4
Liquid- and Liquid/Liquid-phase Reactions

4.1
Micro Reactors for Liquid-phase and Liquid/Liquid-phase Reactions

4.1.1
Tube Micro Reactors

This class is the simplest of all micro reactors and certainly the most convenient one to purchase, but not necessarily one with compromises or reduced function. HPLC or other tubing of small internal dimensions is used for performing reactions. There are many proofs in the literature for process intensification by this simple concept. As a micro mixer is missing, mixing either has to be carried out externally by conventional mini-equipment or may not be needed at all. The latter holds for reactions with one reactant only or with a pre-mixed reactant solution, which does not react before entering the tube.

4.1.1.1 **Reactor 1 [R 1]: Electrothermal Tubing-based Micro Reactor**

The central part of this device (Figure 4.1) is a liquid chromatography (LC)-type steel tubing suitable for high-pressure operation which is resistance-heated using electrical current from an external power supply [1]. On the tube, along the flow passage, a series of voltage taps monitor real-time temperature profiles. Thereby, the course of the reaction can be followed stage-wise provided that heat is released or consumed. The typical volume of a stage involves about 200 μl.

Reactor type	Electrothermal tubing-based micro reactor	Tubing length	1.5 m
Tubing material	300-series HPLC grade steel	Maximum working pressure for tubing	70 MPa
Tubing outer diameter	1.59 mm	Injection of further streams by	HPLC-type sample injection valves
Tubing inner diameter	1.27 mm		

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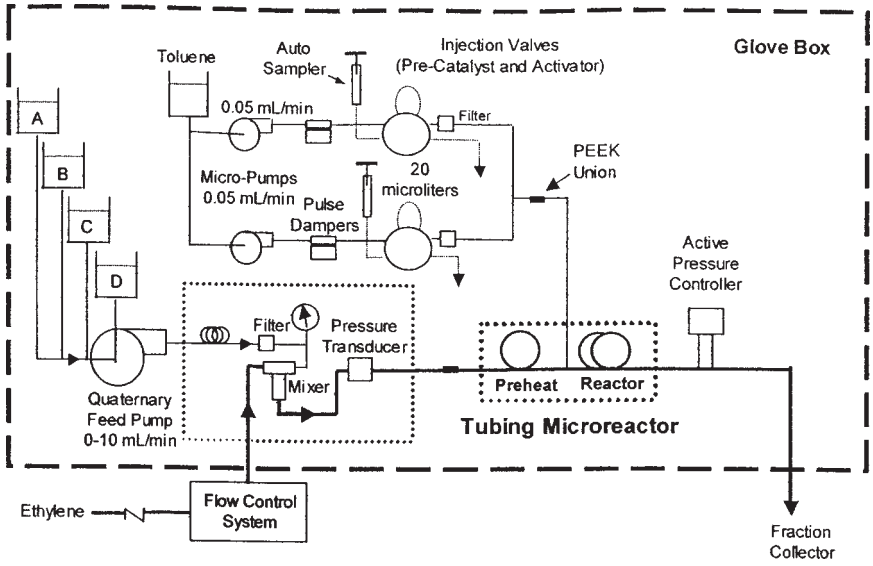

Figure 4.1 Flow scheme of a plant comprising an electrothermal tubing-based micro reactor configured for ethylene polymerization [1].

Before the actual reaction tube, a pre-heating tube is attached to bring the fluids close to reaction temperature [1]. Injection of further streams is performed by HPLC-type sample injection valves.

4.1.1.2 Packed-bed Tube or Capillary Micro Reactors

When performing catalytic reactions or reactions with immobilized reactants, a bed or support has to be filled into a tube or capillary. The filling may be a bed of powder, a bed of granules or a three-dimensional material network (e.g. a polymerized foam). By special choice of the filling, e.g. very regularly sized particles, it is attempted to improve the flow characteristics.

These filled tubes or capillaries hence are mini fixed beds with internal micro flow regions. Such approach is a link between real micro structured units and conventional equipment. The type of processing may be analogous to conventional processing, e.g. fixed-bed or trickle-bed operation.

4.1.2.1 Reactor 2 [R 2]: Packed-bed Capillary Micro fFow Reactor

This reactor concept, termed micro flow reactor [2], simply relies on the use of conventional polymer or glass tubing. The tubing has millimeter internal diameter. Functionalized Merrifield resin polymer beads with catalyst moieties attached are filled into the tubing and are held in place by plugs of glass wool. Standard HPLC or OmniFit connectors are attached to the tubing on one end for connection to syringe pumps. The other end of the tubing is connected to a syringe needle to enter into a vessel to quench the experiment.

Reactor type	Packed-bead capillary micro flow reactor	Packed-bead bed length	2–10 mm
Capillary material	Polypropylene; glass	Merrifield resin	200–400 mesh
Capillary inner diameter	2 mm (polypropylene); 1 mm (glass)	Nickel catalyst loadings	2–6 wt.-%

4.1.2.2 Reactor 3 [R 3]: Porous-polymer Rod in Tube Micro Reactor

A porous glass rod serves as holder for a polymer block. This material is introduced as monomer in the carrier and polymerized therein [3]. Such a glass rod was encapsulated within a pressure-resistant fiber-reinforced housing (Figure 4.2).

