Green Process Synth 1 (2012): 281–290 © 2012 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/gps-2012-0032

Microwave-assisted continuous flow synthesis on industrial scale

Roman Morschhäuser[1],*, Matthias Krull[1], Christoph Kayser[1], Cornelia Boberski[2], Ralf Bierbaum[1], Peter A. Püschner[3], Toma N. Glasnov[4] and C. Oliver Kappe[4]

[1] Clariant Produkte Deutschland GmbH, D-65926 Frankfurt/Main, Germany,
e-mail: roman.morschhaeuser@clariant.com

[2] Innoturn GmbH, Unter den Eichen 2, D-65779 Kelkheim, Germany

[3] Püschner GmbH and Company KG, Steller Heide 14, D-28790 Schwanewede, Germany

[4] Christian Doppler Laboratory for Microwave Chemistry (CDLMC) and Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-80010 Graz, Austria

* Corresponding author

Abstract

A continuous flow microwave system based on a transmission line short-circuited waveguide reactor concept is described. The continuous flow reactor is capable of operating in a genuine high-temperature/high-pressure process window (310°C/60 bar), applying a microwave transparent and chemical resistant cylindrical γ-Al_2O_3 tube as reaction zone. The system can be operated in an extremely energy efficient manner, utilizing 0.6–6 kW microwave power (2.45 GHz). The application of the reactor for processing four chemical transformations in a high-temperature/high-pressure regime with a throughout of 3.5–6.0 l/h is demonstrated.

Keywords: continuous flow chemistry; high-temperature/high-pressure process windows; microwave chemistry; process intensification.

1. Introduction

The design of new and improved chemical processing techniques that are economically viable and at the same time follow the principles of sustainable chemical process development (“green process engineering”) are of paramount importance to the chemical industry [1]. Radical improvements in this area are likely to be achieved only by a complete reorganization of production processes, including new reactor configurations and novel process conditions. For these reasons, the chemical industry has started to explore different means of so-called “process intensification” technologies, which demand abrupt changes in traditional processing and a search for game-changing improvements [1–5]. The idea to deliberately explore harsh or otherwise very unusual process conditions for process intensification of chemical reactions is a recent concept termed “novel process windows” [1, 6]. Here, the general notion is to operate at conditions that considerably increase reaction rates while maintaining selectivity. One key principle in this area is to operate chemical transformations in a high-temperature/high-pressure (high-T/p) process window, taking advantage of often dramatic rate increases based on the Arrhenius relationship [$k=A\exp(-E_a/RT)$] [6].

High-T/p processing offers many distinct advantages as demonstrated by the recent success of microwave-assisted organic synthesis performed on a laboratory (ml) scale [7–14]. In microwave chemistry, reaction times can often be reduced from days or hours to minutes or seconds. This is accomplished by efficient and rapid direct volumetric heating of the reaction mixture in a sealed vessel to temperatures far above the boiling point of the solvent under atmospheric conditions (typically up to 300°C/30 bar under sealed vessel microwave conditions are routinely possible) [7–14]. Recent dedicated equipment specifically designed for chemical applications allows exquisite control of the optimized reaction temperature and other important process parameters. In many instances, microwave processing has not only been shown to dramatically reduce reaction times, but also to provide increased product yields and to enhance product purities compared to conventionally heated experiments [15, 16]. These unique features explain the growing popularity of this non-classical heating method in synthetic organic chemistry with currently more than 6000 publications demonstrating the benefits of this technology [7–14].

Unfortunately, using traditional batch-type processing, microwave chemistry is difficult to scale to larger volumes, mainly due to penetration depth issues-volumetric heating being genuinely effective on a comparatively small scale only [17]. Although impressive progress has been achieved over the past few years in translating small scale microwave chemistry from the laboratory scale (ml) to a larger “kilolab” scale (l) format using dedicated batch microwave instrumentation [17], it is obvious that this technology will not be able to deliver industrially relevant product quantities (>100 t/year) in an economically viable way. Also, it should be emphasized that in moving to larger and larger batch reactors, many of the genuine benefits of small scale microwave chemistry are in fact lost. In particular, the rapid heating and cooling profiles obtained on a small scale cannot be transferred to a larger scale. In addition, due to safety concerns, many of the large scale reactors do not have the same temperature/pressure ratings as the small scale instruments (300°C/30 bar) [17]. Thus, the high reaction temperatures and rapid heating rates responsible for the fast kinetics in a typical small-scale microwave experiment can generally not be mimicked on scale, which leads to prolonged reaction and overall processing times [17].

As a consequence of the apparent limitations of large-scale batch microwave processing, recent efforts have focused on performing microwave chemistry under continuous flow conditions [17–31], a concept pioneered by Strauss in the mid-1990s [32]. The typically short reaction times – on the order of a few minutes or even seconds – experienced in high-temperature microwave chemistry protocols form an ideal basis for continuous flow processing/manufacturing where short residence times are essential to achieve a high throughput. Using either single-mode or multimode microwave instruments, several successful examples of microwave-assisted continuous flow synthesis on a g or kg scale have been reported in the literature using a variety of different formats [17–31, 33]. However, the commercially available or prototype instruments introduced so far [17–32] are neither designed to operate in a genuine high-T/p process window (300°C/30 bar), nor has their application for industrial scale performance (>100 t/year) been demonstrated. The realization of industrial scale microwave synthesis a new concept and it is necessary that it fulfills the following criteria: 1) safe and reliable equipment, 2) high reproducibility, 3) good reaction control, 4) fast heating (time), 5) reasonable volume (capacity), 6) acceptable energy balance, 7) comparable or higher yield to conventional systems, and 8) acceptable cost. In particular, low energy efficiency, poor reaction control and safety issues have so far been the main arguments against microwave synthesis on large scale.

Herein, we describe a conceptually novel single-mode microwave flow reactor that can operate in a genuine high-T/p process window (310°C/50 bar) and that allows a throughput of 20 l/h, therefore operating on a commercially relevant scale. The use of this platform for the industrial scale synthesis of a variety of relevant chemicals is briefly demonstrated. Particular emphasis is placed on the energy efficiency of the microwave flow synthesis design.

