] \\ \langle h \rangle &= \text{overall heat transfer} \\ &\quad \text{coefficient } [\mathrm{J \cdot s^{-1} \cdot m^{-2} \cdot K^{-1}}] \\ A &= \text{surface } [m^2] \\ (\Delta T)_{\ln} &= \text{logarithmic mean} \\ &\quad \text{temperature difference [K]} \\ (\Delta T)_{\ln} &= \frac{(T_{\mathrm{out}} - T_{\mathrm{blade}}) - (T_{\mathrm{in}} - T_{\mathrm{blade}})}{\ln\left(\dfrac{T_{\mathrm{out}} - T_{\mathrm{blade}}}{T_{\mathrm{in}} - T_{\mathrm{blade}}}\right)} \end{aligned} \tag{9}$$

In case of *p*-xylene ($\lambda = 0.124$ W·m^{-1}·K^{-1}) and a relatively low stirrer constant ($c_r = 0.36$; blade stirrer, no baffles; $d_{\mathrm{imp}} = 30.5$ mm; $D_{\mathrm{tube}} = 34.3$ mm)[23] the Nusselt number will range from 100 to 200 depending on temperature (50−100 °C) and stirrer speed (200−400 rpm). The heat transfer coefficient (*h*), consequently, is calculated to range from 360−725 W·m^{-2}·K^{-1}. Typically the surface of the blades ($A = 95$ cm^2) can reach a temperature of 160 °C when an incoming stream of *p*-xylene at room temperature is heated up to 120 °C for an efficient microwave-induced power input of 277 W into the system.

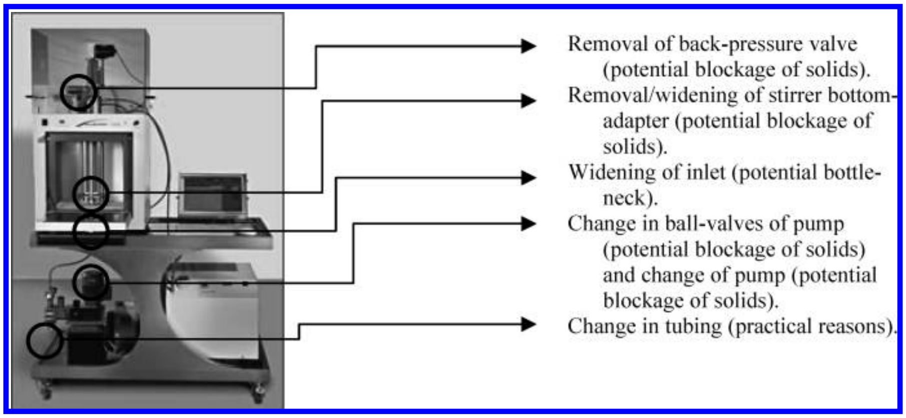


Figure 6. **Various modifications of the original Milestone FlowSynth apparatus.**

3. Flow Chemistry: A Continuous Operation

Most studies with continuous-flow reactors are reported in the field of organic chemistry and describe the application of conventional heating; so-called flow chemistry.[24−27] The use of continuously operated reactors demands for relatively fast reactions, otherwise flow rates have to become extremely low or reactors become too large. Residence time is the key parameter determining the degree of conversion. One way to combine a high flow rate with complete conversion is to completely recycle the reactor outlet, resulting in batch-loop operation. In this way, the advantages of a tubular reactor and a batch reactor are combined.

As mentioned before the penetration depth (δ_p) of microwaves is limited to the range of centimetres depending on the composition and physical properties of the reaction mixture. The penetration depth is expressed as the distance at which the energy is reduced to 37%, see eq 10.[28] Therefore, the reactor diameter for microwave heating equipment ranges between 5 to 100 mm.

$$\begin{aligned}
\delta_p &= \frac{\lambda_0\sqrt{\varepsilon'}}{2\pi\varepsilon''}\\
\delta_p &= \text{penetration depth [m]}\\
\lambda_0 &= \text{free space wavelength [m]}\\
\varepsilon' &= \text{dielectric constant}\\
\varepsilon'' &= \text{dielectric loss}
\end{aligned} \tag{10}$$

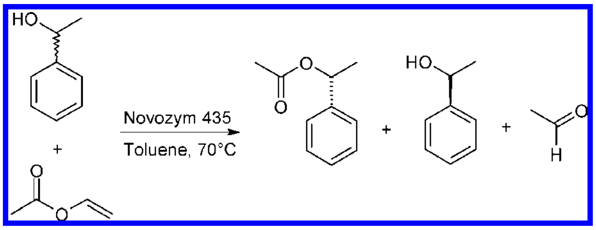
Two chemical reactions were investigated in a batch-loop setup and one reaction in a continuous operation.