The polymerization applied produces spherical polymer particles (1–10 μm diameter) connected by polymer bridges [3]. Thus, a one-piece polymer phase is obtained. The interstices between the particles have a characteristic length of a few micrometers. Overall, the polymer structure can be ascribed as lose.

This polymer resin is in a first step chemically functionalized, yielding initial reactive moieties [3]. In a second step, other groups can be introduced by chemical reaction of these moieties, e.g. creating ammonium groups. By ion exchange, reactive anions are bound which serve as reactants for the reactions to be carried out later on [P 56].

Reactor type	Porous-polymer rod in tube micro reactor	Polymer load	10%
Polymer rod carrier material	Porous glass	Polymer type	Polystyrene-divinylbenzene
Polymer rod carrier inner diameter	50–300 μm	Polymer mass	250 mg
Material for housing for carrier	PTFE	Reactive group	Quaternary amine
Housing for carrier: diameter; length	5.3 mm; 110 mm		

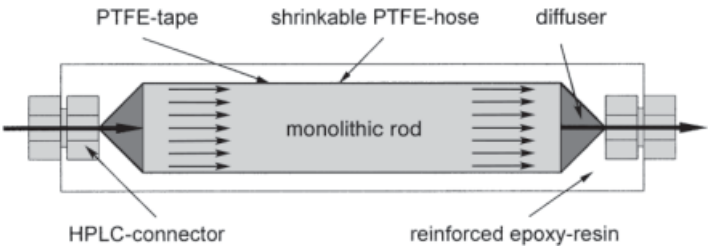

Figure 4.2 Schematic of the porous-polymer rod in a tube micro reactor [3].

4.1.3
Chip Micro-reactor devices

This section describes micro-channel reactors that are made by silicon micro machining, thin-film techniques and other related techniques, originally developed for microelectronic fabrication. In the following, only components are considered that are more or less completely made via this route. Typically, these reactors have a mixing function, e.g. as a mixing tee or Y-piece and a subsequent channel section for reaction. Additional functions, especially concerning sensing, controlling and heating, are easily implemented owing to the microelectronic fabrication route chosen. Typically, the way of assembly is to have a layered structure which is bonded or clamped. The overall size of the device is small, similar to a cheque card.

Liquid transport is achieved by hydrostatic action, pumping or electroosmotic flow (EOF). So far, chip reactors have been employed at low to very low flow rates, e.g. from 1 ml min^{-1} to 1 µl min^{-1}. Applications consequently were restricted to the laboratory-scale or even solely to analytics. However, this is not intrinsic. By choosing larger internal dimensions, similar throughputs as for the other classes of liquid or liquid/liquid micro reactors are in principle achievable.

4.1.3.1 Reactor 4 [R 4]: Chip Reactor with Micro-channel Mixing Tee(s)

A micro reactor comprising one or several (up to three) micro-channel mixing tees was made by photolithography and etching (Figure 4.3) [4–13]. Species transport is achieved by means of EOF and electrophoretic mobility (a detailed description on EOF is given in [14]). The number of mixing tees mainly derives from the number of reactants to be added. For instance, when using four reactants, such as for the Ugi reaction, three micro-channel mixing tees result. The mixing tees usually are fed by counter-flow (180°) or cross-flow (90°) arrangements of the two streams to be mixed.

Microfabrication is achieved by photolithography and isotropic etching of glass using HF [4–13]. Thermal bonding serves for interconnection. Holes are drilled in the top plate for connection to the fluidic peripherals.

Some of the chip reactors are equipped with micro porous frits (see, e.g., [13]).

Version (a) comprises one mixing tee only (Figure 4.4) [11]. Version (a2) can be heated up to 70 °C [9]. A T-shaped Peltier heater attached to the lower plate was used to adjust temperature.

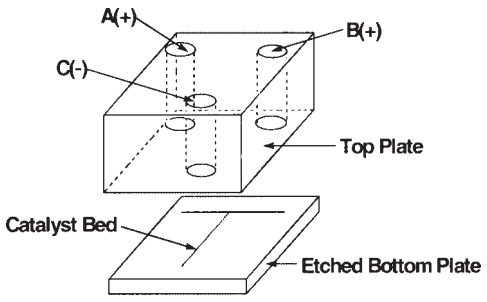

Figure 4.3 Schematic of the chip reactor with one micro-channel mixing tee [11].

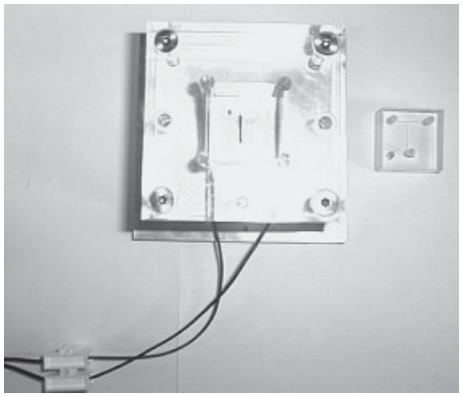

Figure 4.4 Mounted chip reactor with (right) and single micro-channel mixing tee chip (left) [8].

