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Development of an automated microreaction system with integrated sensorics for process screening and production

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Abstract

The development of an automated microreaction system (AuMμRes) is described allowing a systematic screening of process parameters for the design and optimization of chemical processes in the liquid regime. Besides parameter screening, the microreaction system is also dimensioned for automated small-scale production in the kilogram range.

By the adaptation of suitable actors and control techniques an active regulation of process parameters is possible. Pulsation-free actors, integrated sensors (temperature, pressure, flow, density), interfaces for analysis (HPLC, online spectroscopy), and a well-proven process control system are essential parts of the automated microreaction system.

Microfluidic structures with improved flow and mixing performance as well as microstructured flow-through sensors for monitoring pressure and mass flow have been developed and integrated into the microreaction system.

As a test reaction the nitration of 2-(4-chlorobenzoyl-)benzoic acid was considered. In order to handle this highly corrosive reaction all components that are in direct contact with the reagents consist of corrosion-resistant material.

Keywords: Automated microreaction system; Sensors; Nitration reactions; Online analysis

1. Introduction

Over the past years microreaction technology has impressively demonstrated its potential to deliver promising new approaches for chemical processes, e.g. by achieving improved heat and mass transport. Hence, it currently receives a growing acceptance as a complementary technology for process development and process optimization [1]. However, to establish microreaction technology as an effective tool for process design in industrial practice a more regulable and controllable operation of microreaction processes has to be achieved.

Here we report on the development of the automated microreaction system AuMμRes with integrated microstructured sensors and analytical interfaces for the monitoring of relevant process parameters (temperature, pressure, and mass flow), selectivities, yields or kinetic parameters. By the adaptation of suitable actors and control techniques an active regulation of process parameters is possible to optimize the entire microreaction process. Moreover, AuMμRes was in particular designed for parameter screenings and series of experiments based on statistical procedures to generate all relevant information for an effective process design within short timeframes. Besides enabling automated parameter screening AuMμRes is also dimensioned for small-scale production purposes up to the kilogram range.

2. Scope of application

The automated microreaction system was designed for conducting very different types of chemical reactions in the liquid regime. The user will be able to vary process parameters systematically over a wide range (Table 1). Flow rates, for example, can be adjusted up to 40 ml/min which is sufficiently high for production purposes in the kilogram

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Table 1
Parameter windows of the automated microreaction system AuMμRes

Parameter	Minimum	Maximum	Tolerance
Volume flow (ml/min)	0.1	40	±0.25%
Retention time (s)	1	600	–
Reaction temperature (°C)	−20	150	±1
Excess pressure (bar)	0	6	±0.1
Viscosity (mPa s)	0.5	100	–
Heat exchange (kW)	0	1	–
Temperature of educts at the reactor inlet (°C)	−20	100	±1

range. In general, the reaction system will allow the user to adjust and vary process parameters like temperature, pressure, flow rate resp. retention time, concentration, and stoichiometry automatically on the basis of a statistical experimental design.

Nitration reactions were chosen as exemplary test reactions as they make high demands on the functionality of an automated microreaction system. The majority of nitrations give off considerable amounts of heat producing a wide spectrum of products with correspondingly low yield and purity. In addition, the highly exothermic heat of reaction along with the acidic corrosivity of the nitrating agent makes nitration processes potentially very hazardous.

In previous studies it was shown that both the hazardous potential of nitrations and the formation of unwanted by-products can be successfully suppressed by employing microreactors [2–7]. Since nitrations are among the basic reactions used in chemical synthesis they were considered in this work as a suitable representative for several other liquid reactions with similar or even less strong demanding process conditions.

3. Setup of the automated microreaction system

Fig. 1 shows the complete flow sheet of the microreaction system. Three main sections can be distinguished: the reaction unit consisting of actors and microfluidic devices, the temperature control, and the automation comprising sensorics, analytics, and process control.

