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DOI 10.1070/RCR4484

Microchannel systems for fine organic synthesis

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Characteristic features of application of microchannel systems in organic synthesis are analyzed. The advantages of such systems over conventional chemical engineering equipment, especially for small-scale processes that require fast implementation in industry to obtain small quantities of the product, are shown. Particular examples of successful use of microchannel reactors for various types of organic synthesis are given, primary attention being devoted to the design features of microchannel reactors.
The bibliography includes 118 references.

Contents

I. Introduction 139
II. Types of microchannel reactors for the processes of fine synthesis 140
III. Application of microreactor systems in organic synthesis 142
IV. Application of microreactor systems in industry 151
V. Conclusion 153

I. Introduction

The small-scale production of fine synthesis (FS) products occupies the largest (as regards the total cost of the products) sector of chemical industry market and implies the most extensive processing of the chemical feedstock characterized by the highest added value.[1] As a rule, the synthesis of complex organic compounds in industry involves a wide range of processing technologies. It is evident that with time, most of traditional production processes of many fine chemicals products display some drawbacks, first of all, large numbers of process stages, complexity of process flow diagrams and high specific material requirement of the equipment. This is often associated with the necessity to perform the synthesis at high temperature and pressure. Furthermore, a multistage and usual moderately selective FS is accompanied by the formation of large amounts of wastes: the so-called environmental factor (*E*-factor equal to the mass of the waste divided by the mass of the product) is, most often, higher than 2 (Table 1). This implies a considerable environmental damage caused by the formation of a large amount of wastes and the use of toxic organic compounds. The highest *E*-factors are inherent in the manufacture of pharmaceutical products.

A new approach to the development of FS is the use of microchannel systems,[2] which provide solution to many problems faced by the design of small-scale production

Table 1. *E*-factors in various branches of industry.[1]

Industry segment	Capacity of a single plant/tonnes per year	*E*-factor
Bulk organic synthesis	$10^4 - 10^6$	$< 1 - 5$
Fine organic synthesis	$10^2 - 10^4$	$5 - > 50$
Pharmaceutics	$10 - 10^3$	$25 - > 100$

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Received 10 July 2014
Uspekhi Khimii **85** (2) 139 – 155 (2016); translated by Z P Svitanko

processes of complex organic compounds in amounts from grammes to several tonnes of the target product per year.

Many processes of organic synthesis involve multiphase conditions (gas–liquid or gas–liquid–solid systems) and high pressures and temperatures and are often accompanied by evolution of a large amount of heat (*e.g.*, selective oxidation of organic substrates with air). Microchannel systems[2] substantially intensify processes of this type as a result of more efficient heat and mass transfer in the reactor compared with conventional reactors. High ratios of the catalyst layer surface area to the microreactor volume enhance the catalyst effectiveness. The laminar flow profile and the uniform distribution of reactant concentration through the channel cross-section result in low spread of residence times, which provides high selectivity of the reaction. Indeed, the reactant flow in the microreactor channels is usually laminar and has a parabolic velocity profile along the radius. Owing to the efficient diffusive stirring, the axial and radial molecular diffusion has a strong effect on the residense time distribution. The radial diffusion along the radius levels off the concentration distribution of the reactants through the channel. This effect is characterized by the Bodenstein number (Bo)

$$\mathrm{Bo} = 48 \times \frac{\tau}{t_{\mathrm{D,\,rad}}}$$

where τ is the average residence time of the reactants in the channel, $t_{\mathrm{D,\,rad}}$ is the time it takes for the reactant to reach the channel wall upon radial diffusion.[2] A Bo > 100 implies a narrow (low variance) residence time distribution of the reactants or a planar (uniform) concentration profile through the channel cross-section. For microchannels with a characteristic diameter of <1000 μm, values Bo > 100 can be achieved, which attests to intensified mass exchange and a narrow residence time distribution.

Finally, the reaction volume of a microchannel reactor (MCR) is several orders of magnitude smaller than the volume of typical reactors that reduce substantially the risk of emergency associated with high pressure, temperature and use of explosive mixtures or environmentally hazardous chemicals.[3] Thus, the use of microchannel systems FS processes can bring about considerable economic and environmental advantages.[4–8]

The present review analyzes examples of using microchannel systems for implementing FS processes. The review mainly covers the publications of the last 10 years; however, when necessary for the logic of narration, earlier publications are also addressed.

II. Types of microchannel reactors for the processes of fine synthesis

The possibility of using MCR for particular chemical reactions is determined by the reactor size and design, the way of reactant supply and withdrawal and by the chemical and physical properties of the reactor material.[9,10] The reaction space of most of the described MCR consists of a system of submillimetre size channels embedded in a massive body, as occurs in natural systems (*e.g.*, in plant and animal tissues). A large experience in the manufacture of MCR has now been accumulated; the reactors are made of a variety of materials, which are chosen considering the properties of reactants and operating conditions to be used. Typical materials include glass, silicon, stainless steel and polymeric materials.

Glass is the most widely used material for the manufacture of MCR. The microchannel systems made of glass are commercially available (see, for example, Ref. 11). One more extensively studied MCR material is silicon. This is due to the presence of numerous silicon processing technologies that have been well tested in the semiconductor industry. These technologies can serve to create microchannels with a unique three-dimensional structure. A typical sequence of operations used for the production of microreactors includes lithography and etching of channels of a specified shape. The reactor is usually sealed by plates made of the Pyrex glass (Fig. 1). The glass and silicon plates are welded together by diffusion anodic bonding at temperatures of <450 °C. Higher thermal conductivity of silicon MCR compared with that of glass allows the use of these reactors for highly exo- or endothermic reactions at both high and low temperatures.[13] There are examples of using silicon microchannel systems under extreme conditions: at temperatures of >400 °C and pressures of up to 30 MPa.[12,14]

Microchannel reactors manufactured from stainless steel have high mechanical strength and can be used for high-temperature and high-pressure processes. In addition, they can be successfully used for the design of integrated production trains in which microchannel systems function not only as reactors but also as mixers and heat exchangers. Note that the size of a stainless-steel MCR is usually greater than the sizes of glass or silicon microreactors for the same operation efficiency.[15,16]

Microchannel systems made of polymeric materials are rather simple for fabrication and have relatively low cost. As a rule, they are manufactured using chemically resistant polymers, for example, polydimethylsiloxane. The reaction volumes of these reactors range from several nanolitres to microlitres.[17] The main drawbacks of polymeric microreactors are related to moderate stability in the presence of organic solvents, low operation temperatures, low mechanical strength and low thermal conductivity. Therefore, the scope of applicability of polymeric MCR is usually limited to biochemical processes taking place in aqueous solutions at nearly atmospheric pressure and temperatures of up to

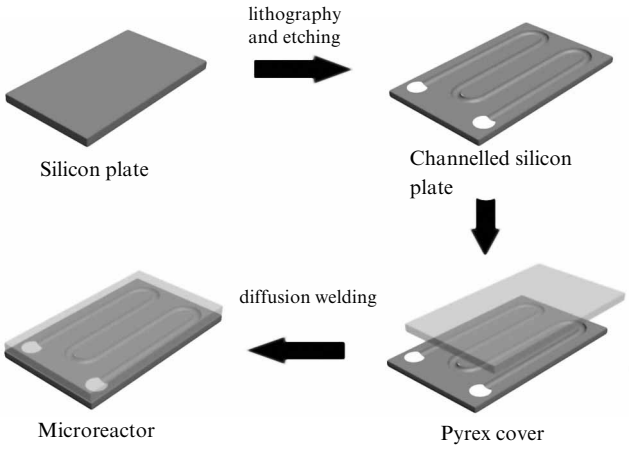


Figure 1. Typical technology of the manufacture of the silicon microreactor.[12]

100–150 °C.[18,19] A promising polymeric material for the manufacture of MCR is polyamide, which almost does not swell in typical organic solvents (acetone, tetrahydrofuran, toluene, dimethyl sulfoxide, dimethylformamide, dichloromethane, *etc.*) as well as in water and concentrated sulfuric acid.[20] A book [21] presents examples of using a high-temperature polymer, poly(aryl-ether-ether-ketone), to fabricate microchannel equipment (microreactors and heat exchangers) operating at temperatures of <250 °C.

The fluid movement along the microchannels is driven, depending on the reactor design and the fluid characteristics, by various types of pumps: piezoelectric, electrostatic, compressed-air, magnetodynamic, electro-hydrodynamic, diffusion, electroosmotic and other pumps. A compressed-air pump can provide a very broad range of pumping velocities for almost any liquid; however, its considerable drawback is the presence of a valve system, which can be corroded by the fluid being pumped. A valve-free electroosmotic pump is able to pump an electrically conducting liquid in a channel with a 20×100 μm cross-section at a velocity of up to 500 μm s^{-1}. However, the electrodes that generate the electric field for movement of the liquid directly contact the flow and can induce the formation of gases.[22,23]

Special techniques are required for mounting a catalyst bed in the bulk or on the surface of microchannels. Depending on the mounting method, MCR can be classified into two types. In MCR of the first type, the channels are filled with catalyst particles. These microreactors resemble the conventional packed-bed reactors, their key distinctive feature being small (<1 mm) characteristic size of the channels, resulting in high mass and heat transfer intensity. In the second type MCR, the catalyst is supported on the channel walls as a thin layer. In this case, the flow resistance of the channel is several-fold lower than that in the first type reactors. The decrease in the flow resistance is very important in those cases where fast processes take place in the microreactors and short residence times of the reactants in contact with the catalyst are needed. Furthermore, a thin catalyst layer supported on the walls has a good thermal contact with the microreactor material. This provides for efficient heat supply (or withdrawal) to the (or from the) reaction zone and, hence, it is possible to perform high-energy transformations under isothermal conditions. However, for this type of microreactors, a serious problem is to choose the method for firm anchoring the catalyst on channel walls. Indeed, during the microreactor operation, the catalyst layer is exposed to the reaction medium. Sharp changes in the reactor temperature (thermal shocks) are possible. As a result, the catalyst layer can be destroyed through exfoliation and/or gradually washed out, which reduces the MCR performance. The problems of depositing the catalyst on the microchannel walls are widely discussed in the literature (see, Ref. 24).