4. Performance for Batch-Loop Operation

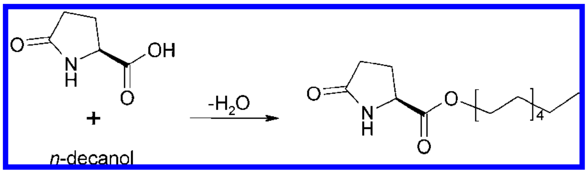
Roughly, the setup for batch-loop operation that we have used involves flow chemistry in a microwave oven. This approach is basically an ideal situation to accommodate reactions requiring different reaction times, to transfer a small-scale batch reaction into a flow setup and to increase the productivity by means of parallel circuits (i.e., scaling out). On the basis of the experience gained in initial studies, the FlowSynth reactor was adapted at various places to enable processing of heterogeneous reactions. Our modifications are marked with circles in Figure 6.[27]

Two chemical reactions (i.e., a biocatalyzed esterification and the esterification of (*S*)-pyroglutamic acid in the production of a cosmetic product, Laurydone)[30−33] with each a set of two experiments were executed in the FlowSynth (Schemes 1 and 2). Each set of experiments was compared with the corresponding batch experiment. The Laurydone reaction is to the best of our knowledge, the only fine chemical reaction performed on an industrial scale similar to our approach.

Scheme 1. **Esterification of (*R,S*)-1-phenylethanol with vinyl acetate in an enantiomerically selective reaction using Novozym 435**



Scheme 2. **Esterification of (*S*)-pyroglutamic acid with *n*-decanol**



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4.1. Biocatalyzed Esterification. It was demonstrated that the enantioselective esterification of commercially available (*R*,*S*)-1-phenylethanol with vinyl acetate and Novozym 435 in toluene is relatively fast (Scheme 1).[34] Similar to the batch experiments an excess of vinyl acetate was used for reactions in the FlowSynth to enforce a high conversion within a reasonable time (2−3 h). Although many reports claiming positive microwave effects in biocatalyzed processes,[35−41] we were unable to observe any difference with conventional heating.[4a]

The scale of the continuous-flow experiment (0.4 mol 1-phenylethanol) was a factor of 100 larger than the batch mode reaction (4 mmol). The reaction mixture without biocatalyst (Novozym 435 beads) was premixed in a 1 L round-bottomed flask and magnetically stirred. After a short period this homogeneous mixture was pumped through the loop. The temperature in the top of the tubular reactor (T^1) was set at 70 °C. The microwave power was automatically adjusted to maintain the temperature at T^1 of this set point, see Figure 7.

The esterification was performed twice (experiments A and B) in the FlowSynth. In experiment A the reaction mixture should have been distributed evenly over the batch-loop setup. In experiment B the catalyst was retained on purpose in the microwave-heated tubular reactor (R^1).

4.2. Experiment A. The flow rates were measured before and after the addition of Novozym 435. In both cases the flow rate was 175 mL·min^{-1}. Once the reaction setup reached a steady state (in which the temperature was constant in time) Novozym 435 was charged to flask R^2. During the reaction aliquots were taken just after point T^2, but before vessel R^2 (see Figure 7). Figure 8 shows the time−conversion history. It is noteworthy to mention that the amount of Novozym 435 appeared to be higher inside the reactor than in vessel R^2 or outside R^1.

The liquid velocity in the tubing (v_{tub} = 0.15 m·s^{-1}) was considerably higher compared to that in the tubular reactor (v_{react} = 0.012 m·s^{-1}), which might explain settling of Novozym 435 in the column R^1. The narrow exit after T^2 can also lead to a hold-up or plugging of the spherical particles of Novozym 435. The temperature in vessel R^2 has been monitored manually and never exceeded 30 °C. The total slurry volume was 0.940 L and the volume of the tubular reactor was 0.180 L. With a flow rate of 0.175 L·min^{-1} and a total residence time of 173 min, the number of cycles was calculated to be 168 with an average residence time of a little more than one minute per cycle in column R^1. Consequently, for this batch-loop experiment only 19%[42] of the reaction mixture was exposed to the temperature of 70 °C, while in the batch experiment, however, 100% of the reaction mixture was subjected to that temperature. The uneven distribution of Novozym 435 over the complete reaction mixture hampers a quantitative comparison of the reaction rates for thermal and microwave heating.