The reaction unit consists of two educt supply lines for adjusting concentration, temperature, pressure, and flow rate of the reaction partners. The two educt streams are guided into the microreactor which is directly connected to additional microstructured retention time modules. A back pressure valve at the end of the process (V7) allows to adjust the process pressure (up to 6 bar), e.g. to ensure liquid-phase reactions in cases of low-boiling solvents or other components with high vapor pressure.

Since AuMμRes is intended for handling highly corrosive reactions like nitrations, suitable materials are required, in particular for those parts of the reaction system which are in direct contact with the reactants. Although much literature and several databases exist that describe the corrosion stability of metals and other materials [8–10], less information is available about the corrosion stability of materials in the microscale. Since macroscopic corrosion is described in dimensions of “millimeter degradation per year”, such information is only of limited value to evaluate the corrosion stability of microstructures. Therefore, own experiments were conducted to investigate corrosion stability of different metals (1.4571, 1.4539, 1.4439, 1.4435, 1.4404, and 1.4401), fluorinated polymers (PTFE, PFA) as well as silicon, Si_3N_4, and SiO_2. The corrosion tests focused on the stability against concentrated sulphuric acid, fuming nitric acid, and mixtures thereof. Gravimetric methods according to Refs. [9–11] and

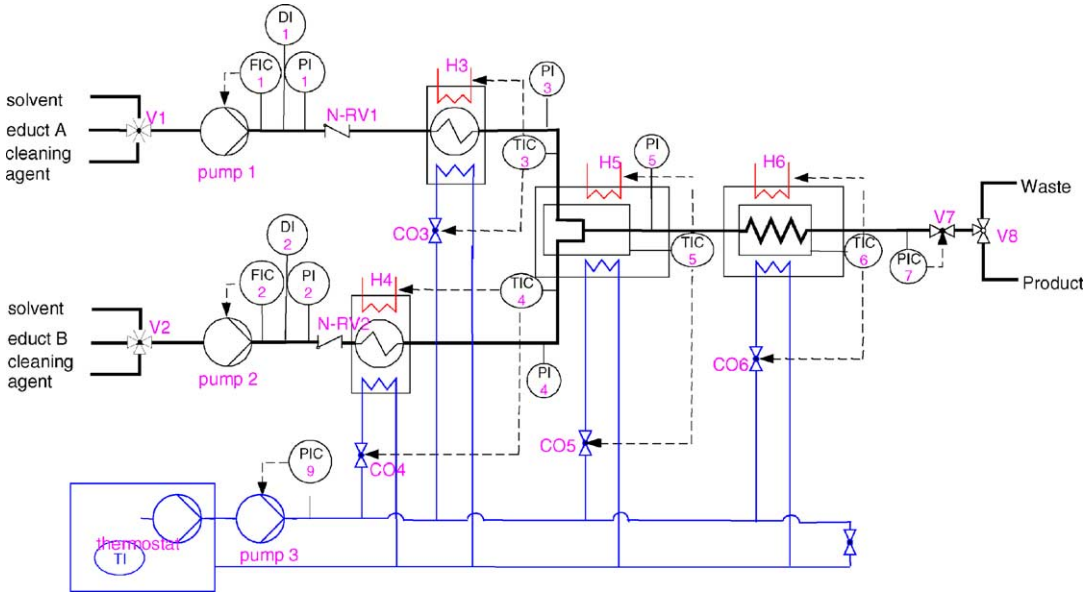

Fig. 1. Flow sheet of the automated microreaction system (V: valve, H: electrical heating, N-RV: non-return valve, CO: cooling, T: temperature, P: pressure, F: flow, D: density).

additional elemental analysis of the acids by employing atomic emission spectroscopy were applied. The results obtained showed clearly that even so-called corrosion-resistant metals undergo a significant corrosion in the microscale, whereas silicon, Si_3N_4, SiO_2, and fluorinated polymers turned out to be corrosion-resistant [11]. Therefore, in the AuMμRes microreaction system consequently only PTFE (e.g. tubings, fittings, and valves), glass (e.g. syringes), and silicon (e.g. microfluidic devices) are used in those parts of the system that are in direct contact with the reactants.