Reactor type	Chip micro reactor with one micro-channel mixing tee	Channel width; depth	200 μm (at top) × 100 μm
Micro reactor material	Borosilicate glass	Thickness of top plate	17 mm
Outer dimensions	20 × 20 × 25 mm^3	Diameter of inlet and outlet holes	3 mm

Version (b) has a four-channel flow guidance that encompasses two mixing tees in two simple mixing tees (Figure 4.5) [8]. An example of this function is the flow guidance for the Michael addition. In a first step, the base and 1,3-dicarbonyl compound streams merge. The enolate stream thus formed is then mixed with the Michael acceptor. Microporous silica frits are set into the channels to minimize

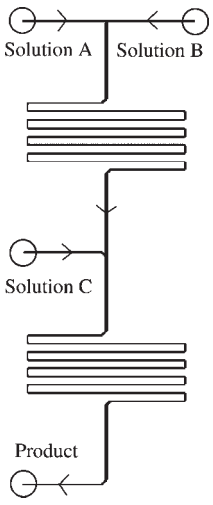

Figure 4.5 Schematic of the chip reactor with two micro-channel mixing tees.

hydrodynamic effects. Electroosmotic flow was applied to transport the reactants. Voltage setting and monitoring of the platinum electrodes, which are placed in the reservoirs, was achieved by the Lab-View program.

Reactor type	Chip micro reactor with two micro-channel mixing tees	Micro reactor material	Borosilicate glass
Channel dimensions	$150 \times 50\ \mu m^2$	Outer dimensions	$20 \times 20 \times 25\ mm^3$

In version (c), three mixing tees were realized in another version of the above-mentioned chip reactor concept [16].

Reactor type	Chip micro reactor with three micro-channel mixing tees	Micro reactor material	Borosilicate glass
Channel dimensions	$200 \times 100\ \mu m^2$	Outer dimensions	$20 \times 20 \times 25\ mm^3$

4.1.3.2 Reactor 5 [R 5]: Chip Micro Reactor with Multiple Vertical Injections in a Main Channel

This reactor is generically and according to fabrication closely related to the reactor concept [R 4]. Although the micro channel geometry is, on a first sight, only slightly different from [R 4], the functional principle and details on the liquid feeding (by EOF and electrophoresis) are not. A detailed description of EOF is given in [14].

The chip micro reactor [R 5] comprises a long micro channel connected to two vertically positioned shorter channels at each end which lead to two reservoirs [17]. These shorter channels are oriented in opposite directions so that a Z-type flow configuration results. In the downstream section of the long channel, two other vertically oriented shorter channels are also attached. These channels are each connected to a liquid reservoir. A total of five reservoirs are made in this way (Figure 4.6).

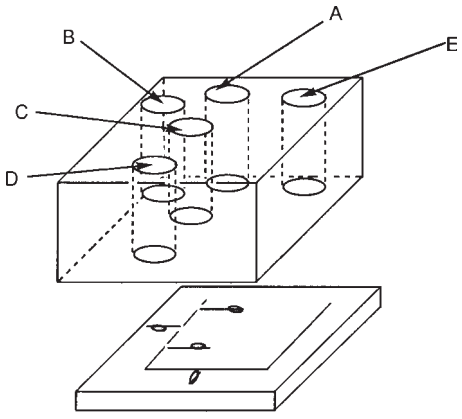

Figure 4.6 Schematic of the chip reactor with multiple vertical injections in a main channel [17].

Besides continuous operation, the flow of one or the other solution from the two feed reservoirs, or compounds, can be triggered by proper setting of voltages so that a slug of one solution (compound) in another can be formed [17]. By this means, migration of one component into a front of another, leading to mixing and subsequent reaction, can be performed as the mobilities of species are different when applying an electrical field.

In a special version of the device [17], all four shorter channels were discontinuous in the sense that they each comprised an array of very small channels which act as flow resistors. This ensures suppression of pressure-driven flow resulting from differences in the reservoir heights.

Reactor type	Chip micro reactor with multiple vertical injections in a main channel	Micro-channels etch mask width; etch depth	146 μm; 38 μm
Micro reactor material	Borosilicate glass	Flow resistor channels: etch mask width; etch depth	183 μm; 3 μm
Outer dimensions	25 × 25 × 20 mm^3		

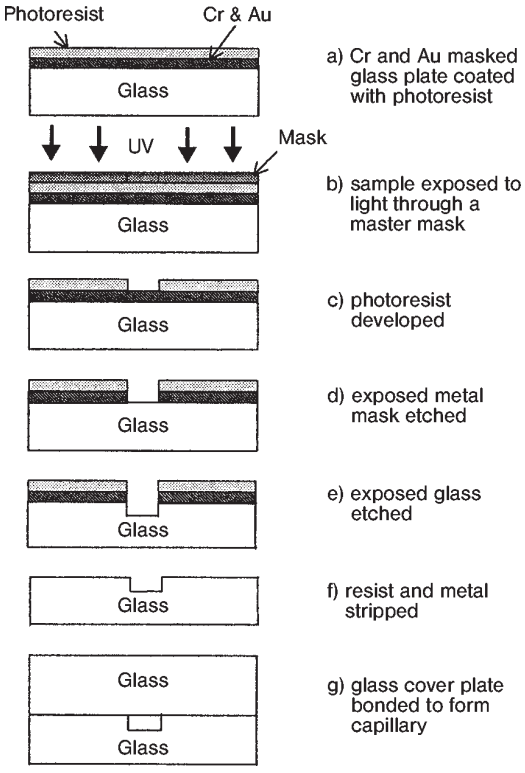

Figure 4.7 Steps in microfabrication of the chip reactor with multiple vertical injections [17].