Deverella *et al.*[25] described a method of formation of a porous polymer layer on the glass and plastic microchannel plates followed supporting of the catalyst. The porous layer was formed by polymerization of 2,2-dimethoxy-2-phenylacetophenone or bis(2,4,6-trimethylbenzoyl)phenylphosphine oxide induced by UV irradiation at 365 nm.

The chemical methods for modification of the microchannel wall surface in silicon reactors are less complicated. For example, a capillary with an inner diameter of 300 μm and a length of 20 cm made of fused silicon was first treated with a mixture of concentrated sulfuric acid and 30% hydrogen peroxide for 12 h and then with amino-containing organic compounds.[26] As a result, amino groups were immobilized on the silicon surface to be subsequently used for deposition of enzymes.

The formation of a porous catalyst layer on a steel surface requires different approaches. A procedure for the preparation of thin films of zeolites (mordenite, zeolites Y, ETS-10) from suspensions containing initial components of the future zeolite catalyst was reported.[27] The active component was supported on the zeolite by impregnation followed by calcination. In 500 μm stainless-steel channels, a 400–700 nm thick zeolite film was thus formed and the surface density of the zeolite catalyst was ~0.3 mg cm^{-2}. A thin mesoporous silicate layer can also be prepared in this way.[28]

A nano-sized zeolite NaA film was anchored on a stainless-steel surface using trimethoxy(3-chloropropyl)silane or (3-aminopropyl)trimethoxysilane, the pyramidal zeolite NaA crystals with (111) orientation being grown *via* hydrothermal synthesis in the microchannels of the plate.[29,30] This gave a uniform zeolite layer covering the whole porous stainless-steel surface.

There are several more ways for catalyst anchoring in the second type microreactors involving special treatment of channel walls. For example, on the metallic wall of a slit-like channel, microcavities can be formed to be subsequently filled with a catalyst. In a patent,[31] a 0.1 mm thick stainless-steel plate was subjected to anodic electrochemical etching in a iron(III) chloride solution or in a sodium chloride solution with addition of sulfuric acid. This procedure gave drop-shaped wells 50–400 μm in diameter with an average volume of 4×10^{-4} cm^3 on the plate surface, the surface density of the pits being 250–350 cm^{-2}. Then the wells were filled with a powdered catalyst with a binding component. The plate prepared in this way (Fig. 2) was placed into an MCR. A drawback of this method for the fabrication of microchannel plates is the relatively low density of the surface wells, which precludes supporting of a sufficient amount of the catalyst.

According to another process for the fabrication of microreactor plates, the problem of supporting the specified amount of the catalyst was solved by using metal (copper, nickel) foams with an open volume porosity of 0.8 and an average pore diameter of 250 μm.[32] A suspension was prepared from a catalyst powder obtained beforehand and a binding component. By ultrasonic treatment, the suspension was introduced into the metal foam plate. After short

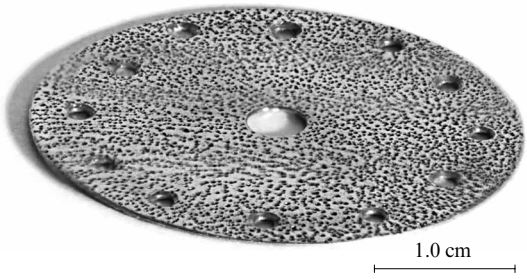


Figure 2. Stainless steel microchannel plate after electrochemical etching in a iron(III) chloride or sodium chloride solution.[31]

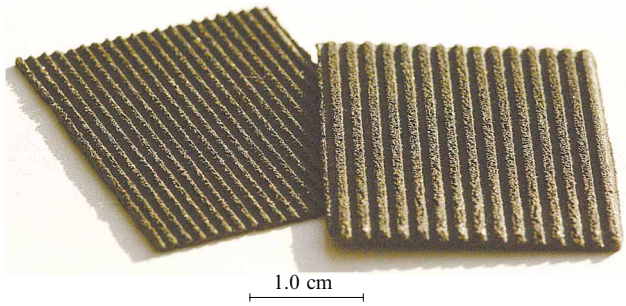


Figure 3. Metal foam microchannel plates with a pressed-in catalyst.[32]

pre-drying, the plate was pressed in a specially shaped matrix. This gave a microchannel plate with submillimetre-sized channels (Fig. 3), which was tested in methanol steam reforming. The amount of the supported catalyst depends on the thickness of the initial metal foam plate.[33,34]

A considerable problem arising during the operation of metallic microchannel plates is the difference between the thermal expansion coefficients of the supported catalyst film and the metallic substrate. This results in exfoliation of the supported film at high temperatures or thermal shocks. A way to solve this problem is the use of a buffer intermediate layer of an oxide, for example, α-Al_2O_3, which is sandwiched between the metal substrate and highly porous oxide coating bearing the catalyst active component (Fig. 4). The buffer layer protects the metal from corrosion and promotes adhesion of the external porous ceramic layer. The buffer layer is supported by various methods, including detonation sputtering.[35] The outer highly porous layer is deposited by immersing the microchannel plate into a suspension containing aluminium oxynitrate and a surfactant (polyethylene oxide). After every impregnation procedure, the plate was dried in an air flow and calcined at 900 °C. Examples of using carbon materials as the catalyst supports are also known. De Loos *et al.*[36] employed carbon nanofibres with a thread diameter of <100 nm, which were grown on a carbon plate. The growing procedure was as follows: nickel metal nanoparticles were chemically supported process onto the surface of a $5\times6\times0.36$ mm graphite plate and, after that, ethylene

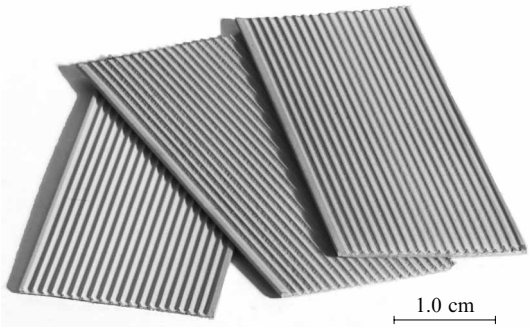


Figure 4. Microchannel plates fabricated by mechanical mill operation with a buffer α-Al_2O_3 oxide coating deposited by detonation sputtering.[35]

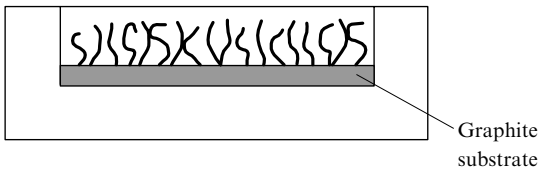


Figure 5. Carbon nanofibre grown on a graphite substrate.[36]

pyrolysis was carried out in a hydrogen and argon atmosphere at 773–873 K. As a result, carbon fibres grew on the graphite surface under the action of nickel nanoparticles, which catalyzed pyrolysis (Fig. 5). After removal of nickel, a palladium catalyst was deposited on the obtained nanofibre.

The experiments on hydroxyalkyne hydrogenation demonstrated that the efficiency of the palladium catalyst deposited on nanofibres is 3.5–4 times higher than that of palladium nanoparticles supported on the surface of a pure graphite plate, while high selectivity to the final hydrogenation products is retained.

Apart from the above methods for the manufacture of microchannel plates, methods of catalyst supported and choice of the microreactor material, an important issue is the channel configuration at the inlet and outlet of the reactor, which ensures a uniform distribution of the flow through the channels.[37–39]

III. Application of microreactor systems in organic synthesis

The use of MCR for the synthesis of organic compounds appears especially attractive in the case of reactions rate-limited by mass and/or heat transfer.[40,41] Numerous examples demonstrating the possibility of substantial intensification of reactions by using microchannel systems have been accumulated.[42] These reactions include oxidation, nitration, synthesis of alkenes from alkanes, peptide synthesis, epoxidation, multistep organic syntheses and so on. The application of microchannel systems for combinatorial synthesis and screening of catalyst properties and for the synthesis and identification of nucleic acids revolutionized the search for biologically active compounds by pharmaceutical companies.[41] It is expected that the elaboration of fast screening methods for catalyst properties and finding new methods for their synthesis could bring about a similar acceleration of the development of chemical engineering processes.[43,44]

Among the chemical processes that can fully benefit from the advantages of MCR, a special place belongs to liquid-phase catalytic FS processes using heterogeneous catalysts. In this case, a significant feature of microchannel systems, namely, a large ratio of the working surface area to the volume of the reactor, takes effect. The replacement of the traditional 30 m^3 reactor with a characteristic linear size of ~1 m by MCR with a characteristic channel size of 30 μm increases this ratio by five orders of magnitude.[45] This substantially increases the exposure and effectiveness of the heterogeneous catalyst supported on the walls, which in turn increases the reaction rate. Furthermore, the use of MCR may change the transformation pathway with respect to that in traditional systems, which in some cases results in the preparation of new products with a high selectivity.

Owing to high thermal conductivity of microchannel plates, the reaction mixture can be rapidly heated and cooled at 500 K s^{-1} rates, which is of prime importance for high-energy reactions. Finally, using MCR, it is possible to switch from periodic autoclave processes to safe continuous processes in small volumes, which reduces the risk of emergency when high pressure and temperature and hazardous chemicals are used.

III.1. Catalytic hydrogenation

An illustrative example demonstrating the good prospects of the use of microchannel reactor systems for FS is the catalytic hydrogenation of organic substrates. Note that catalytic hydrogenation is one of key chemical transformations, the proportion of which in pharmaceutical industry is ~10%–20% with respect to the total production output.[46]

Hydrogenation processes under flow conditions were carried out using MCR in which the channels were formed by a set of tubes[47–49] or engraved on the flat plate surface.[50, 51] The reactor materials were polydimethylsiloxane,[50] glass,[51] stainless steel,[48] silicon,[52] gas-tight polymers [for example, Teflon AF-2400 (see Ref. 47)].

High specific surface areas of MCR considerably increase the efficiency of three-phase hydrogenation reactions of organic compounds. The process can be arranged in such a way that the solid phase (catalyst) is located on the channel walls, the liquid phase with the dissolved reactant is located in the thin near-surface layer of the channel, and the gas phase is in the central part of the channel (Fig. 6 *b*).