2. Results and discussion

2.1. Microwave cavity concept and design

Currently two different concepts with respect to microwave reactor design have been established: multimode and monomode (also referred to as single-mode) [34, 35]. In the so-called multimode instruments, the microwaves that enter the cavity are reflected by the walls and the load over the typically large cavity. In many multimode instruments, a mode stirrer ensures that the field distribution is as homogeneous as possible to avoid the formation of areas of high and low field intensity (leading to so-called hot and cold spots). In the much smaller monomode cavities, only one mode is present, and the electromagnetic irradiation is directed through a precision-designed rectangular or circular waveguide onto the reaction vessel mounted at a fixed distance from the radiation source, which creates a standing wave [34, 35]. Compared to multimode reactors, the field densities in single-mode cavities are significantly higher as all microwave energy is “concentrated” into one mode. Therefore, energy release inside the mode is very high, and in many cases the microwave field is too dense to be completely absorbed by the reaction mixture [36, 37]. Applying the standard 2.45 GHz microwave frequency used in most microwave systems (corresponding to a free space wavelength of ~12.25 cm) means that the dimension of a single mode is limited to ~6 cm. Homogeneous microwave field conditions are therefore realized in a comparatively small volume only, which severely limits the scale-up potential of single-mode microwave reactors. In principle, multimode cavities, where a three-dimensional pattern of many modes exists, do not have this limitation, and vessel sizes can be significantly larger [9–14, 17]. High levels of microwave power are necessary to generate the field densities required for operating in a high-T/p process window in a multimode cavity. In addition, small changes in dielectric properties of the media can significantly influence the entire field distribution. Proper parameter control in these circumstances is difficult to realize, which could lead to uncontrolled conditions lacking reproducibility.

Taking the advantages and disadvantages of single- and multimode cavities discussed above into account, it would appear reasonable to combine the benefits of both technologies into a fundamental transmission line short-circuited waveguide reactor concept for the desired continuous flow approach (Figure 1), where the short circuit along the traveling axis of the microwave would allow 3–10 modes. The main idea of this concept is the combination/alignment of a number of modes along the direction of the reaction tube. The rotationally symmetric positioning of the reaction tube inside the modes would guarantee a field distribution where all products passing the tube to be heated receive the same amount of energy at the end. Aligning the modes along the reaction tube would also allow significantly longer residence times and, therefore, a high throughput.

The concept shown in Figure 1 can be put into practice by creating a standing wave that, in general, is generated by a short circuit at the end of a monomode resonator. Due to this self-interference, the wave modes remain at their position and only the polarization of the modes changes with the frequency

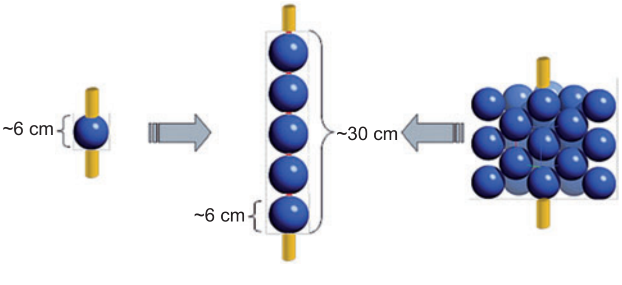


Figure 1 Monomode resonator concept for a microwave flow reactor merging the benefits of existing mono- and multimode technologies.
Left: monomode flow concept; right: multimode flow concept; center: cylindrical waveguide in the fundamental mode TM_{01}. An idealized cylindrical reaction tube is shown in yellow.

of the electromagnetic wave. By using a resonator comprising a stainless steel tube with a diameter somewhat larger than the wavelength of the standing wave, it is possible to generate a standing wave pattern (Figure 2). This monomode (transversal E_{01n} mode) is symmetric in respect to the central axis of the applicator. The number of modes (n) is determined by the length of the resonator and correlates with the wavelength of the electromagnetic wave [38, 39].

Two major issues in conventional single-mode continuous microwave processing are energy efficiency [40] and the residence time of the reaction medium in the microwave heating zone (Figures 1 and 3). Both issues can be solved by the short circuit transmission line resonator concept. Microwaves coupled into the stainless steel transmission line resonator at the front end propagate rotationally symmetric with the flow of the reaction medium inside the microwave transparent reaction tube. On the way to the short circuit, microwave energy will be absorbed by the reaction mixture and transferred into heat. Consequently, the field strength of the individual modes exhibits an exponential decay along the tube. Any remaining energy at the short circuit will be reflected back along the tube but now in the opposite direction. Compared to a conventional single-mode batch reactor the energy released from the magnetron will be able to interact with the reaction medium over several modes of the standing wave. Dipoles inside the tube do have more time to convert the provided microwave energy into heat via dielectric heating mechanisms. The wave will be reflected and sent back; on the way back to its origin, microwave energy transfer into heat occurs. To prevent damage to the microwave generator by reflected microwave radiation, a ferrite isolator is used to eliminate reflected microwave power, which can be easily measured using a watt-meter. The difference between forwarded energy released from a magnetron and reflected energy coming back from the applicator unit provides direct access to the efficiency Q_{eff} of the system (see below):

$$Q_{eff}=(Q_{generated}-Q_{reflected})/Q_{generated}$$

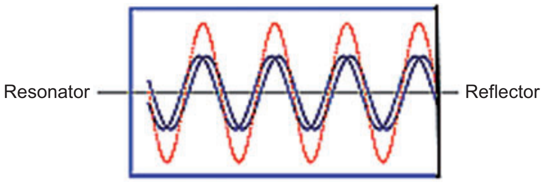


Figure 2 Creation of a standing wave in a monomode resonator.

2.2. Microwave flow reactor

The implementation of the short-circuited transmission line resonator concept discussed above has been realized by Püschner GmbH & Co KG (Schwanewede, Germany) in a commercially available flow microwave heating system: µWaveFlow0610 (2.45 GHz, max power 6 kW) [41]. The system was initially designed to rapidly provide hot water on demand by employing a microwave transparent ceramic tube [38, 39]. For synthetic chemistry in a genuine high-T/p process window, the flow reactor was suitably modified, paying particular attention to safety and reliability. Figure 4 displays the general set-up of the continuous flow microwave processing unit using the standing wave concept for energy transfer.