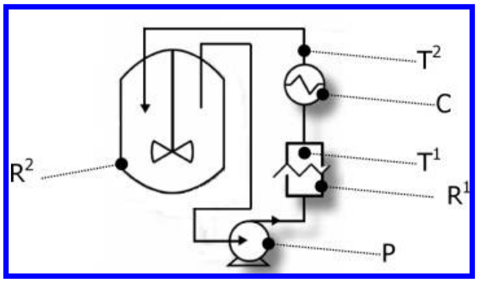

Figure 7. **Setup for batch-loop operation for the esterification of (*R*,*S*)-1-phenylethanol with vinyl acetate and the esterification of (*S*)-pyroglutamic acid with *n*-decanol (Laurydone process): R^1 = microwave-heated tubular reactor; R^2 = round-bottomed flask with magnetic stirrer; P = (membrane or gear) pump; C = cooler with Archimedes' screw; T^1 = temperature sensor inside the upper part of the tubular reactor and T^2 = temperature sensor just downstream the cooler.**

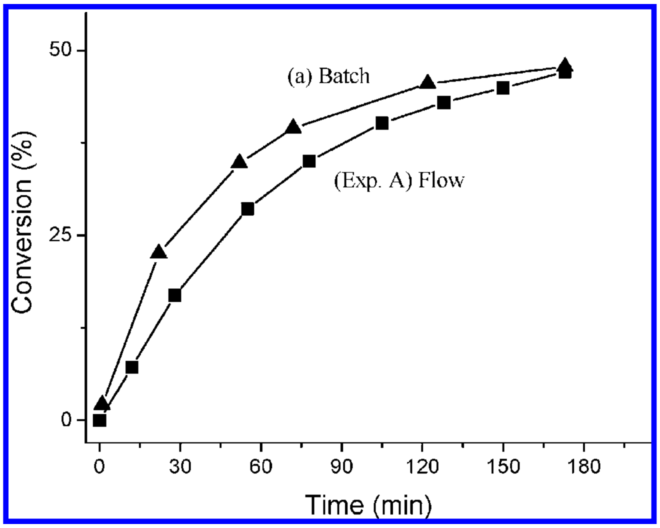

Figure 8. **Esterification of (*R*,*S*)-1-phenylethanol with vinyl acetate in toluene at 70 °C catalyzed by Novozym 435 in (a) an oil-bath-heated (25 mL) batch reactor (4 mmol scale); (*R*)-1-phenylethyl acetate (—▲—) and (experiment A) in a microwave-heated batch-loop-wise operated reactor setup shown in Figure 7 (0.4 mol scale) at ϕ_v = 0.175 L·min^{-1}; (*R*)-1-phenylethyl acetate (—■—).**

Note that comparison of batch experiments with respect to both heating methods demonstrated the absence of a rate enhancement effect by microwave heating.

4.3. Experiment B. The procedure applied in Experiment A was repeated for the esterification in the continuous-flow reactor operated in a batch-loop mode. Now, Novozym 435 was charged directly into the tubular reactor system, and the reactor was put together to operate under flow conditions with complete retention of the Novozym 435 inside the microwave cavity, because the system was not stirred. During the reaction, aliquots were taken after point T^2, but before vessel R^2. The results are plotted in Figure 9. The conversion−time history in Figure 9 is comparable with that of Figure 8. This observation confirms that the majority of the solid particles in the experimental setup for experiment A resides nearly completely in the

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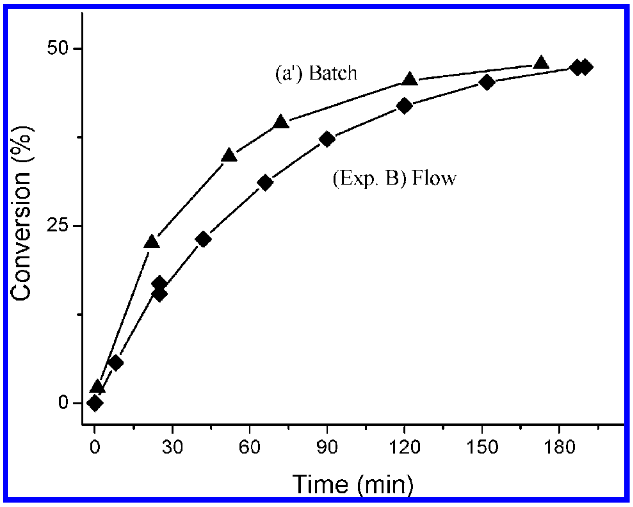

Figure 9. **Esterification of (*R*,*S*)-1-phenylethanol (4 mmol) with vinyl acetate in toluene at 70 °C catalyzed by Novozym 435 in (a) an oil bath-heated (25 mL) batch reactor; (*R*)-1-phenylethyl acetate (—▲—) and (experiment B) in a microwave-heated batch-loop-wise operated reactor setup shown in Figure 7 (0.4 mol scale) with catalyst charged in the tubular reactor at $\phi_v = 0.12$ L·min^{-1}; (*R*)-1-phenylethyl acetate (—◆—).**

tubular reactor. As compared to the small-scale batch experiment the concentration of Novozym 435 in the tubular reactor is greater by a factor of 5.2. The total mean residence time per pass has decreased with the same factor. Note that the effect of the increased catalyst concentration and the decreased mean residence time in the tubular reactor on the (*R*,*S*)-1-phenylethanol conversion approximately cancel out (for plug flow the net effect of catalyst concentration and residence time is exactly zero).