3.1. Educt supply

From previous studies it is known that pump pulsation may have a significant impact on the mixing performance of microreactors, and thus on the overall microreaction process [7]. Even continuously operating syringe pumps are known to exhibit pulsations when they switch over from an empty piston to a freshly refilled one. Therefore, the commercially available syringe pumps (Sykam GmbH, Fuerstenfeldbruck, Germany) that are used in the setup were modified in order to suppress temporary pulsations. Fig. 2 shows how pulsation spikes could be damped after installation of an additional switching valve in combination with a microcontroller for the individual control of both pistons. The remaining fluctuations are rather caused by small gas bubbles within the syringes than by the switching procedure itself.

Additional valves were integrated along the educt supply lines to allow a safe and long-term stable automated processing. Microstructured silicon flap valves [12] were installed behind the pumps as non-return valves (N-RV1, N-RV2) to avoid contamination of the educt reservoirs or even uncontrolled reactions within the educt supply lines. For purging and cleaning of the reaction system AuMμRes can automatically switch between the educt solution, the pure solvent, and a cleaning agent (valves V1 and V2).

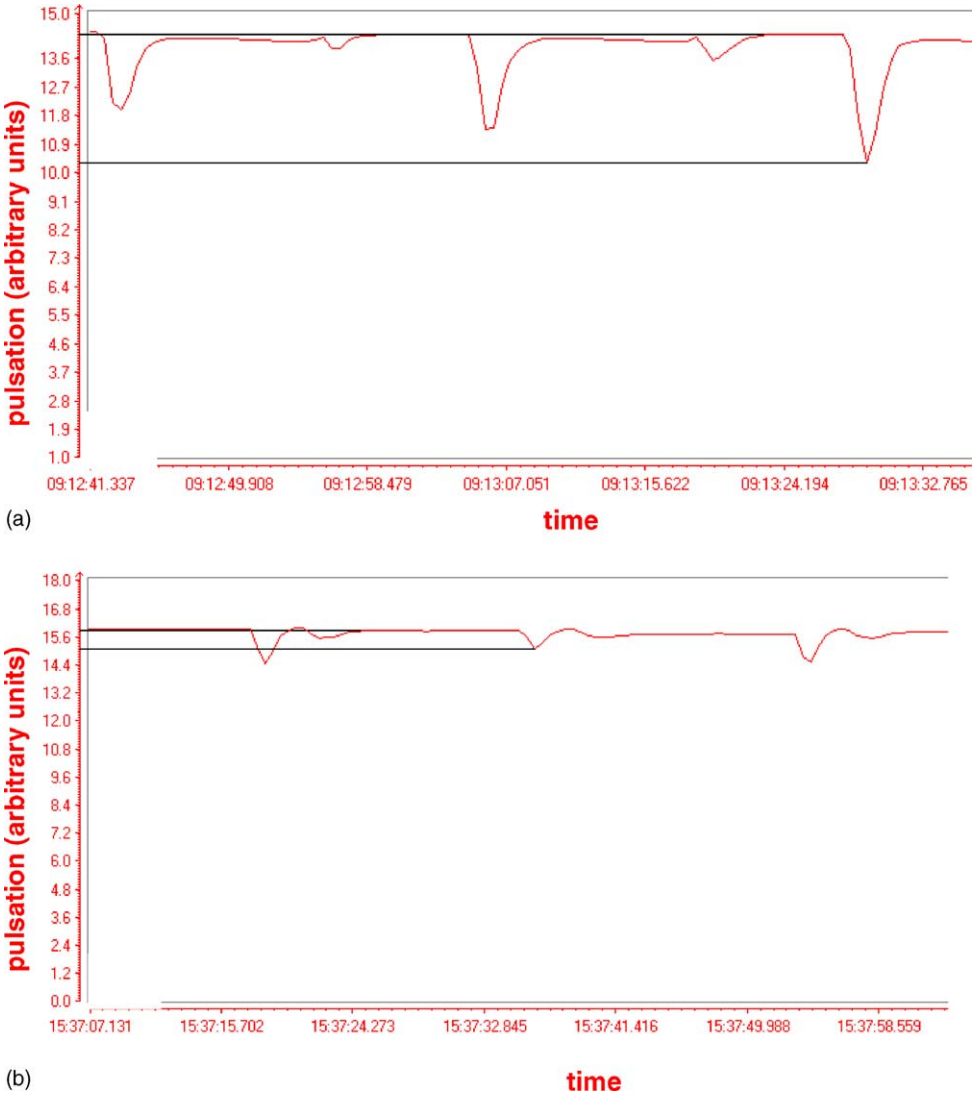

Fig. 2. Pulsation of continuously operating syringe pump before (a) and after (b) installation of additional valve (here at a flow rate of approximately 20 ml/min).

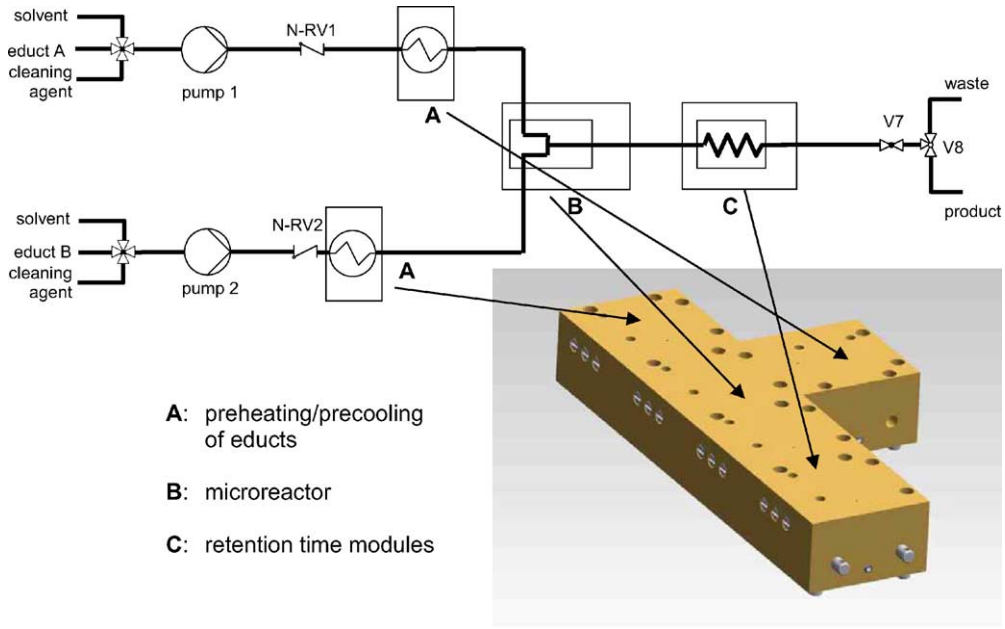

Fig. 3. Scheme of the microfluidic modules.

3.2. Microfluidic devices

Microfluidic devices are used in the setup for the preheating or precooling of the educts, for mixing and reaction as well as for hold-up. They are made of silicon with typical channel widths in the 300 μm range.

All microfluidic devices are integrated into cubical modules of identical shape and size, and can be easily replaced (Fig. 3). The modules are equipped with an individual temperature control, integrated pressure, and/or temperature sensors and—if required—additional actors like non-return valves. The modular concept of the AuMμRes reaction system ensures a flexible interconnection of the microfluidic devices. However, the development of a toolkit concept as considered in other works [22] was not intended.

The microfluidic structure that is applied in all modules is based on a well-known "split-and-recombine" mixing principle [13]. Fluids are forced to flow through parallel microchannels along a series of three-dimensional, G-shaped structures to intensify mixing (Fig. 4).