In this system, microwave power is generated with a standard magnetron with variable power output from 0.6 to 6 kW (currently flow systems for 2.45 GHz microwave frequency with a power release up to 20 kW are commercially available) [41]. Here, 0.6–6 kW represents the adjustable power released from the magnetron measured by a watt meter. The energy provided to the dielectrically active medium will be absorbed instantaneously to almost 100%. The microwave power generated by a magnetron is guided via a rectangular waveguide to a launching section that couples the microwave power into the stainless steel transmission line resonator. A standing wave is created along the length (approx. 70 cm) of the transmission line waveguide (see Figure 2).

The main criteria for the actual reaction tube contained inside the steel resonator are microwave transparency, physical stability and chemical resistance. Several different microwave transparent materials are available and have been used previously in microwave chemistry systems [17–32], including polytetrafluoroethylene (PTFE), polyetheretherketone (PEEK), quartz or Pyrex glass and sapphire. Most of these materials, unfortunately, are limited in their chemical or physical resistance. The broadest range in terms of temperature-, pressure- and chemical resistance is realized by microwave transparent ceramics such as γ-aluminum oxide (Al_2O_3). For the experiments described herein, a microwave transparent standard 75 cm×1 cm i.d. Al_2O_3 ceramic tube tested at 220 bar was employed, centered inside the applicator for heating the reactants. The maximum temperature and pressure for continuous processing was about 300–310°C and 30–60 bar, respectively, depending on the reaction type. The pipe work outside the microwave field consisted of stainless steel (EN-standard 1.4571), including a cooler spiral and a residence time coil of adjustable length (if required). Corrosion tests are highly recommended to assess the durability of the steel equipment.

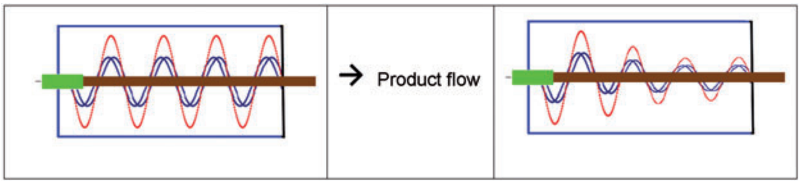


Figure 3 Left: Reaction tube centered in the monomode resonator microwave field without medium. Right: Exponential decay of field strength along the reaction tube in presence of reaction medium with dielectric loss.

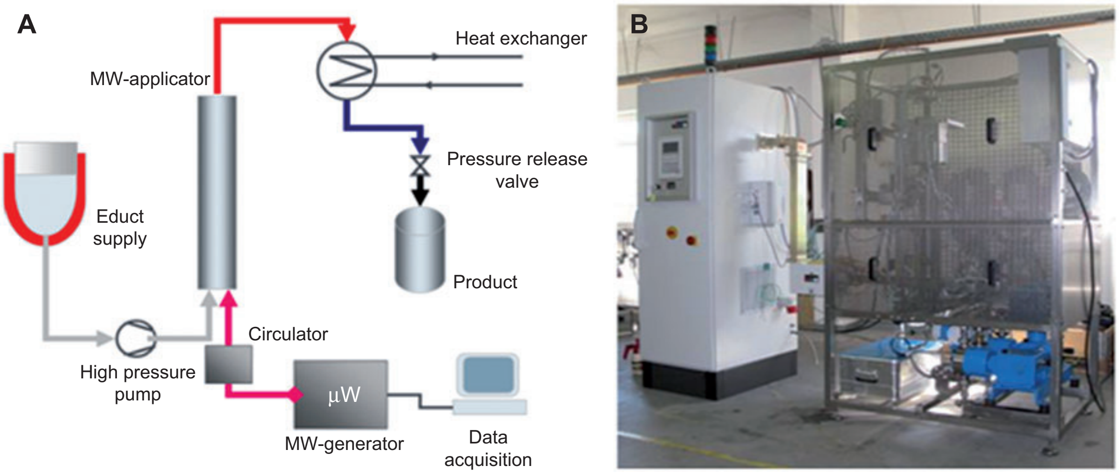


Figure 4 (A) General design of the continuous microwave synthesis unit; (B) graphical image of the unit.

Standard PC equipment was used to monitor temperature (PT 100, ceramic tube inlet at the bottom and outlet at the top), pressure (pressure cell, ceramic tube inlet and outlet), and flow (Coriolis type flow measurement system, Siemens, Frankfurt, Germany). In addition to the microwave power generated by the magnetron, the reflected microwave power was measured with a detector diode in the waterload of the circulator.

For homogeneous processing, double or triple head PTFE-membrane pumps with adjustable flow were used to minimize pulsation phenomena (a snubber unit can be used if necessary). Typical pressure values for laboratory use were 20–50 bar for continuous flow, controlled by a standard back pressure regulator. Typical flow rates for laboratory use were about 3–5 l/h. To prepare larger samples of a given product, up to 20 l/h have been realized (pump limit). The limitation for laboratory use is only a function of the quantity of chemicals manageable in a research laboratory at a given time. Technical limitations are the maximum power output of the magnetron, the cooling capacity of the heat exchanger and pump flow limits.

To work in the desired high-T/p range, several precautions must be taken with respect to safety issues. The most critical issue for scaling up microwave processing is the requirement to use microwave transparent tubing to ensure a high energy transfer into the dielectrically active reaction mixture. Only material with very low ε'' such as some polymers, quartz glass and some ceramics can be used as tube material [9–14]. No materials can be considered as inherently safe, and a mechanical breakdown must be taken into safety considerations. An inert nitrogen atmosphere with control of oxygen content inside the applicator system ensures safety in case of a leakage or breakdown of the reaction tube. Additionally, to avoid plasma formation, arcing sensors protect the system by continuously monitoring the inner part of the applicator. In case of energy accumulation due to any technical dysfunction, arcing or even plasma formation can occur. The arc sensors employed are optical photomultipliers that monitor the inner part of the microwave applicator. In case of arcing, a sharp increase in photon detection leads to an immediate shut down of power release from the magnetron.