Microfabrication was achieved by isotropic etching of glass using HF (Figure 4.7) [17]. Thermal bonding served for interconnection. Holes were drilled in the top plate for connection to the fluidic peripherals.

4.1.3.3 Reactor 6 [R 6]: Chip Micro Reactor with Multiple Micro Channel–Mixing Tees

This reactor concept is generically similar to [R 4], but relies on a more complex network of micro channels having more reservoirs (seven) [18]. The corresponding chip is a commercial product of Caliper Technologies Company (110 Caliper chip™), originally designated for μTAS applications. The version actually used for performing organic chemistry was optimized for hydrodynamic flow control (Figure 4.8). The chips were constructed from two glass plates by means of standard photolithography.

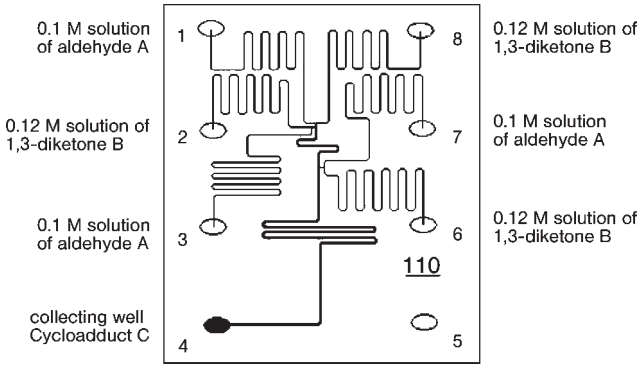

Figure 4.8 Schematic of the commercial 110 Caliper chip™ micro reactor for performing organic chemistry [18].

The etched micro channels have different widths for more stable flow, e.g. to avoid a dependence on capillary forces in the reservoirs [18]. The glass chip is glued to a polymer caddy for interfacing with a multiport control device, the Caliper 42™ Workstation.

Reactor type	Chip micro reactor with multiple micro-channel mixing tees	Caddy material	Polypropylene
Chip material	Soda lime glass	Widths of two sets of micro channels	29 μm; 74 μm

4.1.3.4 Reactor 7 [R 7]: Chip Micro Reactor with Z-type Flow Configuration

This reactor concept is generically similar to [R 4] and uses the same fabrication and assembly techniques, so the reader is referred to the corresponding description [19]. However, it has only one micro channel as it serves for transporting one liquid (or solution) only, i.e. was constructed for reactions with one reactant only such as eliminations [19].

The micro reactor contained a heating function (unlike [R 4] and the other versions of this reactor concept [R 5] and [R 6], decribed below) via a heating wire connected to a potentiostat [19]. This wire was integrated into the micro reactor by placing it in the mold before pouring the liquid PDMS.

For electroosmotic flow transport, a tube was inserted into the base plate, connected to the micro channel [19].

Reactor type	Chip micro reactor with Z-type flow configuration	Heater type/material	Nichrome wire
Micro reactor material	Borosilicate glass	Wire outer diameter	250 µm
Top plate material	Polydimethyl-siloxane (PDMS)	Tube for electro-osmotic flow: inner diameter; length	500 µm; 20 mm
Micro channel: width; depth; length	200 µm; 80 µm; 30 mm		

4.1.3.5 Reactor [R 8]: Chip Micro Reactor with Extended Serpentine Path and Ports for Two-step Processing

This is also (see [R 6]) a commercial chip ('Radiator'), provided by MCS, Micro Chemical Systems Ltd., The Deep Business Center [20]. A bottom plate contains an extensively wound serpentine channel. A top plate covers this microstructure. The two reactant solutions enter via capillary tubing through holes in the top plate. The first reactant is fed at the start of the serpentine path and the second enters this path in a short distance. Shortly before the end of the serpentine, a third stream can enter which may serve, e.g., for dilution and thus quenching of the reaction. After a very short passage, the diluted streams enter via a fourth port analytics. Commercially available capillary connectors were employed.

Microfabrication was made by wet-chemical glass etching [20]. Sealing was achieved by thermal bonding.

Reactor type	Chip micro reactor with extended serpentine path and ports for two-step processing	Serpentine micro channel: width; depth	100 µm; 25 µm
Chip material	Borosilicate glass	Type of commercial connectors	Standard fused-silica capillary connectors

4.1.3.6 Reactor 9 [R 9]: Chip System with Triangular Interdigital Micro Mixer–Reaction Channel

This system is a chip version of three dimensional micro mixer–tube reactor setups [21]. It comprises a triangular interdigital micro mixer with a focusing zone that thins the multi-lamellae and a subsequent reaction channel that is surrounded

by two heat-transfer fluid channels (Figure 4.9). These channels themselves are surrounded by two insulation gaps to prevent heat losses. At the end of the reaction channel a temperature sensor may be placed.