This phase distribution in a submillimetre channel gives rise to large interfacial surface area between the reacting components and, as a consequence, to fast diffusive exchange between the phases, which markedly increases the reaction rate. Kobayashi *et al.*[53] carried out hydrogenation of alkenes (including cycloalkenes) in MCR with a 45 cm-long serpentine channel with a 200 × 100 μm cross-section and a Pd-catalyst supported on the channel walls (see Fig. 6 *a*). Hydrogen was mixed with the reactants in a T-shaped mixer. A comparison of the specific capacity of microchannel and autoclave reactors showed a considerable advantage of the former: the specific capacity was an order of magnitude higher for the MCR than for the autoclave. At room temperature, the reaction was over in 2 min.

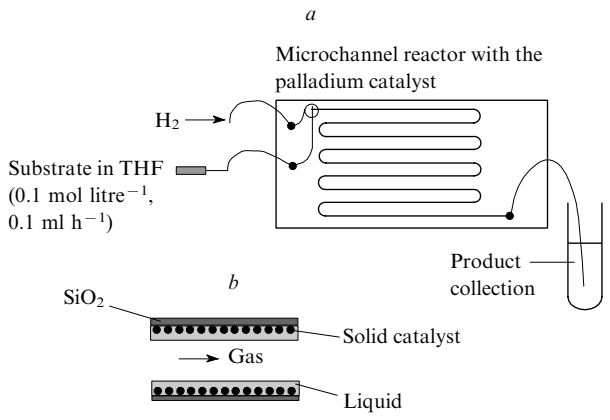
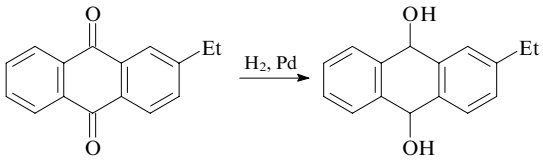


Figure 6. Scheme of the microchannel alkene and cycloalkene (*a*) hydrogenation reactor and ideal distribution of the gas–liquid flow in the channel (*b*).[53]

Hydrogenation of nitrobenzene on a Pd catalyst in a stainless-steel MCR was reported.[54] The reactor comprised 64 vertical parallel channels with a cross-section of 300 × 100 μm and a length of 78 mm separated by 100 μm thick walls. The < 100 μm thick liquid film of the reactants moved down under gravity through the channels into which hydrogen was simultaneously fed from the bottom. This arrangement of the flow provided efficient heat and mass transfer, which considerably enhanced the efficiency of hydrogenation compared with the conventional process.

Halder and Lawal[55] also demonstrated a benefit of MCR over the conventional fixed bed reactor. They measured the specific capacity for 2-ethyl-9,10-anthraquinone hydrogenation on a palladium catalyst to 2-ethyl-9,10-anthrahydroquinone (Scheme 1). Note that this reaction is the first step of the conventional industrial production of hydrogen peroxide. An SS316L stainless-steel tube with the internal diameter of 0.775 mm and length of 9.5 cm served as the MCR. The reactor was charged with 13 mg of the pelletized catalyst (1 mass % Pd/SiO_2) with a particle size of 75–150 μm. For improving the heat and mass transfer, the catalyst was diluted with 15 mg of glass beads of diameter 63–75 μm. The dependences of the specific yield of the final product on the reaction temperature, reactant flow rate, liquid to gas phase ratio, concentration of 2-ethyl-9,10-anthraquinone and reactor pressure were measured. The highest (100%) conversion of 2-ethyl-9,10-anthraquinone was achieved at 70 °C. The comparison of the MCR and the conventional fixed bed reactor as regards the efficiency the desired product demonstrated a considerable advantage of the former, namely, a 30-fold higher efficiency value.

Scheme 1



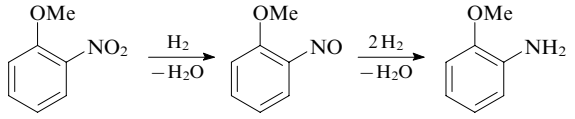
Hydrogenation of benzene to cyclohexane is accompanied by evolution of a large amount of heat; hence, the temperature control and heat withdrawal from the reactor are critically important for this process. In industry, cyclohexane is produced in a multistage reactor consisting of alternating main exothermic reaction zones and cooling zones. The use of MCR providing efficient heat removal and reliable temperature control was proposed to solve this problem. The experiments demonstrated that the MCR can indeed substantially improve the operating characteristics of benzene hydrogenation to cyclohexane.[56] Furthermore, the amount of side products having an adverse impact on the environment is lower than in the case of conventional process.

The benefit of MCR over traditional reactors was also demonstrated for the preparation of *o*-anisidine by selective hydrogenation of the *o*-nitroanisole nitro group.[57] *o*-Anisidine is used in the synthesis of azo compounds to prepare naphthol AS, acidic and oil-soluble dyes and guaiacol — the raw material for the synthesis of fragrances (vanillin, eugenol, isoeugenol, santalidol) and medicinal drugs (ftivazide, papaverine). Tadepalli *et al.*[57] obtained and compared the kinetic data for catalytic hydrogenation of *o*-nitroanisole on palladium catalysts in the conventional reactor

(autoclave) and in the MCR. In the former case, the reaction was catalyzed by a commercial catalyst containing 2 mass % Pd supported on zeolite (sodium aluminosilicate, 75–150 μm fraction), which was placed into a 25-ml batch reactor. The reaction mixture in the autoclave was mechanically stirred (800–1000 rpm). It was found that the fast reaction in this reactor in a gas–liquid–solid three-phase system is rate-limited by the hydrogen mass transfer from the gas phase to the catalyst surface. In the autoclave, heat withdrawal from the reaction space was impossible, which resulted in the appearance of superheated spots in the bulk of the reaction mixture and decreased the efficiency and selectivity to the target product.

It was shown that the use of MCR [55] makes it possible to solve these problems. The researchers used a one-channel reactor similar in design to the 2-ethyl-9,10-anthraquinone hydrogenation reactor. It was found experimentally that owing to the effective mass and heat transfer in the MCR, hydrogenation proceeds in a kinetic regime and can be efficiently controlled by external factors (pressure, temperature and reactant flow rate). The yield of *o*-anisidine was somewhat lower than the stoichiometric one as the reactor effluent contained also a hydrogenation intermediate — 2-methoxynitrosobenzene. This indicates that hydrogenation includes two successive steps (Scheme 2). The detection of the intermediate product is due to the fact that MCR operation in hydrogenation is similar to the plug-flow reactor regime.

Scheme 2



Trachsel *et al.*[58] utilized the MCR to carry out cyclohexene hydrogenation to cyclohexane on the 2 mass % Pd/Al_2O_3 catalyst in supercritical carbon dioxide at 40–70 °C and 80–150 bar. The high-pressure microchannel reactor was fabricated from silicon and glass and had a capillary channel with a cross-section of 400 × 300 μm and an internal volume of 3.8 μl; this substantially increased the mechanical strength of the reactor under high internal pressure. Catalyst particles of 115 μm size (0.5–1.0 mg) were placed into the MCR channel. The mixture $CO_2 : C_6H_{10} : H_2 = 90 : 5 : 5$ (mol.) was fed to the reactor inlet, the inlet flow rate (in relation to CO_2) was 200 μl min^{-1}. It was found that the reactor performance increases with temperature rise, which is determined by not only the increase in the reaction rate constant but also by enhancement of the mass and heat transfer. High thermal conductivity (150 W m^{-1} K^{-1}) of the MCR material was also favourable for the reactor performance. The experiments showed that the specific productivity of the MCR was much higher than that of the conventional reactor. For example, the specific capacity for a conventional 5 ml packed-bed tubular reactor [59] at a temperature of 340 °C and a pressure of 120 bar with the 5 mass % Pd/Deloxan catalyst † was 2.5×10^2 kg h^{-1} dm^{-3}(cat.), whereas the specific capacity for the MCR at 70 °C and 136 bar with 2 mass % Pd/Al_2O_3 was almost an order of magnitude higher, namely, 1.5×10^3 kg h^{-1} dm^{-3}(cat.).

The results of kinetic investigations of the three-phase biphenyl hydrogenation process at 140 °C and 50 bar conducted in an MCR with pelletized $Pt-Pd/Al_2O_3$ catalyst were reported.[60] The reactor represented six parallel tubes with an internal diameter of 2.2 mm and a length of 500 mm. The attention was focused on the effect of factors such as hydrodynamic anomalies, stagnant zones of gas and liquid and non-uniform distribution of the catalyst and the diluent (inert material) on the microreactor performance. This task was set up in relation to the commonly accepted opinion that it is often sufficient to decrease the volume of the reaction zone of the reactor to increase the performance.[61] Meanwhile, a small size of the reaction zone does not eliminate by itself the non-uniform distribution of the heterogeneous catalyst in the bulk and the non-uniform wetting of the catalyst with the reaction mixture.[62] Meanwhile, it was shown [63] that insufficient wetting of the catalyst surface and insufficient efficiency of the external mass exchange may be predominant factors affecting the appropriateness of the kinetic measurements for the reaction. These undesirable factors could be eliminated and good wetting could be achieved by using a recycle flow regime of the reactor at high reactant flow rates. However, it was shown [60] that catalyst loading into the microreactor and the arising non-uniformity of packing of the catalyst bed preclude good reproducibility of the experimental results (conversion, selectivity). Nevertheless, the rate constant for the process in question virtually does not change. It was also shown that the catalyst dilution has a less pronounced effect on the substrate conversion in a gas–liquid–solid three-phase system than in systems free of the gaseous component. Flow visualization in a fixed bed reactor demonstrated the presence of stagnant zones in the segregation sites of the pelletized catalyst. A relatively small size of the fixed bed reactor still mitigates the undesirable effect of the catalyst loading and distribution in the reaction volume on the efficiency of reaction in a three-phase system.[60]

III.2. Catalytic dehydrogenation

Dehydrogenation of light alkanes is an important industrial process for production of alkenes.[64] These reactions take place at high temperature (550–650 °C) and are accompanied by absorption of a large amount of heat; therefore, MCR with highly efficient heat and mass exchange are perfect devices for this type of processes.