The remaining difference in reaction rate is partially related to either a small temperature gradient in the microwave-heated tubular reactor or to some mass transfer limitations inside the reactor (without stirring). Without stirring (and with a laminar flow) the global reaction rate can change as a result of a change in (intraparticle) mass transport limitation (see Figure 10).[43]

This example of a biocatalytic esterification exemplifies a direct correlation between batch and continuous operation. Approximately the same final conversions are achieved for comparable reaction times (i.e., for the batch-loop operation reaction times are somewhat larger than for the small-scale batch experiment, see Figure 9).

4.4. Esterification of (*S*)-Pyroglutamic Acid with *n*-Decanol (Laurydone Process). At the moment, the only example in the field of microwave-assisted fine chemical applications is the Laurydone process, see Scheme 2.[27,29] This example illustrates the ability to execute microwave heating on a large scale. Despite the successful large-scale operations with microwave heating, the originators failed to demonstrate the superiority of microwave heating technology over conventional heating. A wrong conclusion about a probable microwave effect could be drawn as a result of poor stirring (see Figure 11). Figure 11 (left) depicts the results of two experiments in which the reaction mixture was magnetically stirred, either microwave or conventionally heated. However, in Figure 11 (right) overhead stirring has been used for the same experimental setup as performed in Figure 11 (left), resulting in identical conversion−time profiles. By efficient stirring the presence of a temperature profile over the reaction mixture is minimized, leading to a vanishing microwave-induced reaction rate enhancement.

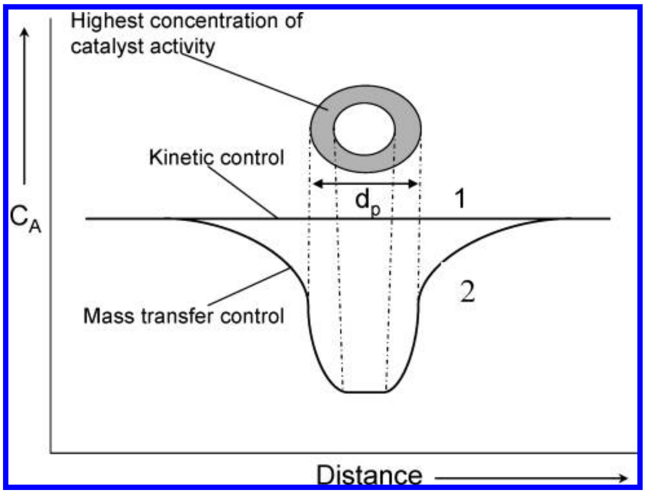

Figure 10. **Concentration profile (C_A) around and inside a catalyst particle (with shell catalyst such as Novozym 435) with strong mass transfer limitation (2) and with intrinsic kinetics (1).**

All our batch reactions of the Laurydone synthesis have been performed with a high concentration of substrate ((*S*)-pyroglutamic acid) in *n*-decanol. Such a solid weight percentage (47 wt %) appeared to be impractical to handle in the continuous-flow reactor. Reduction of the acid weight percentage to 10 wt % guaranteed a smooth flow for the initially heterogeneous reaction mixture. Again, two different conditions have been applied for this type of esterification (Table 5). It is important to point out that the membrane pump in experiment A was replaced by a better performing gear pump in experiment B. Compared to a membrane pump, a gear pump is more suitable for handling viscous reaction mixtures, like those containing *n*-decanol. The flow scheme of the setup for experiments A and B is schematically depicted in Figure 7.

4.5. Experiment A. After charging vessel R^2 with reactants and stirring with a mechanical impeller, the resulting solid/liquid mixture was pumped through the tubular reactor (without heating). This procedure enabled to run the flow system for many hours without any complications.

Subsequently, heating was applied to the tubular reactor R^1 (Figure 7, 150 °C). Cooling agent of 8 °C was supplied to the jacket of cooler C. Cooling of vessel R^2 was started by pumping a coolant of 12 °C through the jacket. Shortly after starting up the heating and cooling, plugging occurred in the cooler C. This prevented any flow. Also stirring of the coil in the tubular reactor R^1 was not possible. A deposit of solid material on the walls of cooler C was observed.