The whole system is constructed from two silicon wafers, fabricated using photoresist by deep reactive ion etching (DRIE) [21]. The wafers were thermally bonded. Thereafter, inlet and outlet ports were machined and the single reactors isolated by DRIE.

Owing to the transparency of silicon in most parts of the IR spectrum, such systems can be used also for in-line chemical analysis, utilizing them as flow-through analysis cells (see Section 4.2.1.4, In-line IR monitoring) [21].

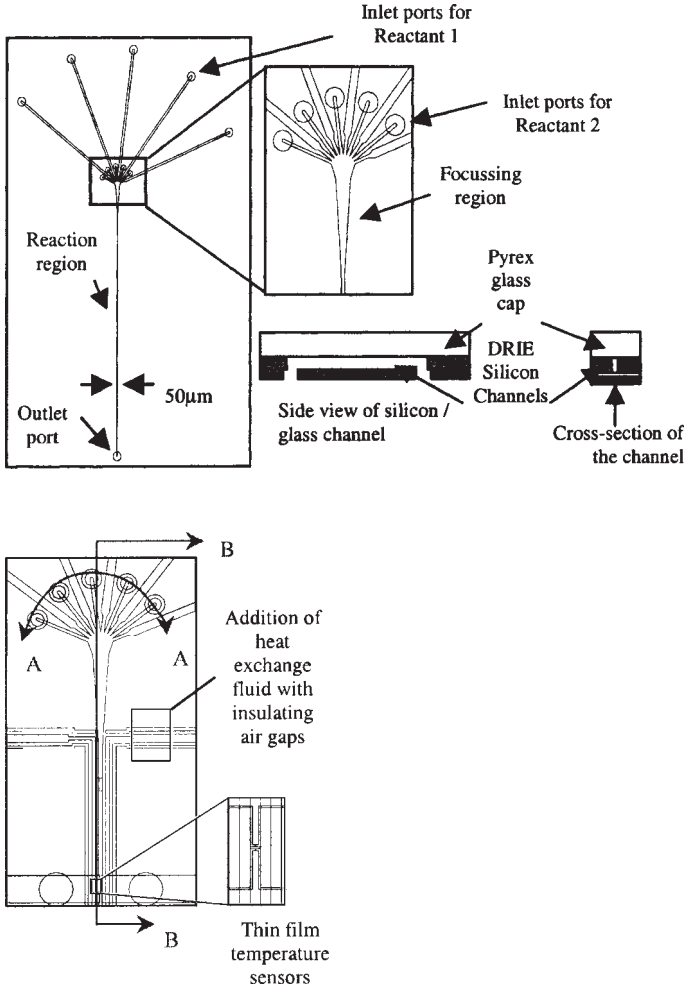

Figure 4.9 Chip system with triangular interdigital micro mixer–reaction channel. First- (top) and second- (bottom) generation reactor designs [22].

Reactor type	Chip system with triangular interdigital micro mixer–reaction channel	Mixing channel width	50 μm
Outer dimensions	24 × 29 mm² (1st generation); 21 × 27 mm² (2nd generation)	Heat transfer channel width; depth	50 μm; 350–500 μm
Feed channel width	60 μm		

4.1.3.7 **Reactor 10 [R 10]: 2 × 2 Parallel Channel Chip Reactor**

On this chip, two sets of two channels each branch in a T-configuration yielding eight channels [23, 24]. The latter are guided so that they merge to four channels in which the reactions are carried out (Figure 4.10). These channels comprise the full set of all 2 × 2 combinations of the reactants.

The idea of the chip is that all four permutated compounds from two reactants of one sort and from two of the other sort are created [23, 24]. To avoid crossing of reactant streams, a multi-layered architecture has to be used for construction, separating one sort reactant streams in one layer from the other sort in another layer. Extension of this principle to $n \times n$ parallel prepared permutations could be termed combinatorial.

Two microstructured layers of the 2 × 2 chip were fabricated by photolithography and wet etching in glass (Figure 4.11) [23, 24]. These top and bottom layers and a third thinner layer containing holes as conduits were thermally bonded to yield the chip. The way of guiding the micro channels, as described above, is referred to as two-level crossing.

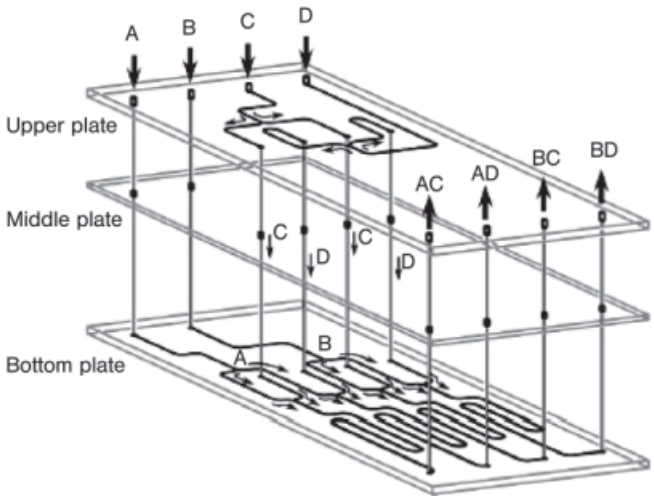

Figure 4.10 Schematic of a 2 × 2 micro-channel-array chip reactor; a generic design for performing combinatorial chemistry [23].