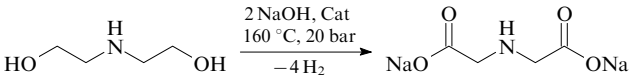
Novakova *et al.*[65] investigated gas-phase dehydrogenation of isobutane to isobutene catalyzed by $Pt-Sn/Al_2O_3$ (0.75 mass % Pt, 0.4 mass % Sn) in two reactors — a conventional fixed-bed reactor and a microreactor. The conventional adiabatic fixed-bed reactor was a quartz tube with an internal diameter of 11 mm in which the catalyst with 650–800 μm particle size was loaded. The microreactor with 5.1 × 1.3 cm size was constructed from the Inconel-625 alloy and had a rectangular channel with a cross-section of 0.05 × 0.95 cm and a length of 5.1 cm. The pelletized catalyst with a particle size of 250–400 μm was loaded into the channel. The performances of the reactors were compared at equal temperatures and contact times (0.08 s). The microreactor demonstrated higher conversions and higher yields of the final product (isobutene) — 40% and 27%–34%, respectively, whereas for the conventional

† Deloxan is functionalized polysiloxane.

adiabatic reactor these values were 29% and 19%–24%, respectively.

Aminocarboxylic acids are usually prepared by dehydrogenation of amino alcohols in alkaline medium in the presence of copper and silver catalysts. The dehydrogenation of diethanolamine (DEA) to iminodiacetic acid (IDAA) was found [66] to have high selectivity when catalyzed by the Raney copper. However, pure Raney copper is deactivated fairly rapidly as a result of agglomeration of small particles and a decrease in the surface area exposed to the reactants. For stabilization of copper, doping with other metals such as chromium, molybdenum, vanadium, nickel and so on was proposed.[67,68] It was shown [69] that copper-substituted Raney nickel is also suitable as the catalyst. Dehydrogenation of DEA to sodium iminodiacetate occurs at a temperature of 160 °C and a pressure of up to 20 bar in alkaline medium (Scheme 3).[69]

Scheme 3



This process is usually carried out as a batch process in an autoclave, which brings about some inconveniencies when the final product is used in the subsequent steps, for example, in the synthesis of the herbicide glyphosate. A flow type system using, for example, MCR could solve this problem. Moreover, the advantages of microreactors noted above may create favourable conditions for the synthesis of IDAA.

Andreev *et al.*[70] investigated the synthesis of IDAA in two reactors — a conventional bulk reactor (autoclave) and a flow type MCR (Fig. 7). In both cases, the reaction was catalyzed by the powdered copper zirconium oxide catalyst Cu/ZrO_2, which was prepared by co-precipitation with oxalic acid or sodium hydroxide from an aqueous solution containing copper and zirconyl nitrates. After drying the precipitate at 100 °C for 24 h, the resulting powder was calcined for 6 h in air at 500 °C. The reaction space of the autoclave was a stainless steel cylinder with an inner diameter of 60 mm and a height of 25 mm. The reactor was charged with 0.48 g of the powdered catalyst and an aqueous solution of the substrate. The reaction was carried out under continuous mechanical stirring, at temperature of 160 °C and a pressure of 1.5 MPa. In the case of MCR, the catalyst was fixed on four microchannel plates moulded from copper foam, each containing four 20 mm-long channels with a 0.2×5.0 mm cross-section. It was found that in both reactors, DEA dehydrogenation proceeds *via* the intermediate formation of *N*-(2-hydroxyethyl)glycine (HEG) sodium salt.

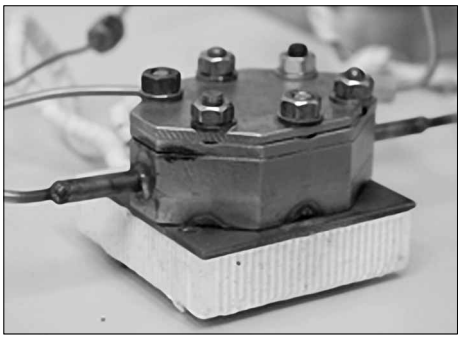


Figure 7. Dismountable microchannel reactor for the synthesis of iminodiacetic acid.[70]

The performances of the two reactors were compared in terms of the following parameters: the amount of IDAA formed over a certain period; the IDAA concentration in the reaction products; the volume and mass specific productivity of the reactor. Analysis of the operation of two reactors showed the following. The autoclave containing 12 ml of the initial solution provided a 94.4% conversion of DEA after 6 h of continuous operation. The yield of IDAA was 57.8 mass %, which corresponded to its 1.8 mol litre^{-1} concentration in the reaction products. The total amount of IDAA formed in this period of operation was 0.021 mol, which corresponds to the autoclave productivity of 3.5 mmol h^{-1}. In the flow type MCR with a reaction volume of 0.4 cm^3, the DEA conversion over a 2 min residence time was 57.5%. The yield of IDAA was 34.3 mol.%, which corresponds to its 1.06 mol litre^{-1} concentration in the reaction products. Over a similar period of operation (6 h), 0.078 mol of IDAA can be produced in the MCR. Hence, the MCR productivity was 12.78 mmol h^{-1}, which is almost 4 times as high as the autoclave productivity.

For a more exact comparison of the reactor operation, the specific productivities per unit catalyst mass and the unit volume of the reaction zone were calculated. Table 2 presents the initial parameters of the reactors, the calculated effective rate constants and the specific productivities of the reactors. The calculations were performed for equal DEA conversions (57.5%).

The effective rate constants for dehydrogenation of DEA were several orders of magnitude higher in the MCR than in the autoclave. This difference is caused by many factors influencing the reaction rate in the autoclave and in the MCR. They include the reaction volume, catalyst mass, external- and internal-diffusion regimes, *etc*. It can be seen that for the same conversion of DEA, the specific productivity of the MCR calculated in relation to the volume occupied by the MC-plate is 240 times higher than a similar

Table 2. Comparison of autoclave and microreactor performances in the alkaline dehydrogenation of diethanolamine at 160 °C.[70]

Characteristics	Autoclave	MCR
Reaction volume /cm^3	12	0.4
Catalyst mass /g	0.48	3.6
Maximum DEA conversion (%) (see [a])	94.4	57.5
Effective rate constantss/litre mol^{-1} min^{-1} (see [b])	$k_I = 1.1 \times 10^{-3}$ $k_{II} = 8.6 \times 10^{-4}$	$k_I = 0.11$ $k_{II} = 0.22$
Specific productivity /g h^{-1} cm^{-3} (see [c])	0.018	4.38
Specific productivity /g h^{-1} g^{-1} (cat.)		0.46
0.49		

[a] In the residence time of 6 h and 2 min, respectively; [b] k_I and k_{II} are the effective bimolecular rate constants for two successive steps:

$$\text{DEA} \xrightarrow{k_I} \text{HEG} \xrightarrow{k_{II}} \text{IDAA}$$

[c] For DEA conversion of 57.5%.

characteristics of the autoclave. However, the specific productivities calculated in relation to the total mass of the catalyst were nearly equal.

The considerable difference between the specific productivities referred to the reaction volume is caused by the small reaction volume in the MCR, which apparently considerably improves the mass exchange. The absence of noticeable differences in the specific productivity values referred to the catalyst mass can be attributed to structural features of microchannel plates:[32] the main bulk of the catalyst in the MCR was pressed into the MC plate made of copper foam and, therefore, was poorly accessible to the reactants. Presumably, the real mass of the catalyst accessible to the reactants in this case is concentrated in a thin layer with a size of about the copper foam unit (250 μm) and amounts to 0.37 g. Considering this fact, the specific productivity per mass of the accessible catalyst is found to be 4.7 g h^{-1} g^{-1}(cat.), *i.e.*, it is also an order of magnitude higher than this parameter for the autoclave.

III.3. Nitration of organic substrates

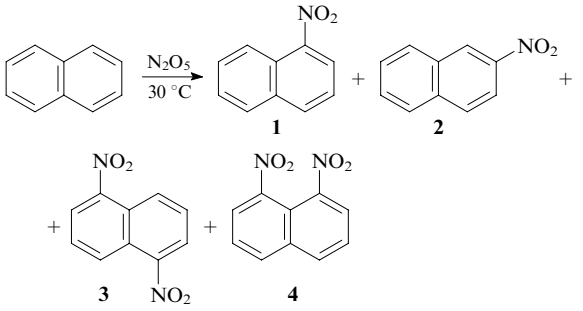
Nitration of aromatic compounds is an important step of the preparation of precursors for the synthesis of drugs, dyes, explosives, pesticides and so on (see, for example, papers [71–75] and patents [76–78]). These processes are highly exothermic; therefore, conducting them in conventional reactors without special safety precautions can lead to explosion hazard. Often, special measures still cannot ensure safe operation of the reactor because of difficulty of controlling heat evolution during the reaction. Furthermore, considerable temperature gradients and a low mass exchange rate in the conventional reactor can reduce the process selectivity and give rise to undesirable side products. A practicable way to solve these problems is the use of MCR. The results of numerous studies have now been published, demonstrating that the use of MCR for the nitration of organic compounds provides reliable control over highly exothermic reactions. In addition, short residence times and high mass exchange rates in the microchannels prevent the formation of side products.[79, 80]

The nitration of toluene in a conventional reactor is conducted, most often, in a two-phase liquid–liquid system using a mixture of concentrated sulfuric and nitric acids, which is immiscible with the reaction substrate.[81] In this process, neutralization of the acids in the resulting product mixture presents difficulty. A number of papers report [82–85] the nitration of toluene in a MCR with a fixed bed of solid acidic ZSM-5 catalyst in the presence of concentrated nitric acid. It was found that the efficiency of toluene nitration virtually did not change when concentrated nitric acid was replaced by a mixture of concentrated sulfuric and nitric acids. A comparison of the efficiency of toluene nitration in a 25 ml autoclave and in the MCR (a stainless steel tube with an inner diameter of 0.775 mm and a length of 120 cm) demonstrated that the toluene nitration rate was much higher in the MCR. The product at the outlet of the MCR was a mixture of three nitro compounds, *o*-, *m*- and *p*-nitrotoluenes, as in the reaction carried out in the presence of liquid mineral acids.