In the restarted experiment cooling was only applied to vessel R^2, the jacket of cooler C was not filled, and the jacket was open to air. Under these operating conditions plugging occurred again, and this could be attributed to the pump. Due to a larger temperature difference over the pump-head section, settling occurred. This settling hampered the flow through the pump

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(43) The intra-particle diffusion limitation is determined with the Weisz−Prater criterion ($N_{W\text{-}P}$). Below 0.3 this limitation can be excluded. In our case, it has been estimated to be 0.11; Weisz, P. B.; Prater, C. D. *Adv. Catal.* **1954**, *6*, 143.

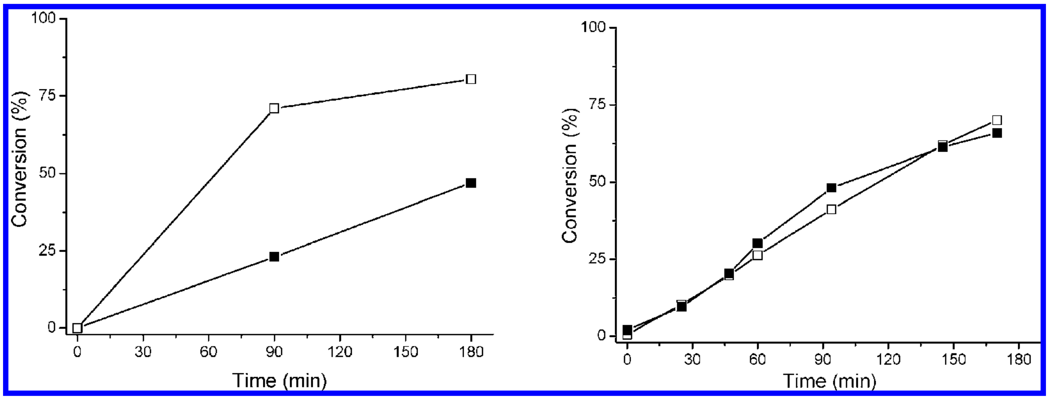


Figure 11. **Esterification of pyroglutamic acid with *n*-decanol; initial experiments with (*R*,*S*)-pyroglutamic acid (7 mmol) at 145 °C in a test tube with magnetic stirring (left) and (*R*,*S*)-pyroglutamic acid (97 mmol) at 145 °C in a 50 mL glass vessel with mechanical stirring (pitched-blade impeller, four blades) (right) applying conventional heating (—■—) and microwave heating (—□—).**

Table 5. **Esterification of (*S*)-pyroglutamic acid with *n*-decanol at different reaction conditions (experiments A and B) in the batch-loop-wise operated setup shown in Figure 7**

entry	parameters	experiment A	experiment B
1	(*S*)-pyroglutamic acid	69.1 g 0.54 mol	69.0 g 0.53 mol
2	*n*-decanol	622 g 3.93 mol	622 g 3.93 mol
3	wt % substrate	10	10
4	flow rate	115 mL·min^{-1}	343 mL·min^{-1}
5	pump	membrane	gear
6	total reaction time	140 min	178 min
7	mixing speed R^2/suction line from R^2	medium/bottom	low/top
8	interruption:	plugging	manual

and ultimately the flow stopped. Therefore, a fair comparison between the batch-loop operated, microwave-heated reactor system and the conventionally heated, small-scale batch experiments could not yet be made.

4.6. Experiment B. Experiment A was repeated, adopting the previous procedure. Instead of a membrane pump, a gear pump was applied in experiment B. Introduction of large particles relative to the tube diameter led in this case also to plugging in the suction line. During the first period this plugging problem could be circumvented by stirring the contents of vessel R^2 slowly. Suction occurred via the top of vessel R^2. In this way the reaction mixture was always saturated in substrate, although not completely homogeneously mixed.

The Laurydone process can be divided into three stages (see Figure 12): stage I is the start-up, stage II is that of predominant esterification, and stage III removes the reaction product water.

Stage I is not appropriate for making a comparison between conventional and microwave heating.

Microwave heating is much faster than oil-bath heating. For oil-bath heating it takes more than 10 min to reach the desired temperature. For the flow experiments heating is, however, almost instantaneous. In stage II the esterification is predominantly at a constant temperature, making this stage suitable for a comparison. Stage III is dominated by the presence of water. Water removal governs the reaction rate in stage III because it shifts the equilibrium to the product side. Also the difference in setup, i.e. batch/batch-loop, plays an important role in the removal of water.