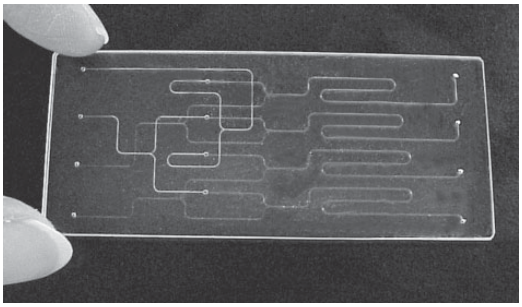

Figure 4.11 2 × 2 micro channel-array chip reactor realized in glass [23].

Reactor type	2 × 2 parallel channel chip reactor	Dimensions middle plate	30 × 70 × 0.2 mm^3
Material	Glass	Micro-channel width; depth	240 μm; 60 μm
Dimensions top and bottom plate	30 × 70 × 0.7 mm^3		

4.1.3.8 **Reactor 11 [R 11]: Bifurcation-distributive Chip Micro Mixer**

This device is based on multiple parallel bi-lamination using bifurcation cascade for generating multiple thin fluid olamellae [25]. The first feed stream is split into multiple sub-streams via a bifurcation cascade; in a similar way this is done for the second feed stream in another level. The corresponding sub-streams enter via nozzles into the first level. Here, the end of the channels of the bifurcation cascade and the nozzles lie next to each other. Thereby, bi-laminated sub-streams are formed and enter many parallel channels of an inverse-bifurcation cascade. These are recombined to multilayered stream in one main channel which has a serpentine shape, i.e. comprises extended length.

Reactor type	Bifurcation-distributive chip micro mixer	
Material	Glass/silicon	

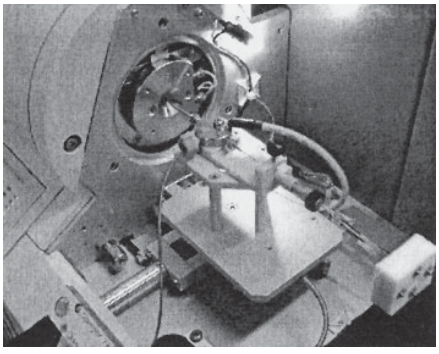

Figure 4.12 On-line coupling of the bifurcation-distributive chip micro mixer to a Perseptive Biosystems Mariner™ TOF-MS [25].

4.1.3.9 **Reactor 12 [R 12]: Micro Y-Piece Micro-channel Chip Reactor**

This device is a generically simple reactor comprising a micro-channel Y-piece section and an elongated reaction micro channel attached [26, 27]. The microstructures were mechanically fabricated in PMMA using a flat end mill. A top plate was joined with the microstructured plate by baking under vacuum. The reaction temperature was fixed using a hot-plate.

Reactor type	Micro Y-piece micro-channel chip reactor	Micro-channel width; depth; length	200 μm; 200 μm; 400 mm
Material	PMMA		

Chip reactor of similar design was also proposed by [91].

4.1.3.10 **Reactor 13 [R 13]: Triple Feed Continuous Multi-phase Chip Reactor**

This device contains one main reaction and processing path to which several channels are attached, feeding the main stream with additional phases, miscible or immiscible, or withdrawing such phases [28]. As a consequence, phases are either mixed or move as continuous streams side-by-side without intermixing. By this means, bi- or even tri-layered phase arrangement are created. If needed, one phase leaves the other by moving into a side channel.

The chip comprises five inlet ports and two outlet ports [28]. Three streams, two aqueous phases and one organic phase, are contacted initially; a layered system is created in this way (Figure 4.13). The aqueous phase is removed from the main stream; two other aqueous streams encompass the remaining organic phase. The two streams fulfil different functions. In total, several (up to 10) chemical unit operations may be conducted in series in this way.

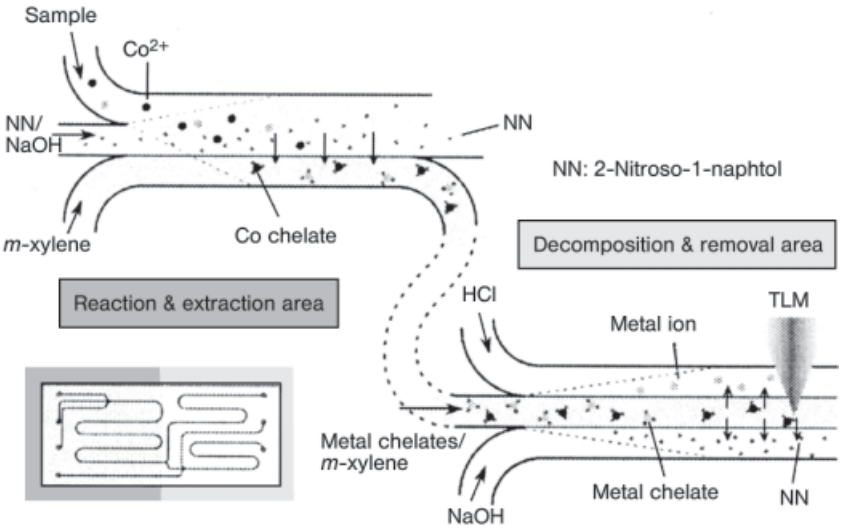

Figure 4.13 Schematic of the triple-feed continuous multi-phase chip reactor [28].