Homogeneous nitration of naphthalene was performed in a microchannel system, resulting in nitro- and dinitronaphthalenes (Scheme 4).[86, 87]

The microreactor represented a 150 mm long Teflon capillary tube. The reaction was carried out at 30 °C. If

Scheme 4



gaseous nitrogen pentoxide is used as the nitrating agent, dinitronaphthalenes predominated in the final product at high substrate conversions. However, if a dilute solution of nitric acid in dichloromethane is used instead of N_2O_5, monosubstituted naphthalenes were formed as the major reaction products. High naphthalene conversion was achieved at residence times of 15–45 s. To conduct similar experiments accompanied by large heat evolution in an autoclave, it is necessary to substantially reduce the temperature (down to −50 °C). In this case, gaseous N_2O_5 was used as the nitrating agent. The final reaction products contained 1-nitro- (**1**), 2-nitro- (**2**), 1,5-dinitro- (**3**) and 1,8-dinitronaphthalenes (**4**), their ratios were **1**:**2** = 20:1, **3**:**4** = 1:3.6 in the autoclave and **1**:**2** = 32:1, **3**:**4** = 1:2.8 in the MCR.

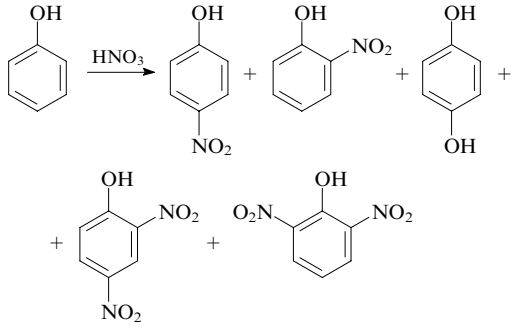
The potential of the MCR for the conduction of fast processes with large heat evolution, which may be accompanied by explosion in the case of conventional methods of synthesis, was demonstrated.[88] One of such processes is nitration of isooctanol with a mixture of concentrated nitric and sulfuric acids. This process was studied in the MCR made of stainless steel and containing sixteen 0.5 × 0.5 × 78 mm microchannels. It was shown that the use of MCR allows reliable control over the process. Indeed, for preventing uncontrolled warming up of the reaction mixture in the conventional reactor, the temperature has to be maintained below 15 °C, whereas the reaction in the MCR was carried out at 25–40 °C. This made it possible to considerably increase the transformation rate without decreasing the substrate conversion (98.2%) and thus surpass the performance of the conventional reactor.

Yang *et al.*[89] investigated the MCR with a microporous structure in which the reaction zone was integrated with a heat exchanger. The microporous material with a bulk porosity of 94.5% was prepared in the following way. The SS-316L stainless steel (5 g) as 2–3 mm-long fibres 8 μm in diameter and 0.1–1.0 mm-long cellulose fibre 30–40 μm in diameter (1.67 g) were placed into a mixer containing 1 litre of water and the mixture was vigorously stirred until a homogeneous suspension formed. Then the suspension was poured into a mould, excess water was removed with a cloth and the material was dried at 110 °C. The plate thus formed was annealed at 450 °C. The final sintering was carried out under a hydrogen atmosphere at 1100 °C for 60 min. The heat exchange plates were manufactured from 0.1 mm-thick metallic foil with dimensions 53.7 × 10.0 mm. The reaction zone of the microreactor with a volume of 0.412 ml was formed by alternating heat exchange and microporous plates. Finally, MCR was able to provide efficient mixing of the reactants and high efficiency of heat- and mass

exchange at high ratios of the reactor surface area to the reactor volume. The nitration of benzene with a mixture of concentrated acids at the molar ratio $HNO_3 : H_2SO_4 = 0.48$ in this MCR was carried out at a relatively high temperature (60 °C). Benzene and mixed acid were fed to the MCR reaction zone at 0.2 and 0.64 ml min^{-1} flow rates, respectively. For the contact time of 30 s, the conversion was 91.7% and the selectivity to nitrobenzene was 99.4%.

The nitration of phenol in the presence of concentrated nitric acid in a glass MCR with the reaction volume of 2.0 ml and 10×500 μm cross-section of the channels was studied.[90] Theoretically, this reaction can afford *o*- and *p*-nitrophenols, hydroquinone and 2,4- and 2,6-dinitrophenols (Scheme 5).

Scheme 5

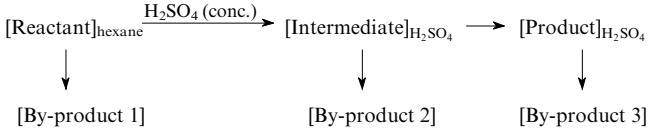


It was shown[90] that the kinetics and the product yield of the autothermal nitration of phenol substantially depend on the temperature. At 55 °C, the process starts almost immediately. However, a decrease in temperature by 10 °C gives rise to an induction period of about 1 min. At lower temperature, the reaction does not proceed at all. The productivity of the MCR referred to the reaction volume in the flow reaction regime was much higher than in the case of the autoclave. In the MCR, unlike the autoclave, the reaction products almost did not contain undesirable polymerization products.

III.4. Other reactions involving corrosive and explosion- and fire-hazardous compounds

An illustrative example of using MCR is conduction of the reaction in a two-phase liquid–liquid system. It was noted[91] that the synthesis of a vitamin precursor (the particular compound is not indicated) in industry (batch process in a bulk reactor) is accompanied by fast formation of undesirable side products and the yield of the target product does not exceed 70%. Conduction of the reaction in the two-phase liquid–liquid system is accompanied by considerable heat evolution (Scheme 6). The starting reactant (substrate) is dissolved in n-hexane (the first liquid phase) and the second liquid phase is sulfuric acid serving as the catalyst. The product formed passes to the second phase. Meanwhile, in a flow type system consisting of a mixer, reactor and separator, the product yield increases to 80%–85% but in the mixing area of two liquids, a considerable superheating is observed (by 35 °C). In order to decrease the superheating, a heat exchange type MCR, manufactured from stainless steel and containing thirty two 900×600 μm channels, was designed together with the Institute of Microtechincs (Institut für Mikrotechnik Mainz, IMM). The channels in which the reaction took place were arranged between the channels with the coolant. In this case, warming up was not more than 1 °C. It was found that the yield of the target product depends strongly on the residence time and even more appreciably on the maintenance of isothermal conditions in the reactor. At 50 °C and a residence time of 4 s, the product yield was 85%, while at 20 °C and 30 s, it reached 90%–95%.

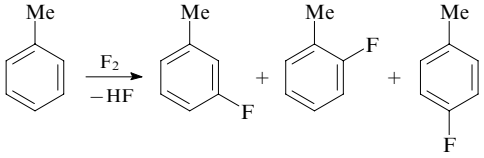
Scheme 6



A new promising interdisciplinary technology related to microchannel systems is microfluidics, which makes it possible to manufacture new functional materials and handle very small volumes of liquids or gases, crystalline and polymer particles, animal, plant and bacterial cells, bubbles and droplets.[92] Microfluidics can be used to accomplish precision chemical syntheses in flow type microreactors at a high rate due to elimination of diffusion limitations existing in conventional reactors.

Direct fluorination of organic substrates with molecular fluorine is accompanied by pronounced heat evolution, which is difficult to control. A review[93] describes a large number of direct fluorination experiments of organic substrates with molecular fluorine. As an example, consider the results of toluene fluorination carried out in gas–liquid microreactors, namely, a falling film microreactor and a microchannel bubble column.[94] It was shown that during direct fluorination of toluene with molecular fluorine, hydrogen substitution at each position takes place (Scheme 7). The designs of the stainless steel MCR are shown in Fig. 8.

Scheme 7



In the MCR, a thin (several tens of micrometres across) falling film of a liquid is formed (see Fig. 8 *a*) under the action of gravity on an MC plate containing a large number of channels with a cross-section of 100×300 μm. When isopropyl alcohol is used as the liquid, the film thickness is 25 μm. As a result, the specific interfacial surface area reaches 40 000 $m^2\ m^{-3}$, which is much greater than this area in laboratory and industrial reactors. The microchannel bubble column (see Fig. 8 *b*) consists of a mixer and a reactor. The reactants are fed to the mixer along channels with 20×7 μm cross-section for gases and 20×20 μm cross-section for liquids. The reactor used in the experiment had microchannel plates with two types of channels: narrow channels of 50×50 μm size and wide ones of 300×100 μm size. It was shown that in both MCR versions, the enhancement of mass and heat transfer leads to higher conversion and selectivity compared with the laboratory reference. For the falling film microreactor, the yields of *ortho*- and *para*-monofluorinated products were up to 28% for 78% conversion. Note that these values are roughly similar to those achieved in the industrial process. However, the geometric

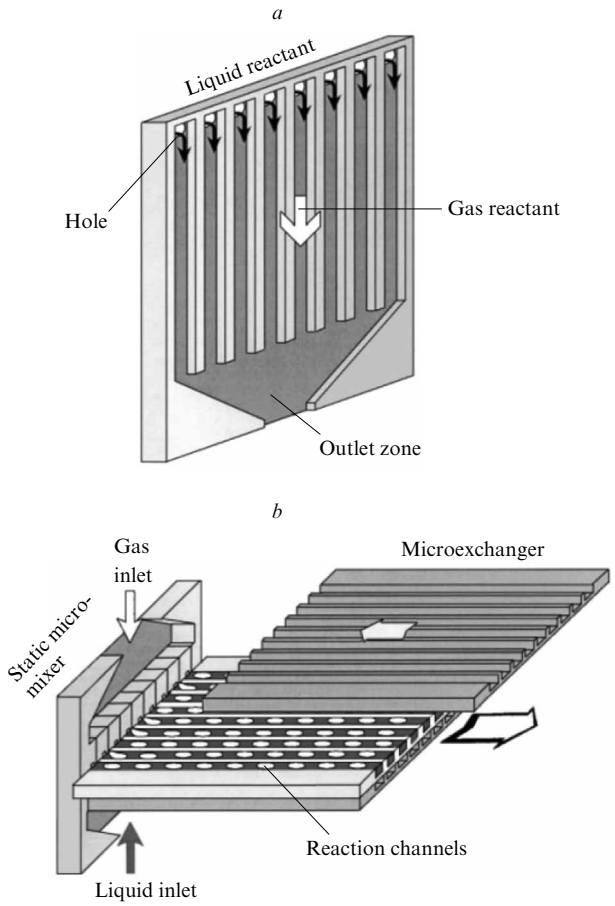


Figure 8. Design types of gas–liquid microchannel reactors for high-energy processes.[94]
(*a*) Falling film MCR, (*b*) microchannel bubble column.