For the AuMμRes setup the microfluidic structure has been improved in several ways. To achieve a more uniform flow distribution over the parallel microchannels the inlet and outlet channels were shaped trapezoidally according to Refs. [14,15]. In addition, the number of parallel channels was increased from 9 to 11 and the number of G-shaped mixing elements along one microchannel was increased from six to seven and a half. Fig. 5 shows infrared images of the previous and the actual microfluidic design. The improved flow distribution and mixing performance of the new microfluidic design could be experimentally verified. Thermographic measurements confirmed the more uniform flow distribution and mixing sensitive model reactions like the Villermaux–Dushman reaction [16,17] confirmed the improved mixing quality in comparison to the previous design.

Several design variations have been realized for the new microfluidic structure, for example devices with only one inlet port (Fig. 6). In the AuMμRes setup these devices are in particular used for the preheating resp. precooling of the educts or as retention time structures. Moreover, also the number of parallel microchannels was varied. Devices consisting of 11, 4 or even 1 channel are available for the AuMμRes setup, mainly differing in throughput, pressure drop, and mixing performance (Fig. 6). The variety of microfluidic devices on basis of a common "split-and-recombine" structure allows the user to apply the most suitable device for his specific application.

One exemplary reaction that demonstrates the differences of the microfluidic structures is the regioselective mono-nitration of 2-(4-chlorobenzoyl-)benzoic acid to 2-(4-chloro-3-nitrobenzoyl-)benzoic acid, a precursor for the synthesis of a pharmaceutical agent [18] (Fig. 7). The

Fig. 4. Scheme of "split-and-recombine" mixing within three-dimensional, G-shaped microchannels.

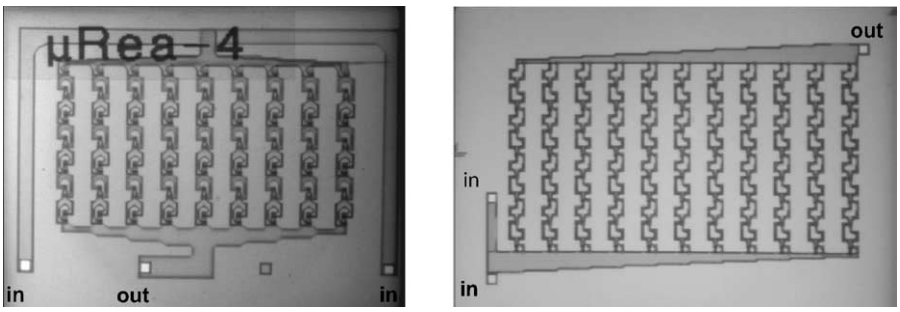

Fig. 5. Infrared images of the original split-and-recombine micromixer (left) and the improved microfluidic design developed in this work (right).

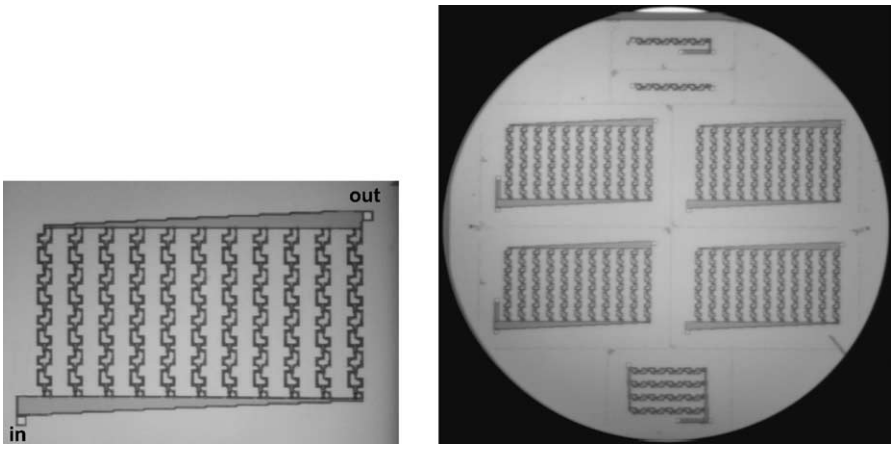

Fig. 6. Microfluidic structures differing in number of fluid ports (one inlet, left) and number of microchannels (1, 4, and 11; wafer image, right).