Pressure control devices in front and back of the reaction tube are installed to monitor the pressure status of the tube. If the upper pressure limit (60 bar) is exceeded, the microwave energy will be automatically stopped by the monitoring system within a fraction of a second. A sharp pressure drop will indicate a tube breakdown and lead to a shutdown of the system. Individually adjustable temperature limits to protect reagents and equipment are installed at several positions. Specifically, a first probe (PT 100 type temperature sensor) detects the temperature of the raw material at the front end of the reaction tube. A second control measures the outlet temperature at the exit of the microwave field, and a third probe monitors the bulk temperature at the outlet of the residence line. A final probe after the cooling section completes the temperature monitoring. All critical parameters are automatically controlled and displayed on one screen, which provides the operator with a comprehensive overview of the status of the reaction. A detailed knowledge of critical reaction parameters like thermal stability and reaction enthalpy are mandatory. The maximum operating temperature in this reactor is 310°C.

Microwave leakage is continuously monitored by online sensors at different positions in the laboratory. The control limit is 5 mW/cm^2 based on industrial safety standard IEC 519-6. If any microwave radiation is detected, the magnetron will be stopped instantaneously.

In any event, because of the comparatively small tube volume (60 ml), the hazard potential, even in case of a tube breakdown at a maximum pressure of up to 60 bar (and the resulting impact on the stainless steel applicator), is rather limited [42].

2.3. Performance validation and energy efficiency

At present, poor transformation of microwave energy into heat is one of the strongest arguments against microwave processing of chemical transformations [40]. In the case of small scale (ml) laboratory single-mode equipment, typically <10% of radiation energy is transferred into heat [36]. To assess the efficiency of the transmission line reactor system in terms of energy conversion, two sets of heating experiments based on water and methanol as model compounds for dielectric active media were designed. These two liquids were chosen for two reasons: 1) all required physical parameters of water and methanol are well known in the literature, especially the specific heat capacity at constant pressure, c_p. In the liquid phase, both coefficients can be considered to be constant (c_p water: 4.22 kJ/kgK; c_p methanol: 2.53 kJ/kgK) for a wide temperature range; 2) the heating of both liquids does not lead to any undesired enthalpy effects that might disturb the energy balance.

In the first experiment, water at 35°C was heated in the microwave processing unit to 180°C at a starting flow rate of 3 l/h. After reaching stable processing conditions, the flow rate was increased. By raising the power output of the magnetron, the temperature was again adjusted to 180°C. Using the same procedure, the flow rate was increased to a maximum of 20 l/h. For each set of parameters, the energy absorbed by the water was monitored. In the second experiment, the same procedure was employed for methanol using an inlet temperature of 31°C, a maximum temperature measured at the tube outlet of 168°C and flow rates of up to 10 l/h. During the entire experiment, a pre-pressure of 35 bar was applied to ensure a liquid state for water and methanol. Temperature measurement was performed directly at the outlet of the ceramic tube outside of the microwave applicator (Figure 4).

Calculation of the energy converted into heat was performed by the standard equation of energy flow [40]:

$$Q=m*c_P*\Delta T$$

Q=energy flow (J); m=mass (kg); cp_{water}=specific heat capacity (for water 4.22 J/kgK); $cp_{methanol}$=specific heat capacity (for methanol 2.53 J/kgK); ΔT_{water}=temperature gradient (35°C→180°C); $\Delta T_{methanol}$=temperature gradient (31°C→168°C)

Figure 5 displays the energy efficiency in transferring microwave radiation into heat per l medium at a given flow rate. It can be seen that an increase in the flow rate (and thus a shorter residence time, see Figure 6) leads to a more efficient energy transfer for both solvents. At first glance, the conclusion might be drawn that higher flow rates will promote the energy transfer from microwave irradiation into heat. This unexpected observation becomes even more astounding when the residence time for both media inside the microwave field is taken into consideration. Because of the fixed dimensions of the ceramic tube (1 cm i.d., 60 cm length inside the microwave field), the residence time decreases significantly with increasing flow rate (Figure 6).

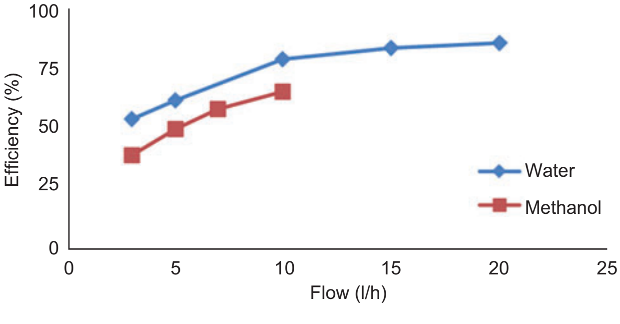


Figure 5 Efficiency of energy transfer of microwave radiation into heat in the continuous microwave unit (Figure 4).

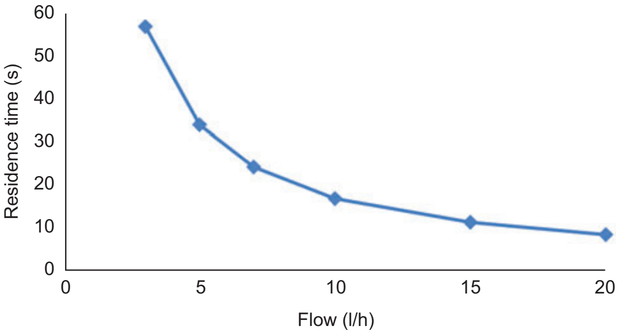


Figure 6 Dependence of residence time on flow rate.