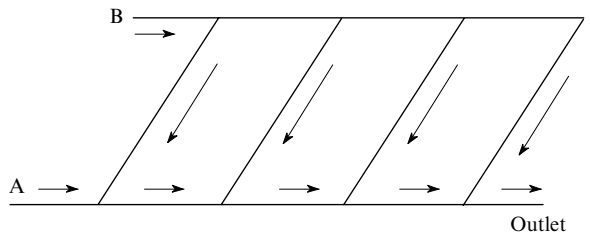


Figure 9. Multi-injector microchannel reactor.[95]

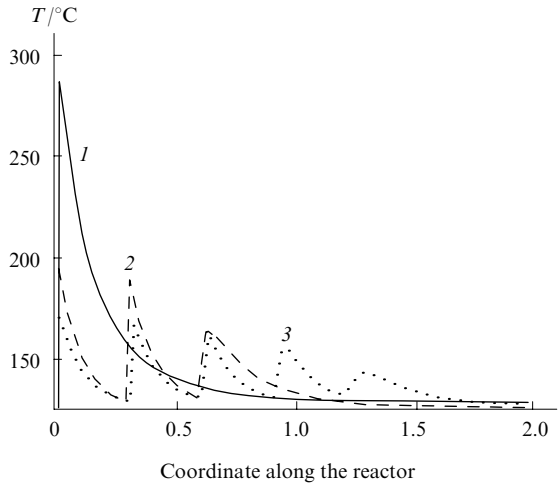


Figure 10. Calculated temperature profile of a multichannel reactor at different numbers of injections.[95]
(*1*) One injection, (*2*) three injections, (*3*) five injections.

volume of the industrial columns was an order of magnitude greater than that of the MCR, which points to economic benefit of the MCR. Furthermore, by changing the fluorination conditions towards intensification (increase in the F_2 : PhMe ratio and temperature rise), it is possible to reach higher yields and toluene conversions.

The major problem arising in the conduction of fast and highly exothermic reactions is the formation of undesirable hot spots in the reactor. This can be observed even in MCR with channels 100–1000 μm in diameter. Therefore, an alternative design of the reactor that prevents uncontrolled heating of separate areas is a multi-injection microreactor implementing the multistep injection principle, according to which one reactant (B) is successively added to the main reactant flow (A) (Fig. 9). This not only decreases the undesirable overheating of particular reactor areas but also improves the temperature control. Note that this principle has long been used by synthetic chemists for the conduction of fast and high-energy reactions: small portions of a reactant are gradually added under intense stirring to the major reactant in a beaker.

Haber *et al.*[95] performed a theoretical and experimental study of a multi-injection microreactor applied for intensification of processes characterized by short reaction times and large heats. The experimental data obtained for cyclization of pseudoionone to α- and β-ionones confirmed the validity of model calculations. Figure 10 shows the calculated temperature profiles along the reactor for different numbers of injections. It can be seen that an increase in the number of injections leads to a decrease in the temperature gradient and local overheating along the microreactor. The maximum overheating temperature for a single injection is ~300 °C, that for three injections is ~200 °C, and for five injections it is ~170 °C, *i.e.*, the temperature profile becomes flatter. However, on further increase in the number of injections (more than six), the observed change in the temperature along the microreactor becomes insignificant.

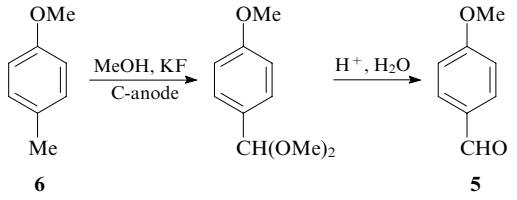
The monitoring of the temperature profile along the microreactor by an infrared thermograph showed that the multi-injection operation of the microreactor reduces the hot-spot temperature 8-fold compared with adiabatic temperature rise. The yield of final products, α- and β-ionones, was >98%, *i.e.*, there was a 500-fold increase in the process intensity with respect to the conventional semi-batch reactor process.

The advantages offered by the MCR over conventional reactors can be successfully utilized in the electrosynthesis of organic compounds. A multitude of these reactions have been investigated to date,[96] but the problem faced by conventional reactors concerns also electrochemical processes. This is the probem of low heat and mass exchange rates, which directly affect the potentials and current distributions in electrochemical cells. In the case of small-scale production, microchannel systems can solve these

problems. More detailed information about the design of electrochemical MCR can be found in the original publication.[97]

The MCR was tested in a model synthesis of 4-methoxybenzaldehyde (**5**) from 4-methoxytoluene (**6**) (Scheme 8).[97] 4-Methoxybenzaldehyde (anisaldehyde) is used as a fragrance compound in perfumery products and food essences and in the synthesis of some medicinal drugs, for example, iodoalphionic acid (bilitrast agent used for X-ray examination of human organs and tissues) and betazin (a drug retarding the thyroid function). The traditional industrial methods for the preparation of anisaldehyde are the oxidation of anethole with ozone or chromic acid mixture in the presence of sulfanilic acid, oxidation of *p*-cresol methyl ether with MnO_2, $KMnO_4$ or $K_2S_2O_8$ (in the presence of Cu^+ or Ag^+ salts and alkali metal oxalates) and the electrochemical method.

Scheme 8



Using MCR, the oxidation of a 0.1 M solution of 4-methoxytoluene in methanol was carried out on a glass carbon anode with addition of a conducting salt (KF, 0.1 mol litre^{-1}). The selectivity of the reaction with respect to 4-methoxybenzaldehyde was >98%, whereas in conventional industrial processes it does not exceed 85%. The authors noted that by increasing the number of channels, it is possible to increase the MCR performance for anisaldehyde.

III.5. Multistep syntheses

Microchannel systems allow rather easy arrangement of multistep processes. This is done using several microreactors with definite functions, which are integrated into a common device continuously giving out the target product. Short residence times and high reactant flow rates between the microreactors provide efficient use of the kinetic and mechanistic features of the reaction, in particular, the formation of unstable short-lived intermediates.

The most impressive results of using microchannel systems in multistep syntheses were achieved in the preparation of peptides, which is of special interest for pharmacological industry. The possibility of multistep peptide synthesis in a glass MCR with electrokinetic flow control was demonstrated.[98] Comparison of the efficiency of peptide synthesis in the MCR and in the conventional bulk reactor showed a substantial advantage of the former. Indeed, the dipeptide was obtained in an MCR over a period of 20 min with a 93% conversion. Meanwhile, the same conversion in an autoclave required 24 h. Thus, the microreactor is a sufficiently efficient device for the formation of peptide bonds and can give long-chain peptides in a successive synthesis.

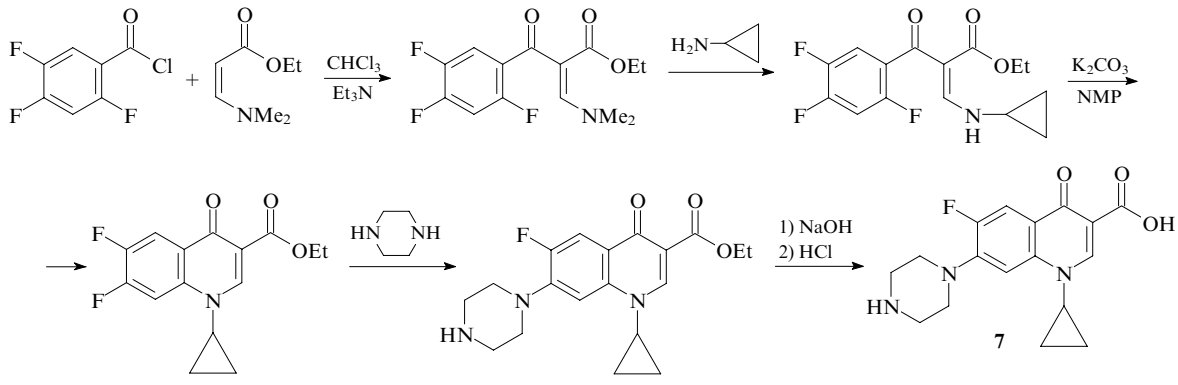
A tubular type MCR was used to prepare ciprofloxacin (**7**), a broad spectrum antibiotic belonging to the group of second-generation fluoroquinolones (Scheme 9).

The oxidation method for primary and secondary alcohols to aldehydes and ketones under mild conditions discovered by Swern in 1978 excludes the use of toxic stoichiometric oxidants such as chromium compounds. This is a multistep process using 'activated' dimethyl sulfoxide. The first low-temperature step is the reaction of dimethyl sulfoxide with oxalyl chloride (**8**). The intermediate **9** thus formed rapidly decomposes with CO and CO_2 evolution and generation of highly active dimethylchlorosulfonium chloride (**10**), which in turn reacts with alcohol **11** to give alkoxysulfonium ion **12**.[99] Then triethylamine comes in by deprotonating intermediate **12** to give ylide **13**, which decomposes yielding dimethyl sulfide and the target ketone or aldehyde **14** (Scheme 10).[100]

The Swern oxidation gives off a large amount of heat. Therefore, in conventional reactors, this synthesis is carried out at −78 °C, which is very inconvenient from the engineering standpoint and makes the process more expensive. In addition, this gives a lot of undesirable side products. By using MCR, acceptable yields of carbonyl compounds were attained in this multistep processes without deep cooling and the selectivity of reactions involving highly reactive intermediates could be controlled.[101]