single-phase reaction, which is barely described in literature [19,20], is conducted by dosing HNO_3 to a solution of 2-(4-chlorobenzoyl-)benzoic acid in concentrated sulphuric acid (97%). Fig. 8 shows the different conversions that were achieved with the described microfluidic devices. To highlight their specific influence no further retention time modules were used in these experiments and thus only conversions of 30–40% were achieved. However, the examples show that both the 4-channel reactor and the 11-channel reactor gave higher conversions than obtained with the original unimproved "split-and-recombine" structure (see Fig. 5). Moreover, due to the higher pressure drop in the 4-channel reactor this device delivers the best mixing performance and thus the highest conversion. This example shows that the selection of the most suitable microfluidic device is determined by the process conditions and in particular by the expected pressure drop. High viscosities and flow rates, for example, will favor the use of the 11-channel reactor.

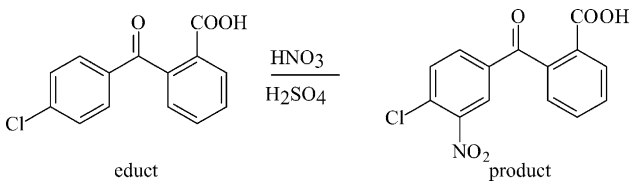

Fig. 7. Nitration of 2-(4-chlorobenzoyl-)benzoic acid.

For the sake of completeness it should be mentioned that higher conversions are achieved for the nitration of 2-(4-chlorobenzoyl-)benzoic acid as soon as microfluidic modules are interconnected in series (Fig. 9).

3.3. Temperature control

Defined thermal conditions over the entire microreaction system are of tremendous importance for a reliable and

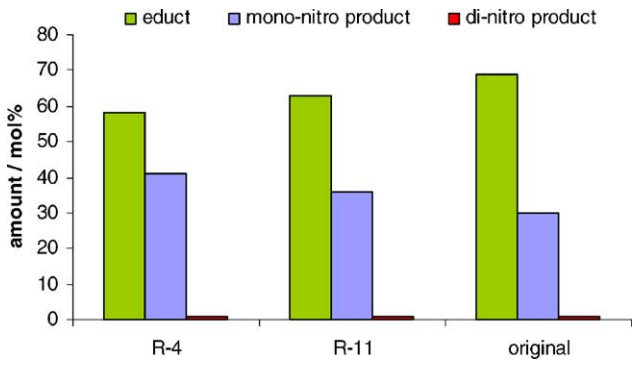

Fig. 8. Conversions achieved within different microfluidic devices for the nitration of 2-(4-chlorobenzoyl-)benzoic acid (R-4: four parallel microchannels; R-11: eleven parallel microchannels; original: nine parallel microchannels/original design; experimental conditions: H_2SO_4 + educt = 0.4 ml/min, HNO_3 = 0.024 ml/min, T = 20 °C).

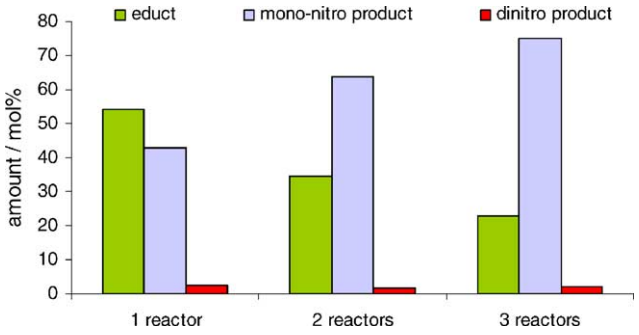

Fig. 9. Improved conversion by interconnection of microreactors.

repeatable processing. Therefore, each microfluidic module is independently temperature controlled by both electrical heating (H3, H4, H5, and H8 in the flow sheet; see Fig. 1) and fluidic cooling via a cryostat (valves CO3, CO4, CO5, and CO6). Temperature sensors that are integrated into the modules or positioned along the educt supply lines deliver continuously the actual values for the automatic temperature control.