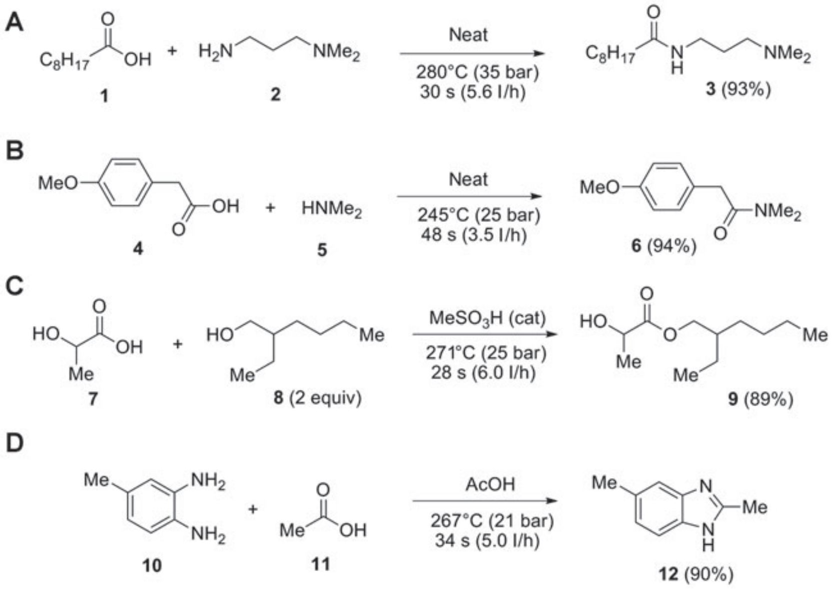
The faster the material passes through the microwave processing unit, the better is the conversion of radiation into heat. Initially this observation was difficult to rationalize. However, by taking the heat loss of the ceramic tube via IR radiation into consideration, this observation becomes more reasonable. A theoretical energy demand of 612 kJ/l ($Q_{min,\ water}$) to heat one liter (kg) of water can be expected. This wattage represents the base line that can be achieved by a theoretical efficiency of 100% energy conversion. Q_{loss} can then be calculated from the measured $Q_{effective}$ as follows:

$$Q_{loss}=Q_{effective}-(Q_{min} * Flow)$$

Calculation of Q_{loss} at a given flow rate indicates a loss of energy of 1740 kJ or 0.48 kWh on average. This more or less constant loss of energy most likely represents the heat loss via IR radiation of the ceramic tube. It can thus be concluded that the short circuit transmission line resonator concept flow reactor described herein can operate with an exceptional degree of energy efficiency [43–45].

2.4. Synthetic applications

In Scheme 1, examples of chemical transformations that have been performed using the flow microwave system introduced above are summarized. In general, all reactions were first evaluated and optimized on a small scale using a monomode microwave batch reactor (Biotage® Initiator, Uppsala, Sweden) to obtain proof-of-concept and basic kinetic data. Subsequently, the reactions were performed in the flow equipment (Figure 4) using a single feed on scales typically ranging from 3 to 60 mol. As outlined above, a 75 cm×1 cm i.d. Al_2O_3 ceramic tube positioned inside the applicator was used as reaction zone. Time data mentioned in Scheme 1 represent the average residence time of the reaction mixture inside of the microwave heated zone. Due to setup reasons, only ~60 cm of the ceramic tube are positioned inside the microwave field. Flow was adjusted at 3–6 l/h depending on the type of reaction, leading to residence times of only 30–60 s. By field



Scheme 1 High-T/p chemistry performed under microwave flow conditions.
Typically, 90% of microwave power was absorbed with a power consumption of 1.35–2.8 kW.

strength adjustment, the temperature was controlled with an accuracy of +/-2°C. A temperature probe (PT 100) was positioned at the outlet of the ceramic tube, and the values discussed below refer to this measurement point. The standard maximum pressure for the reactions described in Scheme 1 was 35 bar, adjusted via a suitable back pressure regulator. Product identity and purity of these known products were determined by ^{1}H-NMR, GC or HPLC.

3. Conclusion and outlook

In summary, the first general purpose industrial scale continuous flow microwave reactor for organic synthesis has been described. The reactor introduced herein allows the safe and highly energy efficient processing of organic reaction mixtures (with or without solvent) under high-temperature/high-pressure conditions. This process window leads to very fast reactions that are nearly impossible to realize in batch mode on scale. Although the present work has focused on highlighting the benefits of this technology for organic transformations at extreme temperatures, the reactor can also be used at more moderate temperatures that are more relevant for the synthesis of pharmaceutical intermediates.

The currently described laboratory-style microwave unit (Figure 4) is capable of processing 20 l/h (~500 l per day), which essentially corresponds to the limits of the pumps currently employed. The throughput of the system can be readily increased by increasing the diameter of the tube, increasing the flow rate and employing more powerful magnetrons (e.g., 30 kW), which can ensure rapid and efficient volumetric heating of the reactor zone. An important additional variable is the microwave frequency, as the use of, e.g., 915 MHz technology allows a higher penetration depth coupled with an even further increase in energy efficiency. Such a plant-size microwave flow system designed for full production scale of a specific product at >1000 t/year is currently under evaluation.

4. Experimental section

4.1. General

General features and processing parameters for the operation of the flow reactor shown in Figure 4 are described and commented upon in the main text of the manuscript (see Section 2). All chemicals and solvents were obtained from standard commercial vendors and were used without any further purification except where stated otherwise.

4.2. Preparation of *N*-[(3-dimethylamino)propyl] octylamide (3)

A 10-l Büchi stirred autoclave with gas inlet tube, stirrer, internal thermometer and pressure compensator was initially charged with 2.89 kg of caprylic acid (**1**, 20 mol), which was heated to 45°C. At this temperature, 2.04 kg of dimethylaminopropylamine (**2**, 20 mol) was slowly added while cooling. In an exothermic reaction, caprylic acid *N*-[(3-dimethylamino) propyl] ammonium salt was formed. The ammonium salt thus obtained was pumped continuously through the reaction tube at 5.6 l/h at a working pressure of 35 bar and irradiated with a microwave power of 3.1 kW, 92% of which was absorbed by the reaction mixture. The residence time of the reaction mixture in the irradiation zone was approximately 30 s. At the end of the reaction tube, the reaction mixture had a temperature of 280°C. A conversion of approximately 93% of theory was attained (^{1}H-NMR-analysis, the remainder being unreacted ammonium salt). The reaction product was slightly yellowish and contained <2 ppm of iron. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=0.83 (t, 3H), 1.17–1.30 (m, 8H), 1.5–1.65 (m, 4H), 2.1 (t, *J*=8.0 Hz, 2H), 2.18 (s, 6H), 2.32 (t, J=6.4 Hz, 2H), 3.27 (m, 2H), 6.90 (s, 1H).