The chip is made from glass by photolithography and wet etching followed by thermal bonding.

Reactor type	Triple-feed continuous multi-phase chip reactor system	Micro-channel width; depth; length	Not given in [28]
Material	Glass		

4.1.3.11 **Reactor 14 [R 14]: Chip with Bi-/Tri-layer Flow Configuration Using Y-type Contact**

The polymer chips comprise two feed micro channels which are connected in a Y-type flow configuration to one elongated micro channel which is folded multiple times for compact design [29]. At the end of this channel a split into two channels is made, again by a Y-type flow configuration. The two-channel flow configuration serves for preparing water–oil parallel (bi-laminated) streams.

In another version, a three-channel flow configuration is created for continuous water–oil-water or oil–water–oil parallel streams [29].

The micro-channel chips were fabricated by an imprinting method. The templates for imprinting were made in silicon by conventional photolithography/dry etching [29]. The structural design was prepared on a glass plate serving as a photo mask by a photographic technique. A resist was coated on a silicon substrate, exposed and dry etched. This silicon master was then imprinted on a polymer substrate at elevated temperature. The structured polymer plate was sealed with a flat polymer plate by clamping.

Reactor type	Chip with bi/tri-layer flow configuration using Y-type contact	Outer dimensions	$30 \times 15 \times 1.7$ mm^3
Material	Polystyrene	Micro-channel width; depth; length	100 μm; 20 μm; 350 mm

4.1.3.12 **Reactor 15 [R 15]: Single-channel Chip Micro Reactor**

A single channel is fabricated in a wafer by etching using traditional silicon micromachining [30]. The catalyst is introduced using selective seeding, monolayer self-assembly and hydrothermal synthesis (see [P 47] for more details). The microstructured wafer is bonded to a glass cover. SU8-resist as sort of glue was spin coated on the glass and UV-exposed after joining to the wafer.

Reactor type	Single-channel chip micro reactor	Zeolite catalyst layer thickness	3 μm
Reaction flow-through chamber: width; depth; length	500 μm × 250 μm × 33 mm		

4.1.4
Chip–Tube Micro Reactors

This class of hybrid components comprises chip micro-reactor devices, as described in Section 4.1.3, connected to conventional tubing. This may be HPLC tubing which sometimes has as small internals as micro channels themselves. The main function of the tubing is to provide longer residence times. Sometimes, flow through the tube produces characteristic flow patterns such as in slug-flow tube reactors. Chip–tube micro reactors are typical examples of multi-scale architecture (assembly of components of hybrid origin).

4.1.4.1 **Reactor 16 [R 16]: Liquid-Liquid Micro Chip Distributor–Tube Reactor**

(a) This mixer–tube reactor configuration is composed of a liquid/liquid distributor and a tube [31]. By this means, capillary flow, alternating aqueous and organic slugs, can be created. A set of three distributors, of three-way type, was applied; one commercial and two specially manufactured ones made from the commercial (Figure 4.14). Two syringe pumps were used for liquid feed (acid mixture and organic compound). A collection bottle at the reactor output was used for quenching and separating the reaction mixture by diluting and coalescing the dispersed slug mixture to give two separate phases with a much smaller specific interface.

Reactor type	Liquid–liquid micro chip distributor–tube reactor	Tube diameters (PTFE)	150 µm; 178 µm
Mixing tee channel diameters in connector	150 µm; 500 µm; 800 µm for all (three) channels	Tube length (stainless steel)	Not reported
Tube material	Stainless steel; PTFE	Tube lengths (PTFE)	450 mm; 900 mm; 1350 mm
Tube diameters (stainless steel)	127 µm; 178 µm; 254 µm		

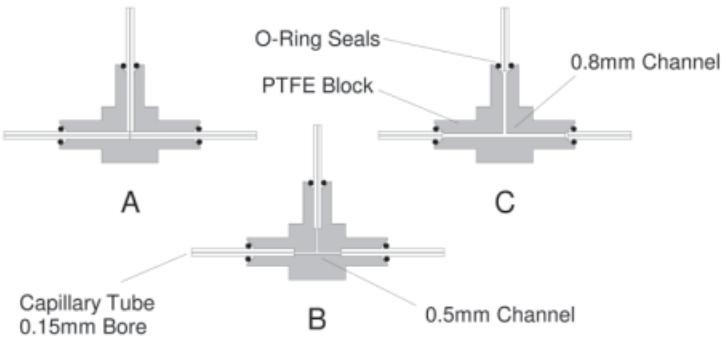

Figure 4.14 Schematic of liquid/liquid micro distributors used as contactors in the reaction system [31].