3.4. Sensorics

Besides temperature sensors (currently Pt 100 devices), also pressure and mass flow sensors are integrated into the microreaction system to adjust and control these two relevant process parameters automatically (see flow sheet in Fig. 1).

Since until now there are no suitable sensors commercially available that fulfil the requirements of corrosion resistance, small hold-up, and negligible dead volume, both sensors have been self-constructed on basis of silicon microstructures.

The microstructured silicon pressure sensor (that will be equipped with an additional temperature sensor in the next generation) was designed for flow-through applications in a pressure range 0–10 bar. The sensor can be operated at temperatures up to 200 °C and has a dead volume of <0.5 μl. Fig. 10 shows the repeatable linear response of the sensor over the entire measuring range at different temperatures.

The microstructured mass flow sensor that is based on the Coriolis principle consists of two silicon loops that are excited to oscillate while the fluids are flowing through (Fig. 11). The design of the sensor is similar to that described by Enoksson et al. [21]. Since the mass flow is directly proportional to the ratio of the excitation amplitudes it can be determined by measuring these amplitudes, for example, optically. A more detailed description of the sensors' operation mode is given in Ref. [21]. In addition, the sensor is also suitable for density measurements. Fig. 12 illustrates the dependence of the resonance frequency on the density of the fluid, here shown for different water–ethanol

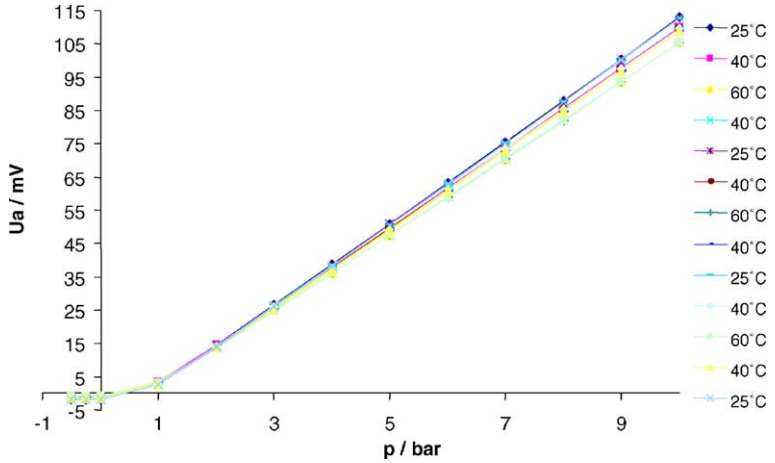

Fig. 10. Linear response of the microstructured pressure sensor at different temperatures over the entire measuring range (0–10 bar).

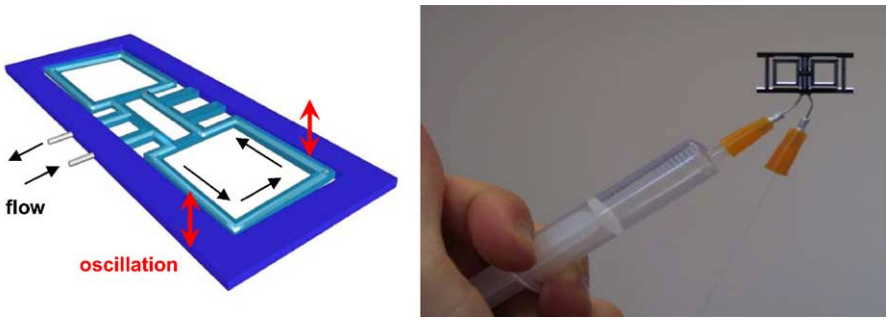

Fig. 11. Microstructured mass flow sensor made of silicon (Coriolis principle).

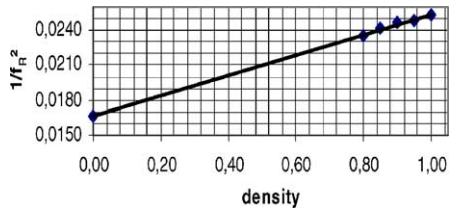

Fig. 12. Mass flow sensor: dependency of the resonance frequency on the density of the fluid (here: different water–ethanol mixtures).

mixtures. In the AuMμRes setup the mass flow (and density) sensor is installed just behind the pumps in the educt supply lines.