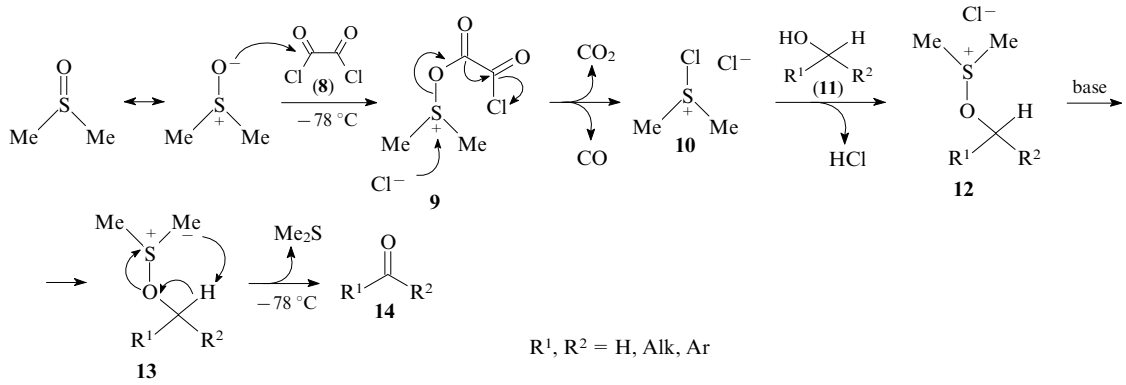
Figure 11 shows a diagram of the microchannel assembly, which served for the multistep Swern synthesis of aldehydes and ketones at temperatures from −20 to 20 °C. A somewhat different process flow diagram for the preparation of carbonyl compounds was used. A cascade of stainless steel tubular microchannel reactors, R1, R2, R3, and R4, was connected to micromixers, M1, M2 and M3,

Scheme 9



NMP is *N*-methyl-2-pyrrolidone

Scheme 10



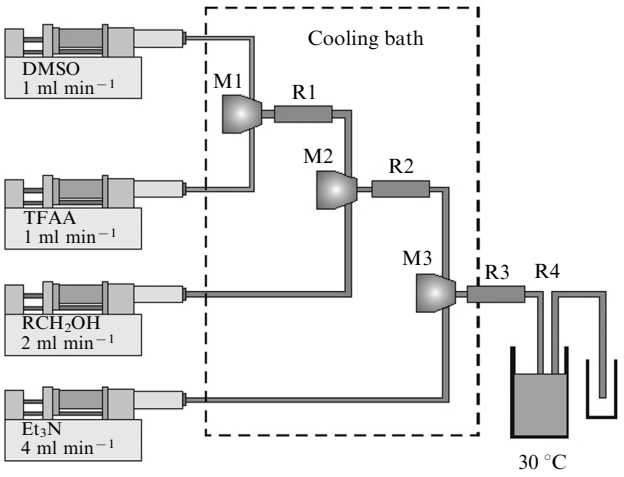
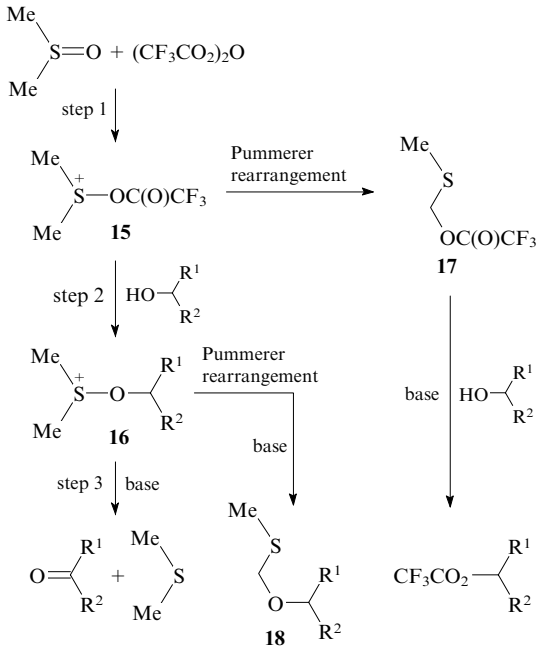


Figure 11. Flow diagram of the cascade of microchannel reactors for the Swern oxidation of alcohols.[99]
TFAA is trifluoroacetic anhydride.

Scheme 11

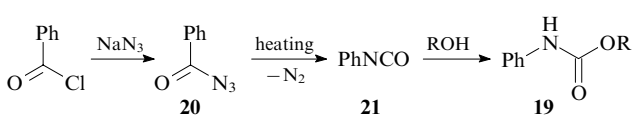


R1 = H: R2 = n-C9H19, Ph; R1 = Me, R2 = n-C6H13; R1–R2 = (CH2)5

containing silver insets with microchannels of 40 μm cross-section. The initial solutions were fed with syringe pumps. The whole MCR assembly was placed into a common tank maintained at a constant temperature. The short-lived high-energy intermediates formed during the process did not cause a hazardous situation during the synthesis even at 20°C. A mechanism for this reaction has been proposed.[98, 101] It was found that intermediates **15** and **16** are quite unstable and undergo fast Pummerer rearrangement at temperatures above −50 °C to give undesirable side products **17** and **18**. The possibility to carry out the process at 20 °C is related to the specific course of the reaction in a microreactor with short residence times. In the example in question, the residence times in reactors R1, R2, R3 and R4 were 0.01–2.4, 1.2, 1.2 and 5.9 s. Indeed, for the residence time in the first reactor of 2.4 s and a temperature of −20 °C, the yield of carbonyl compounds is in the range of 75%–95%, and for the residence time of 0.01 s, the yield is 71%–89%. Thus, the experiments demonstrated[98, 101] good potential of the multistep microchannel system for the synthesis involving short-lived intermediates (Scheme 11).

Fairly abundant FS processes are the syntheses of various carbamates (urethanes) **19** — esters of unstable carbamic acid. These products are used in the production of insecticides, herbicides and some medicinal drugs as well as in the synthesis of diazoalkanes for the production of dyes. The synthesis of carbamates has also been performed successfully using microreactors.[102] In this case, the use of MCR was reasoned by the intermediate formation of azide **20** and isocyanate **21**, which are hazardous compounds and, therefore, scaling up of the process and the use of conventional chemical equipment are difficult. Multistep continuous synthesis of the target product in a microchannel system implies *in situ* consumption of the intermediates. This eliminates the necessity to store the intermediates and thus makes the process safer. The synthesis of carbamates *via* the Curtius rearrangement is shown in Scheme 12.

Scheme 12



R = Me, Et, Bn

The process flow diagram for the continuous multistep synthesis of carbamate is presented in Fig. 12. In the first

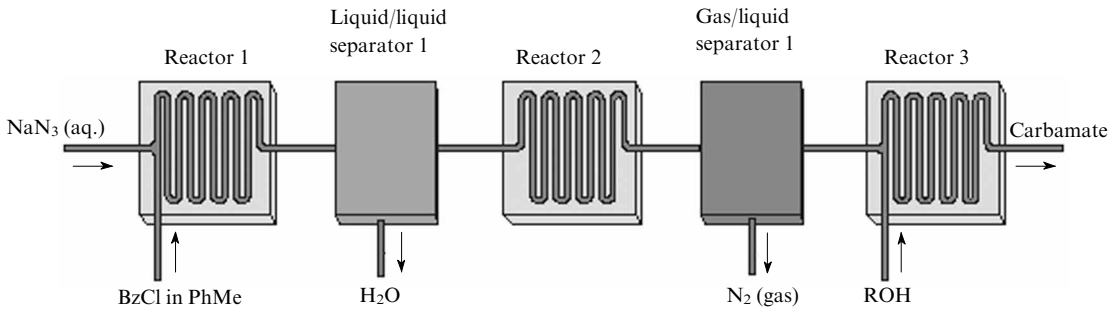


Figure 12. Flow diagram of the multichannel reactor unit for the multistep synthesis of carbamates.[102]

step, the reaction of a 0.4 M aqueous solution of sodium azide (pH 9) with benzoyl chloride (0.36 mol litre^{-1}) takes place in reactor 1. In order to achieve the most efficient two-phase contact, the so-called segmented flow regime was used: reactant mixture and inert carrier (toluene) segments alternate in the microreactor tube; toluene functions also as a buffer minimizing the diffusion between the segments of the reaction mixture. The conversion of benzoyl chloride to benzoyl azide depends considerably on the residence time. The residence time was increased by mounting a T-shaped micromixer and additional tubing for supply of the carrier upstream of reactor 1. The conversion of 65% was observed at a residence time of 90 min, while after 200 min, the conversion was 98%. The downstream continuous separation of the aqueous and organic phases took place in microseparator 1. The device had a thin porous fluoropolymer membrane (pore size 0.1–1 μm), which was selectively wetted with the organic phase, thus preventing the aqueous phase from passing through.

In order to attain high conversion at low temperature (90 °C), the isocyanate preparation in the second process step in reactor 2 was performed in the presence of an acidic H-mordenite catalyst (HS-690 of Wako Chemicals). As a result a 99.9% conversion of the azide to isocyanate was attained (or 92.2% without a catalyst). The nitrogen formed was removed in gas/liquid separator 2 equipped with a selective membrane. The target product — methyl, ethyl or benzyl phenylcarbamate — was prepared in the third step in 96%–99% yield *via* the reaction of the isocyanate with the appropriate alcohol in microreactor 3.

The studies of Sahoo *et al.*[102] demonstrate the advantages of microchannel systems — microreactors, micromixers and separators — for the continuous synthesis of carbamates. The hazardous isocyanates are formed and consumed *in situ* in this case. Thus, the safe operation of microreactors with highly reactive compounds such as azides becomes possible and process parameters can be optimized.

IV. Application of microreactor systems in industry

Microchannel systems were first used in chemical analysis devices.[103, 104] Numerous studies then demonstrated that the use of microchannel systems is justified not only in analytical chemistry but also for kinetic and mechanistic studies of chemical reactions.[103, 105] Recent years have seen increased interest in the industrial use of microchannel devices.[106, 107] There is experience of using them for microstirring in the preparation of stable colloid systems in which the particle size should not exceed ~1 μm, for example, preparation of pharmaceutical or cosmetic emulsions, preparation of pesticide agents and detergents,[108] and for conducting reactions involving explosive, self-igniting or toxic compounds (for example, fluorination of aromatic compounds[109]). Microreactor systems can be also useful for the design of environmentally benign green chemistry processes.