4.3. Preparation of 2-(4-methoxyphenyl)-*N,N*-dimethylacetamide (6)

While cooling with dry ice, 1.35 kg of dimethylamine (**5**, 60 mol) from a reservoir bottle was condensed into a cold trap. A 10-l Büchi stirred autoclave with gas inlet tube, mechanical stirrer, internal thermometer and pressure equalizer was initially charged with 5 kg of 4-methoxyphenylacetic acid (**4**, 60 mol), which was melted at about 100°C. By slowly thawing the amine-containing cold trap, gaseous dimethylamine was introduced slowly through the gas inlet tube directly into the acid melt in the stirred autoclave. In an exothermic reaction, the 4-methoxyphenyl-acetic acid dimethylammonium salt was formed. The molten ammonium salt thus obtained was kept at 95°C and pumped continuously through the reaction tube at 3.5 l/h at a working pressure of about 25 bar and irradiated with a microwave power of 1.95 kW, 95% of which was absorbed by the reaction mixture. The residence time of the reaction mixture in the irradiation zone was approximately 48 s. At the end of the reaction tube, the reaction mixture had a temperature of 245°C. Based on the acid component used, a conversion of 97% of theory was attained in the crude product (the rest being unreacted salt). After workup, a virtually colorless product with >99% purity was obtained in 94% yield. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.95 (s, 3H), 2.98 (s, 3H), 3.64 (s, 2H), 3.77 (s, 3H), 6.84– 6.86 (d, J=7.2 Hz 2H), 7.15–7.17 (d, *J*=7.2 Hz, 2H).

4.4. Production of 2-ethylhexyl 2-hydroxypropanoate (9)

In a 10-l Büchi stirred autoclave with stirrer, internal thermometer and pressure equalizer, 2.5 kg of lactic acid (**7**, as 90% strength aqueous solution, 25 mol) was introduced as initial charge and admixed with 6.5 kg of 2-ethylhexanol (**8**, 50 mol) and also 0.075 kg (0.78 mol) of methanesulfonic acid. The mixture obtained was pumped through the reaction tube continuously at 6 l/h at an operating pressure of 25 bar and irradiated with a microwave power of 3.2 kW, 94% of which was absorbed by the reaction material. The residence time of the reaction mixture in the irradiation zone was approximately 28 s. At the end of the reaction tube, the reaction mixture had a temperature of 271°C. The reaction mixture was cooled to room temperature directly after leaving the reactor using a high-intensity heat exchanger. A conversion of 92% of theory was achieved (estimated via ^{1}H-NMR, the remaining product is unreacted lactic acid). The reaction product was colorless. Following neutralization of the catalyst with hydrogen carbonate solution and removal of the reaction water and unreacted starting materials by distillation, 4.52 kg (89% based on the concentration of the starting lactic acid) of 2-ethylhexyl lactate with a purity of >99% was obtained after vacuum distillation. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=0.88–0.92 (dt, 6H), 1.25–1.33 (m, 6H), 1.34–1.40 (m, 2H), 1,41–1,43 (d, *J*=5.6 Hz, 3H), 1.58–1.65 (m, 1H), 3.25–3.46 (s, 1H), 4.05–4.16 (dm, 2H), 4.26–4.30 (q, *J*=5.2 Hz, 1H).

4.5. Production of 2,5-dimethylbenzimidazole (12)

In a 10-l Büchi stirred autoclave equipped with internal thermometer and water cooling, 2.1 kg acetic acid (**11**, 35 mol) was cooled to 10°C. Under exothermic reaction, 1.22 kg of 3,4-diaminotoluene (**10**, 10 mol) was added carefully under stirring and cooling to keep the temperature at 10°C. To complete dissolution after addition of the amine, the reaction mixture was heated to 35°C and then pumped at a rate of 5 l/h through the reaction tube continuously under a pressure of 21 bar. At the end of the reaction tube, the mixture had a temperature of 267°C. The residence time inside of the microwave field was approximately 34 s. The reaction mixture was cooled to room temperature directly after leaving the reactor using a high-intensity heat exchanger. The crude reaction mixture was poured into ice water, and the pH was adjusted to 9 using 1 M NaOH. At this pH, a gray precipitate forms that can be washed, filtered and dried. Total isolated yield of the reaction was 90% of theory. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.44 (s, 3H), 2.55 (s, 3H), 7.01–7.03 (d, *J*=6.4 Hz, 1H), 7.30 (s, 1H), 7.40–7.42 (d, *J*=6.4 Hz, 1H).