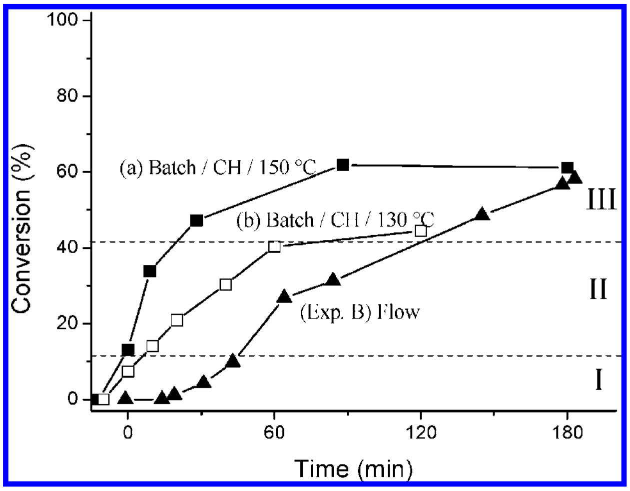


Figure 12. **Esterification of (*S*)-pyroglutamic acid (10 wt %) with *n*-decanol in (experiment B) a batch-loop-operated microwave-heated reactor setup, (a) conventionally heated batch experiment at 150 °C and (b) conventionally heated batch experiment at 130 °C.**

For the batch experiment at 150 °C the conversion reached a plateau of 60% after 90 min. Note that in the reaction in the batch-loop setup a significant induction period can be observed. This probably originates from the slow dissolution rate of the acid in *n*-decanol. As the rate of esterification for relatively low conversions obeys a second-order rate where the rate is $k_2 *$ [acid]$*$ [alcohol], low deviation from the saturation concentration of the acid in the alcohol leads to lower reaction rates than in the saturated situation which is achieved in batch experiments (a) and (b). The conversion−time history resulting from the microwave-heated run in the continuous-flow setup operating in a batch-loop mode approaches the 60% conversion level approximately linearly. The batch-loop setup clearly has another influence on the removal rate of water than the batch operation. In the Laurydone synthesis comparing conversion rates of batch and flow processing is more complicated than in the cases of biocatalysis and racemization. A much higher temperature is measured outside the tubular reactor R^1 than in the other cases. As a consequence, direct correction with the fractional residence time in the tubular reactor is hampered due to a significant continuation of the esterification outside the tubular reactor R^1.

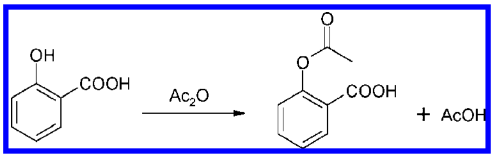
Therefore, to make an estimation for the rate in R^1, a correction has been applied with a combination of the fractional

Table 6. **Conversion rates (interval of 13 and 42% conversion) of the esterification of (*S*)-pyroglutamic acid under different reaction conditions**

entry	conditions	overall reaction rate [Δconv·min^{-1}]	fractional residence time[a]	relative reaction rate [Δconv·min^{-1}]
1	batch (a), 150 °C	1.14	1	1.14
2	batch (b), 130 °C	0.51	1	0.51
3	experiment B, with correction	0.70	0.26	2.68, 1.27[b]

[a] Fractional residence time in the reactor compared to the total reaction time [based on the ratio of the volume of the microwave-heated tubular reactor (R^1, 180 mL) per total reaction volume (700 mL); overall rate = $V_{R^1}/V_{tot}\cdot$ rate (MW, R^1). [b] [Real rate (MW, R^1)] = $V_{R^1}/V_{tot}\cdot$ ([overall rate] − $V_{R^1}/V_{tot}\cdot$[rate, (batch, 130 °C)]); (R^2, 520 mL).

Scheme 3. **Synthesis of aspirin: *O*-acetylation of salicylic acid**



residence time *and* the reaction rate outside the tubular reactor R^1 based on batch (b), see entry 2, Table 6. After correction of the overall reaction rates, Table 6 demonstrates almost identical behaviour for batch ((a), 150 °C) or batch-loop operation by microwave heating. This is, however, only valid for stage II in the Laurydone process. The stages I and III are controlled by the heating rate, the dissolution rate of the acid, and the experimental setup, respectively.

5. Performance of the Continuous-Flow Reactor

The heterogeneous processes studied so far in the FlowSynth demonstrated relatively long reaction times demanding for multiple passes through the microwave-heated tubular reactor to reach an acceptable conversion. To get a more complete picture of the performance of the FlowSynth also a homogeneous reaction has been selected. The step to homogeneous continuous-flow processing has also been reported without further process research involving a fast reaction.[44,45]

5.1. Aspirin Synthesis. The one-step synthesis of aspirin allows investigation of an intrinsically fast, homogeneous reaction in a potentially single-pass operation (Scheme 3).[46] Thus, this aspirin synthesis may be executed as a real continuous process.