Microchannel systems are compact; therefore, it is promising to design small portable small-scale production units. These units can operate directly at the sites of consumption of the products. One more example of using MCR is the preparation of the environmentally safe oxidant, hydrogen peroxide, used for the oxidation of organic substrates in the liquid phase.[110] The industrial implementation of these processes is restricted by the high cost of hydrogen peroxide and the hazard of its transportation by large distances. Ng *et al.*[111] showed the possibility of arranging a continuous hydrogen peroxide production process in a capillary microreactor by the direct catalytic reaction of H_2 with O_2 at room temperature and atmospheric pressure. The reactor consisted of three 34.5 cm long glass capillary tubes with an inner diameter of 2 mm. The catalyst (Pd/polymer) with a total mass of 0.35 mg was supported on the inner surface of the tubes. The H_2 and O_2 flow rates were 2 and 4 ml min^{-1}, respectively. To stabilize the resulting hydrogen peroxide, the initial gas mixture supplied at a flow rate of 0.5 ml h^{-1} was mixed with methanol containing 0.1 mol litre^{-1} of hydrochloric acid and 0.281 mmol litre^{-1} of potassium bromide. At the outlet, the reaction mixture containing hydrogen peroxide entered the separator placed into an ice bath. The researchers[111] noted that leaching of palladium particles in 11 days of test operation was insignificant (within 10%). An important role was played by the liquid flow rate: the increase in the flow rate from 0.2 to 1.0 ml h^{-1} resulted in increasing productivity from 0.24 to 0.46 mol h^{-1} g^{-1}(Pd). This approach demonstrates that it is in principle possible to design a portable hydrogen peroxide production unit directly at the site of its consumption.

Inoue *et al.*[112] also carried out experiments on direct synthesis of hydrogen peroxide in a microreactor. A distinctive feature of this approach is the absence of an organic solvent (methanol). The resulting hydrogen peroxide was stabilized by a mixture of aqueous sulfuric acid (0.02 M), phosphoric acid (0.005 M) and sodium bromide (5.1×10^{-4} M). The test was carried out using two one-channel glass microreactors with channel lengths of 40 mm

and 200 mm. The channel with a 0.6 mm width and a 0.9 mm depth was charged with the pelletized catalyst. As shown previously,[113,114] the chosen cross-section of the channel was crucial for preventing an explosion. The experiments were carried out at room temperature and a pressure of 9.5 bar. The best results — hydrogen conversion of 80% and aqueous hydrogen peroxide with a concentration of 11 mass % at the outlet — were obtained for two microreactors connected in series and $Pd-Au/TiO_2$ as the catalyst.

It should be borne in mind that the development of new production processes for organic compounds using conventional approaches requires scaling-up of the method developed at the laboratory level. This requires additional process optimization at every scaling stage. This way of technology transfer from laboratory to industry is often not only expensive but also time- and labour-consuming. Of course, many problems of reactor scaling up can be solved by mathematical modelling. However, for the industrial synthesis of compounds in small amounts, the scaling up problem could be solved (Fig. 13) by using particularly microchannel systems; in this case, process development and optimization can be carried out in laboratory in a single reactor,[115] as the increase in the production capacity can be attained by merely increasing the number of MCR used.[116,117]

A review[42] presents examples demonstrating the advantages of microchannel systems over conventional chemical equipment for organic synthesis processes. The authors analyzed the available publications in this field and classified the described examples of preparation of organic compounds using microchannel systems in the continuous regime according to the flow rates of reaction components. Flow rates up to 10 ml h^{-1} formed the first group of processes (small-scale applications), while those ranging from tens of millilitres to several tens of litres per hour were called laboratory-scale syntheses. Processes of the first group are usually carried out in one-channel (or several-channel) microreactors, which are, in some cases, combined with micromixers, whereas processes of the second group (as a rule, multistep syntheses) make use of more intricate microreactor designs containing up to 672 microchannels.

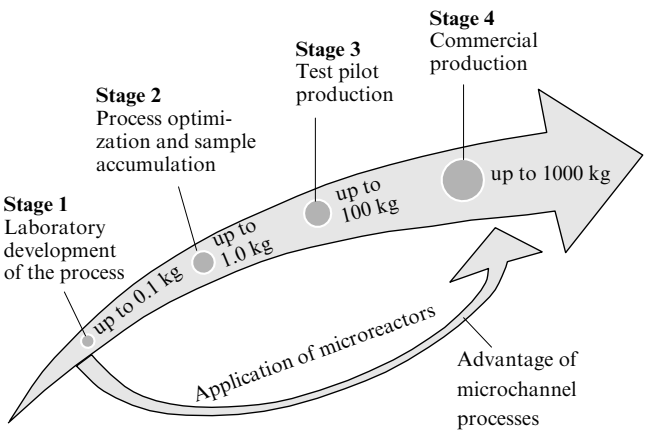
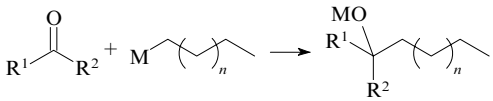


Figure 13. Sequence of the design of small-scale chemical processes in the conventional approach and with the use of microchannel reactors.

One example is hydrogenation of cycloocta-1,5-diene.[42] Another example of intricate design is the tubular microreactor (inner diameter 5–20 mm, length 23–60 m) with 1 to 10 micromixers located inside, which was used for polymerization of acrylates. By better homogenization of the monomer and the initiator and with reactant flow rates of 6–8 kg h^{-1} and residence time of 40 min, a polymer with a narrow molecular-mass distribution was formed free of side products with lower molecular mass.

An industrial process using microdevices for the addition reaction of organometallic compounds to carbonyl compounds was designed. Unfortunately, the authors[42] named only the classes of compounds but did not specify the reactants used and the product obtained (Scheme 13).

Scheme 13



M is metal

It is emphasized that the process parameters were optimized on a laboratory-scale unit, while the production was performed in a unit comprising five mini-reactors. Comparative characteristics for a particular addition of an organometallic compound to a carbonyl compound in different reactors are presented in Table 3. It can be seen from these data that micro- and mini-structurized reactors give high yields at short residence times and allow more efficient temperature control and higher surface area to volume ratios.

More and more manufacturers of chemical products are attempting to make use of the benefits of microchannel systems. Among these are Swiss companies Clariant and Sigma Aldrich (SAFC), German companies BASF and Evonik Indu stries, Dutch company DSM and US company DuPont, as well as the US pharmaceutical companies Schering-Plough, Sanofi Aventis, Roche, GlaxoSmithKline, Novartis and Astra Zeneca and even the consumer giant Procter & Gamble. The Dutch chemical company DSM applied the microreactors developed by Corning (US) for nitration. As a result, 25 tonnes of the target product were obtained in one year. Presumably, the output is going to be

Table 3. Summary data on the use of various types of reactors for the addition of organometallic reagents to carbonyl compounds.[42]

Reactor type	Surface area to volume ratio /m^2 m^{-3}	T/°C	Residence time	Product yield (%)
Conventional laboratory reactor (0.5 litres)	80	−40	0.5 h	88
Conventional industrial reactor (6 m^3)	4	−20	5 h	72
Microreactor (laboratory scale)	10 000	−10	< 10 s	95
Microreactor (pilot scale, pilot run)	4000	−10	< 10 s	92
Five parallel mini-reactors (industrial unit)	5 × 4000	−10	< 10 s	92

soon increased to 100 tonnes per year.[118] A variety of microchannel systems suitable for highly exothermic and high-pressure reactions were developed by IMM and Velocys (USA).

In Russia, studies of microchannel systems as applied to FS processes are at the laboratory level. Nevertheless, with increasing demand in small-scale FS products in the market, new chemical engineering processes using microchannel systems may be implemented in Russian industry in a rather short time.

V. Conclusion

Analysis of the published data shows good prospects of application of MCR for the synthesis of a number of demanded small-scale organic products. In a number of cases, the use of microreactors improves not only economic but also environmental characteristics of the process.

The presence of a set of MCR for different functions enables rather fast variation of the process flow diagrams of small-scale production processes and thus design adjustable mini-plants. In this case, the production capacity can be increased by mere connection of additional microchannel modules in parallel.

Generally, the experience accumulated in this field in the last 20 years has revealed the following benefits of the application of MCR to FOS processes.

Engineering benefits:

— submillimetre-sized channels considerably increase the efficiency of heat and mass transfer, which provides the possibility to carry out chemical, in particular, catalytic processes accompanied by pronounced heat evolution or heat absorption under virtually isothermal conditions;

— high accessibility of the catalyst to the reactants and small free volume of the reaction zone allow efficient conduction of fast chemical processes in the MCR;

— laminar flow profile and narrow residence time distribution increase the process selectivity and efficiency to the target product.

— the *E*-factor considerably decreases because of reduced formation of side products.

Operation benefits:

— lower risk for conduction of processes with explosive and highly toxic compounds;

— possible fast replacement of the spent heterogeneous catalyst or even the whole microreactor by means of easily mountable microchannel modules;

— possible fast deployment of a small-scale plant for the production of a desired product in the logistically difficult areas or areas of the product consumption;

— possible complete automation of FS processes and reliable control of MCR operation, for example, in self-sufficient units;

— possible arrangement of mini-production units and mini-plants with high production flexibility independent of the production capacity.

It is also noteworthy that all of the above listed engineering advantages of microchannel systems are manifested most clearly for the chemical processes having the following features: high reaction rates; high reaction heats; mass transfer as the rate-limiting stage; and toxic, flammable or explosive compounds involved. Drawbacks of microchannel systems include limitations related to their manufacture and characteristics of reactions. If the reaction is devoid of the above-listed features, no process intensification is observed in a microchannel reactor and the use of such reactors in inexpedient. In addition, they are almost inapplicable to reactions resulting in the formation of a solid phase. The engineering problem of reliable attachment of a sufficient amount of the catalyst to the microchannel walls is still unsolved. Currently, the use of microchannel systems for the production of tonne amounts (up to 1000 tonnes per year) is significantly limited by the modern technology level. However, these systems can be used for research purposes and for very small-scale (up to 0.1 tonnes per year) and small-scale (up to 10 tonnes per year) production.

This review was prepared with the financial support of the Russian Foundation for Basic Research (Project No. 13-08-00449) and the RF President grant for the State Support of the Leading Scientific Schools of the Russian Federation (NSh-1183.2014.3).

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