References

[1] Hessel V, Kralisch D, Krtschil U. *Energy Environ. Sci.* 2008, 1, 467–478.
[2] Van Gerven T, Stankiewicz A. *Ind. Eng. Chem. Res.* 2009, 48, 2465–2474.
[3] Hessel V, Löb P, Löwe H. *Curr. Org. Chem.* 2005, 9, 765–787.
[4] Reay D, Ramshaw C, Harvey A. *Process Intensification*, Butterworth-Heineman: Burlington, MA, 2008.
[5] Keil F, Ed., *Modeling of Process Intensification*, Wiley-VCH: Weinheim, 2007.
[6] Hessel V, Cortese B, de Croon MHJM. *Chem. Eng. Sci.* 2011, 66, 1426–1448.
[7] Kappe CO, Dallinger D. *Mol. Diversity* 2009, 13, 71–193.
[8] Caddick S, Fitzmaurice R. *Tetrahedron* 2009, 65, 3325–3355.
[9] Leadbeater NE, Ed., *Microwave Heating as a Tool for Sustainable Chemistry*, CRC Press, Taylor & Francis Group: Boca Raton, FL, 2011.
[10] Polshettiwar V, Varma RS, Eds. *Aqueous Microwave-Assisted Chemistry,* Royal Society of Chemistry: Cambridge, UK, 2010.
[11] Kappe CO, Dallinger D, Murphree SS. *Practical Microwave Synthesis for Organic Chemists: Strategies, Instruments, and Protocols*, Wiley-VCH: Weinheim, 2009.
[12] Lidström P, Tierney JP, Eds. *Microwave-Assisted Organic Synthesis*; Blackwell Publishing: Oxford, UK, 2005.
[13] Loupy A, Ed., *Microwaves in Organic Synthesis*, 2nd ed., Wiley-VCH: Weinheim, 2006.
[14] Kappe CO, Stadler A, Dallinger D. *Microwaves in Organic and Medicinal Chemistry,* 2nd ed., Wiley-VCH: Weinheim, 2012.
[15] Kappe CO. *Chem. Soc. Rev* 2008, 37, 1127–1139.
[16] Strauss CR, Rooney DW. *Green Chem.* 2010, 12, 1340–1344.
[17] Moseley JD. In *Microwave Heating as a Tool for Sustainable Chemistry*, Leadbeater, NE, Ed., CRC Press, Taylor & Francis Group: Boca Raton, FL, 2011, pp. 105–147.

[18] Singh BK, Kaval N, Tomar S, Van der Eycken E, Parmar VS. *Org. Process Res. Dev.* 2008, 12, 468–474.
[19] Baxendale IR, Hayward JJ, Ley SV. *Comb. Chem. High Throughput Screening* 2007, 10, 802–836.
[20] Glasnov TN, Kappe CO. *Macromol. Rapid Commun.* 2007, 28, 395–410.
[21] Ullah F, Samarakoon T, Rolfe A, Kurtz RD, Hanson PR, Organ MG. *Chem. Eur. J.* 2010, 16, 10959–10962.
[22] Dressen MHCL, Van de Kruijs BHP, Meduldijk J, Vekemans JAJM, Hulshof LA. *Org. Process Res. Dev.* 2010, 14, 351–361.
[23] Bergamelli F, Ianelli M, Marafie JA, Moseley JD. *Org. Process Res. Dev.* 2010, 14, 926–930.
[24] Bagley MC, Fusillo V, Jenkins RL, Lubinu MC, Mason C. *Org. Biomol. Chem.* 2010, 8, 2245–2251.
[25] Moseley JD, Lawton SJ. *Chem. Today* 2007, 25, 16–19.
[26] Benaskar F, Hessel V, Krtschil LP, Stark A. *Org. Process Res. Dev.* 2009, 13, 970–982.
[27] Dressen MHCL, Van de Kruijs BHP, Meduldijk J, Vekemans JAJM, Hulshof LA. *Org. Process Res. Dev.* 2009, 13, 888–895.
[28] Leadbeater NE, Barnard TM, Stencel LM. *Energy Fuels* 2008, 22, 2005–2008.
[29] Smith CJ, Iglesias-Sigüenza FJ, Baxendale IR, Ley SV. *Org. Biomol. Chem.* 2007, 5, 2758–2761.
[30] Öhngren P, Fardost A, Russo F, Schanche, J-S, Fagrell M, Larhed M. *Org. Process Res. Dev.*, doi:10.1021/op300003b.
[31] Organ MG, Hanson PR, Rolfe A, Samarakoon TB, Ullah F. *J. Flow Chem.* 2011, 1, 32–39.
[32] Raner KD, Strauss CR, Trainor RW, Thorn JS. *J. Org. Chem.* 1995, 60, 2456–2460.
[33] Batch microwave protocols can also be translated to conventionally heated pressurized high-T/p capillary or chip microreactors in which the high temperatures and pressures attainable in a sealed vessel microwave chemistry batch experiment can be mimicked ("microwave-to-flow" paradigm). Heat transfer to and from the reaction mixture is very fast owing to the high surface-to-volume ratio in these systems (channel or capillary dimensions ≤1 mm). However, the scalability to production scale volumes of this approach has not been demonstrated so far. For details, see: Glasnov TN, Kappe CO. *Chem. Eur. J.* 2011, 17, 11956–11968.
[34] Metaxas AC. In *Industrial Microwaves Heating*, Meredith, RJ, Ed., Peter Peregrinus Ltd for the Institute of Electrical Engineers: London, 1983 (reprinted 1993), pp. 296–321.
[35] Meredith RJ. *Engineers Handbook of Industrial Microwave Heating*, Institute of Electrical Engineers: London, 1998.
[36] Hoogenboom R, Wilms TFA, Erdmenger T, Schubert US. *Aust. J. Chem.* 2009, 62, 236–243.
[37] This assumption is supported by simulations on the field density and energy efficiencies for a commercial single-mode cavity: Robinson J, Kingman S, Irvine D, Licence P, Smith A, Dimitrakis G, Obermayer D, Kappe CO. *Phys. Chem. Chem. Phys.* 2010, 12, 4750–4758.
[38] Püschner PA. (Püschner GmbH), *Microwave Applicator with Cavity Resonator for Thermal Treatment of Materials Has Wave Field Coupling Unit with Metal Coupling Rod Extending into Resonator Interior*, DE10244941, 2003.
[39] Püschner H. *Continuous Duty Microwave Tunnel Oven*, DE 2019012 (A1), 1971.
[40] Moseley JD, Kappe CO. *Green Chem*. 2011, 13, 794–806.
[41] For details, see: www.pueschner.com.
[42] Calculations performed by German TÜV indicate a controllable risk, even assuming worst case scenarios for endothermic or slightly exothermic reactions.
[43] Matsuzawa M, Togashi S, Hasebe S. *J. Therm. Sci. Technol.* 2011, 6, 69–79.
[44] Benaskar F, Ben-Abdelmoumen A, Patil NV, Rebrov EV, Meuldijk J, Hulshof LA, Hessel V, Krtschil U, Schouten JC. *J. Flow Chem.* 2011, 1, 74–89.
[45] Patil NG, Hermans AIG, Benaskar F, Rebrov EV, Meuldijk J, Hulshof LA, Hessel V, Schouten JC. *AlCheE J.*, doi:10.1002/aic.13713.