Starting with a recipe based on a high concentration (25 wt %; 2.3 mol·L^{-1}) of salicylic acid in acetic acid, at which the substrate was completely dissolved at 50 °C, instantaneously led to plugging. Lowering the concentration of salicylic acid of course improved the handling in a continuous-flow mode, but reaction rates were negatively affected. Therefore, a switch from a gear pump to a membrane pump was necessary to ensure a stable and efficient reaction flow through the tubular reactor. After the first 150 mL of the product stream volume ($\langle\tau\rangle \approx 1$) ($R^1$ = 180 mL) operation was at steady state. So, residence time and conversion can be correlated at multiple points (Figure 13). The mean residence time (390 ± 39 s) was determined by measuring the volume of the product stream during 3 min process time. The measurement was repeated 20 times. Also the salicylic acid conversion (57 ± 4%) was measured in these samples, see Figure 13.

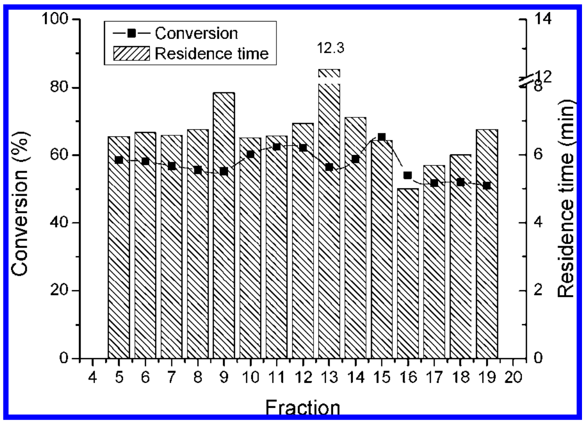


Figure 13. **Conversion profile of the aspirin synthesis in acetic acid (1 M) with 2 mol equiv of acetic anhydride at 120 °C in a continuous-flow experiment. Volumes of the product stream during 3 min process time.**

The actual product stream shows a delay which is similar to the average residence time (the sum of volume of tubing and cooling unit is approximately also 180 mL). The relatively longer residence times of fractions 9 and 13 are witnessed as relatively higher conversions at fractions 11 and 15, respectively. Batch experimentation using either microwave or conventional heating with an identical reaction time (390 s) resulted in closely related conversions of 66% and 64%, respectively.

With the assumption that the *O*-acetylation of salicylic acid obeys apparently first-order kinetics in the first part of the reaction, the reaction constant (k) can be estimated (see eq 11). Together with the model representing the tubular reactor R^1 as a series of CSTRs, the conversion (x_A) related to residence time can be calculated for the continuous-flow process (eq 11). The total volume (V_{total}) of the tubular reactor R^1 is 180 mL, and the flow rate (ϕ_ν) is 0.46 mL·s^{-1}. When the number (n) of equally sized tanks in series is 3 or 2, then the theoretical conversion would be 60 or 57%, respectively; which perfectly agrees with the experimentally observed conversion (57%).

$$x_A = 1 - \left(\frac{1}{1 + k\cdot\dfrac{V_{total}}{n\cdot\phi_\nu}}\right)^n \tag{11}$$

$$k = 2.7\cdot10^{-3}\ \mathrm{s}^{-1}[120\ ^\circ\mathrm{C}]\ \text{(see ref 47)}$$

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(47) The *k* value is obtained from unpublished batch-wise experimentation.

The translation from batch to continuous processing appears to be straightforward, although more knowledge (e.g., on the internal temperature of tubular reactor R^1) is required to allow a rational prediction. However, a longer residence time is not feasible with the current setup, while complete conversion demands a very long mean residence time (~1 h). Presumably, this might be circumvented by the addition of a suitable catalyst. Nevertheless, the batch-loop operation allows high conversions in a short time with a proper temperature control.

6. Concluding Remarks

The transfer of microwave energy into heat, directly or indirectly via the Weflon blades, allows the use of several reaction mixtures in terms of polarity or loss tangent. The combination of stirring and heating gives rise to an efficient energy transfer. The residence time distribution of the CFR (Milestone FlowSynth) with a single pass results in a performance equivalent to that of a series of three equally sized CSTRs.

Recalculating the operational costs is necessary to decide whether microwave heating is still beneficial if larger production scales are planned. In view of the higher operational costs and apart from the safety issue the chances to incorporate microwave heating as a competitive technique seem to decrease with increasing scale.

As demonstrated in our experiments, plugging as a result of solid reactants/products is a point of attention in further process design for solid−liquid organic reactions. Redesigning the equipment, involving Teflon-coating and thermostatic tracing, may overcome fouling and plugging in the present study. Also redesigning the present FlowSynth setup allows coping with issues such as solids and slurry handling.