3.5. Analytics

The automated operation of a microreaction system requires the monitoring of integral parameters like temperature, pressure, and mass flow but also the analytical information about conversion, yield, or kinetics. Therefore, analytical interfaces are integrated into the AuMμRes setup to enable at-line analysis by sampling and subsequent chromatography (HPLC) as well as online analysis by infrared or Raman spectroscopy. Spectroscopic measurements allow a real-time monitoring of the chemical processes by installing suitable optical flow-through cells at selected positions of the microreaction system.

Online near-IR spectroscopy, for example, turned out to be a suitable method for the monitoring of the nitrate resp. HNO_3 concentration during the above-described nitration of chlorobenzoylbenzoic acid. Fig. 13 shows, as an example, the NIR spectroscopic monitoring of the HNO_3 consumption during the nitration process.

Raman spectroscopy is a more differentiating analytical technique that provides more structural information and thus allows distinguishing between educts, products, and intermediates. As an example, Fig. 14 shows spectra of pure sulphuric acid as well as mixtures with HNO_3, the starting material, and the actual reaction product. By applying chemometric methods also quantitative analysis is possible.

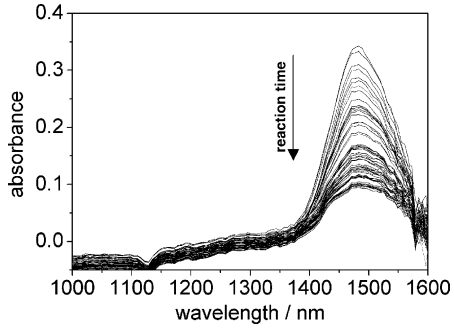

Fig. 13. NIR spectroscopic monitoring of HNO_3 consumption during the nitration of 2-(4-chlorobenzoyl-)benzoic acid.

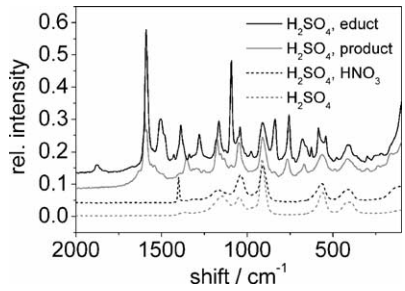

Fig. 14. Raman spectroscopic monitoring of the nitration of chlorobenzoylbenzoic acid dissolved in nitrating acid (H_2SO_4/HNO_3).

3.6. Automation

Automation of the entire microreaction system is realized on basis of a SIMATIC PCS 7 process control system (Siemens, Karlsruhe, Germany). All measured data (temperature, pressure, flow, density, analytical data like concentrations, etc.) are read out automatically and are instantaneously processed for regulation and control of the actors (pumps, valves, etc.). The process control system is able to conduct systematic variations of process parameters on basis of pre-defined statistical DoEs (design of experiments).

The process control software allows different operation modes like automatic processing, semi-manual operation, purging and cleaning modes, etc. Several safety procedures are also integrated into the process control system depending on pre-defined boundary values and shutdown criteria.

4. Conclusions

Microreaction technology is a very promising tool for investigating and optimizing chemical processes. Automation allows a more regulable and controllable operation of microreaction systems and thus gives access to a fast and more reliable process design. Integrated sensors and analytical interfaces as well as a functional process control system are essential elements of the automation concept. With the automated microreaction system AuMμRes developed in this project very efficient parameter screenings can be conducted for a wide variety of chemical reactions in the liquid regime, even under highly corrosive conditions. Such parameter screenings provide all relevant information for an effective process design in chemical industry. Apart from parameter screening AuMμRes is also dimensioned for an automated small-scale production in the kilogram range.

Acknowledgements

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[22] e.g., see: http://www.microchemtec.de, http://www.microreaction-technology.info, http://www.ehrfeld.com.