Received April 21, 2012; accepted May 2, 2012

Roman Morschhäuser is a corporate project manager and member of the application development team in Clariant's detergent business. He studied polymer chemistry at the Johannes-Gutenberg University of Mainz, Germany and received his doctoral degree in 1997 on the anionic polymerization of aminofunctionalized Isprene derivates. After joining the Höchst AG in 1997, he was transferred to Clariant GmbH and worked in several positions within research and development and production technology. Since 2004, he coordinates all microwave related activities within the Clariant group and is currently responsible for further development of this technology. Roman Morschhäuser has several patents in different disciplines like personal care, oil field applications, crop protection and microwave-assisted organic synthesis. In 2007, his team was awarded "Best Innovation Contributor 2007" from Henkel Kg for the development of special laundry additives.

Matthias Krull manages Innovation and Patents in the Business Line Refinery Services at Clariant Produkte (Deutschland) GmbH in Frankfurt, Germany. He received his diploma and doctoral degree in bioorganic chemistry (1989) from the Free University in Berlin, Germany, where he worked on the synthesis of surface active compounds and their characterization in surface monolayers and lipid membranes. In 1990, he started his professional career at Hoechst AG in Frankfurt, Germany as a research chemist in the development of oilfield chemicals. In different R&D positions at Hoechst and later Clariant, his main research interest was the application-oriented design of monomeric as well as polymeric chemicals and their scale-up to commercial scale. He is a named (co-)inventor of numerous patent applications. Since 2002, he focuses on strategies for IP protection and innovation for the oilfield business and for microwave technology.

Christoph Kayser is head of application development for well service additives for Oil and Mining Services at Clariant Produkte (Deutschland) GmbH in Frankfurt, Germany. His group develops application solutions for oil and natural gas well drilling, cementing and stimulation. He studied chemistry at the Johannes-Gutenberg University in Mainz, Germany and the University of Massachusetts at Amherst, USA. He received his diploma and doctoral degree (1999) from the Johannes-Gutenberg University in Mainz, where he worked on the synthesis and phase behavior of soluble graphene-based materials. In 1998, Kayser joined Clariant as a research chemist in polymer chemistry. His main research interest was in the field of functional water soluble polymers for the oilfield industry, the synthesis of macromonomers, surfactants and microwave-assisted chemistry. He worked on the design of polymer plants for specialty polymers and the design of microwave reaction systems. Since 2008, Kayser heads application development for well service additives.

Cornelia Boberski is a project management advisor focused on developing new businesses within the chemical industry. She works on developing breakthrough ideas and positioning the business concepts with customers and suppliers and accompanying these projects to their final implementation with the customers. Cornelia Boberski received her doctoral degree in Experimental Petrology in high pressure synthesis of inorganic compounds (1986) from the Institute of Mineralogy of Ruhr University Bochum, Germany. Following positions at university, she was a researcher with IBM Research Laboratories, Yorktown Heights, New York, USA (1987) and then spent a total of 25 years as a manager in the chemical industry. There, she worked closely with customers across the automotive, raw materials and electronics industries in research and development, marketing and sales and as a business manager for Hoechst and Clariant in Frankfurt, Germany. Cornelia Boberski has patents in material science and has published numerous scientific papers. In 2005, she founded and leads the company Innoturn®, which provides project management advice and implementation of innovation to the industry.

Ralf Bierbaum received his diploma in process engineering from the Technical University (TU) Clausthal (2001) and his doctoral degree in process engineering from the TU Bergakademie Freiberg (2005). Since beginning at Clariant in 2005, he has participated in research of microwave-assisted reaction control. Currently, he is working as an assistant plant manager. He also teaches chemical reaction technology at the University of Applied Science Darmstadt. Other research and development interests include thermal and mechanical separation technology as well as safety technology and plant planning.

Mr. Peter Püschner is the owner of Püschner GmbH +Co. KG. The company was founded in 1970 by his father, who was involved in the development of the first industrial magnetrons at Philips. Peter Püschner studied electrical engineering with a focus on telecommunication and microwaves. After getting his diploma, Peter Püschner worked 7 years for Draeger Medical in R&D for pediatric incubators and ventilators and as a product manager. In 1996, he took over the family business from his father. Currently, Pueschner Microwaves has approximately 20 employees and operates from its headquarters in the north of Germany near Bremen. Pueschner Microwaves is developing and producing industrial microwave machines for the pharmaceutical, medical, chemical, ceramic and food industries. Most applications are developed in close cooperation with the clients. Peter Püschner has patents in microwave technology and has published numerous scientific papers. Pueschner Microwaves is known to be a highly specialized engineering company capable of developing advanced process technology for new industrial microwave applications.

Toma N. Glasnov perused his PhD studies in the group of Prof. C. Oliver Kappe at Karl-Franzens-University in Graz, Austra during the period 2003–2007. After obtaining his PhD, he continued as a research fellow at the Christian Doppler Laboratory for Microwave Chemistry at the same university. His current research interests are in the areas of synthetic preparation/scaffold decoration of biologically active heterocycles, transition metal-catalyzed reactions and microwave and continuous-flow chemistry.

C. Oliver Kappe received his doctoral degree from the Karl-Franzens-University in Graz, Austria where he worked with Professor Gert Kollenz on cycloaddition and rearrangement reactions of acylketenes. After periods of postdoctoral research work with Professor Curt Wentrup at the University of Queensland, Australia, and with Professor Albert Padwa at Emory University, Atlanta, GA, USA, he moved back to the University of Graz where he obtained his “Habilitation” in 1998 and currently holds the position of professor for Organic Synthesis Technology. In 2006, he was appointed director of the Christian Doppler Laboratory for Microwave Chemistry at the University of Graz. His main current research interests include process intensification using microwave and continuous flow technology. He is also the Editor-in-Chief of *Flow Chemistry*.