From a technical point of view scaling up heterogeneous reactions by microwave irradiation is feasible. Not only is it possible to rapidly heat the reaction mixture, but the experimentally observed batch data of the conversion−time history can also be used for process design. Direct temperature control and the opportunity to quench the reaction easily are highly advantageous. High production rates can be achieved for batch-wise operation by numbering up the microwave-heated reactor units.

7. Experimental Section

The continuous-flow reactor was supplied by Milestone srl, Italy. The tubular reactor could either be equipped with a Teflon or a Weflon stirrer. The original setup included a membrane pump of Alldos GmbH (now known under the name Grundfos); type 281-9, 6-1004; 100 bar; 50 Hz. The gear pump was supplied by the manufacturer Gather Industries, type 320; PM8060 L.

General Methods. Chiral gas chromatography (GC) was performed on a Shimadzu 6C-17A GC equipped with a Chrompack Chirasil-DEX CG (DF = 0.25) column, and a FID. Injection temperature was set at 250 °C and the detection temperature at 300 °C. Temperature programs were used to optimize the analysis for each reaction mixture; see each specific procedure. Tetradecane was used as an internal standard.

(*R*)-1-Phenylethyl Acetate. A 1 L round-bottomed flask was charged with a solution of (*R*,*S*)-1-phenylethanol (48 g, 0.4 mol) and vinyl acetate (172.2 g, 2 mol) in toluene (700 L). The reaction mixture was circulated via a membrane pump with a flow of 175 mL·min^{-1} through the continuous-flow reactor of Milestone equipped with a Weflon stirrer and was heated to 70 °C (T^1). On top of the reactor cooling was applied to maintain T^2 below 30 °C. Subsequently, Novozym 435 (5.0 g) was added to the flask (experiment A) or to the tubular reactor (experiment B, including a temporary hold of the flow), and the set temperature was maintained for a period of 180 min. The total reaction volume was 940 mL. Average power usage during reaction was 226 W (experiment A) and 236 W (experiment B). During the reaction, aliquots were taken from the liquid phase and measured by GC. After 180 min the mixture was collected, resampled, and cooled.

Laurydone [Experiment A]. A double-walled reactor was charged with (*S*)-pyroglutamic acid (69.1 g, 0.54 mol) and *n*-decanol (622 g, 3.93 mol). The reaction mixture was circulated via a membrane pump with a flow rate of 115 mL·min^{-1} through the continuous-flow reactor of Milestone equipped with a Weflon stirrer and was heated to 150 °C (T^1). On top of the reactor no cooling was applied. The double-walled reactor was thermostatic at 60 °C at the walls. The reaction time was 140 min, and the total reaction volume was 700 mL. The average power usage during reaction was 294 W. During the reaction, aliquots (~50 mg) were taken, quenched with dichloromethane (3 mL), and measured by ^{1}H NMR (CD_3OD, 200 MHz) typical signals δ (ppm) 4.14 (t, 2H, $CH_2{-}OCO$, product), 3.53 (t, 2H, $CH_2{-}OH$, decanol).

Laurydone [Experiment B]. A double-walled reactor was charged with (*S*)-pyroglutamic acid (69.0 g, 0.53 mol) and *n*-decanol (622 g, 3.93 mol). The reaction mixture was circulated via a gear pump with a flow rate of 343 mL·min^{-1} through the continuous-flow reactor of Milestone equipped with a Weflon stirrer and was heated to 150 °C (T^1). On top of the reactor no cooling was applied. The double-walled reactor was not thermostatic at the walls. The reaction time was 178 min, and the total reaction volume was 700 mL. The average power usage during reaction was 444 W. During the reaction, aliquots (~50 mg) were taken, quenched with dichloromethane (3 mL), and measured by ^{1}H NMR (CD_3OD, 200 MHz) typical signals δ (ppm) 4.14 (t, 2H, $CH_2{-}OCO$, product), 3.53 (t, 2H, $CH_2{-}OH$, decanol).

***O*-Acetyl Salicylic Acid.** A round-bottomed flask was charged with salicylic acid (207 g, 1.5 mol), acetic acid (1228 g, 1.12 L), and acetic anhydride (307 g, 3.0 mol). After 15 min of mixing (almost complete dissolution), the reaction mixture was pumped via a membrane pump with a flow rate of 27 mL·min^{-1} through the continuous-flow reactor of Milestone equipped with a Weflon stirrer and was heated to 120 °C (T^1). On top of the reactor, cooling was applied. The residence time was 6.5 min. The average power usage during reaction was 253 W. During the run, the reaction mixture was collected in fractions, and aliquots were taken and measured by ^{1}H NMR (CD_3OD, 200 MHz) typical signals δ (ppm) 8.01 (d, 1H, CH−C−COOH, aspirin), 7.84 (d, 1H, CH−C−COOH, salicylic acid).

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Supporting Information Available

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