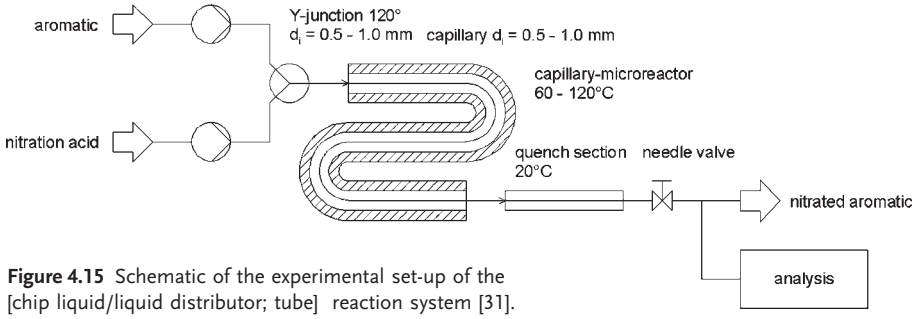

Figure 4.15 Schematic of the experimental set-up of the [chip liquid/liquid distributor; tube] reaction system [31].

(b) In another version of this reactor concept, a Y-piece was employed and attached to a PTFE capillary embedded in a thermostatically controlled jacket (Figure 4.15) [31]. The jacket maintains a uniform temperature by counter-flow with silicone oil. Owing to the high specific surface area of the capillary, it is assumed that isothermal processing is achieved in the reactor.

Reactor type	Liquid-liquid micro chip distributor–tube reactor	Tube diameter (PTFE)	150; 178 µm
Y-piece channel diameter	500–1000 µm	Tube length (PTFE)	1–8 m
Tube material	PTFE		

(c) In a further version of this reactor concept, a T-piece was employed and attached to both steel and PTFE capillaries embedded in a temperature bath [31]. The T-piece was drilled out, allowing a tight connection of all three capillaries. The organic and aqueous phases were fed through two incoming tubes into the T-piece, the merged phase leaving through a third tube. Flow rates were controlled by a single syringe driver loaded with 1 ml and 100 µl syringes. Isothermal behavior was assumed for the set-up.

Reactor type	Liquid/liquid micro chip distributor–tube reactor	Capillary tube length (reactor)	500–1800 mm
Capillary tube material	Stainless steel; PTFE	T-piece inner diameter	~1.59 mm, fits to capillary tubes
Capillary tube outer diameter	1.59 mm	Flow velocities	20–200 mm s^{-1}
Capillary tube inner diameter	127–254 µm	Flow ratio: acid : organic phase	10.5 : 1
Capillary tube length (feed)	300 mm		

4.1.4.5 **Reactor 17 [R 17]: Fork-like Chip Micro Mixer–Tube Reactor**

Central part of this reaction unit is a split–recombine chip micro mixer made of silicon based on a series of fork-like channel segments [32–36]. Standard silicon micro machining was applied to machine these segments into a silicon plate which was irreversibly joined to a silicon top plate by anodic bonding (Figure 4.16).

The fork-type chip mixer was used in connection with conventional tubes. PTFE tubing was applied in some studies [37, 38].

Reactor type	Fork-like chip micro mixer–tube reactor	Characteristic structure of the mixing stage	'G structure'
Brand name	accoMix (μRea-4 formerly)	Inner device volume	70 μl
Micro mixer material	Silicon	Outer device dimensions	$40 \times 25 \times 1.3$ mm^3
Inlet channel width	1000 μm	Tube material	PTFE
Number of parallel mixing channels to which the inlet flow is distributed	9	Tube diameter	Not reported
Number of mixing stages within one mixing channel	6; 3 in top plate, 3 in bottom plate	Tube length	Not reported
Channel width; depth of micro mixer	360 μm; 250 μm (triangular-shaped)		

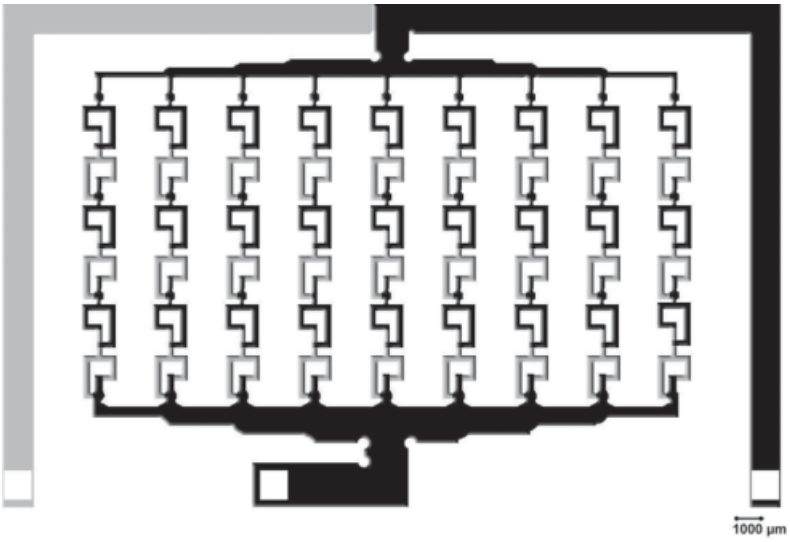

Figure 4.16 Schematic of fork-like chip micro mixer–tube reactor (Accoris GmbH).

4.1.5 3-D Microfab Reactor Devices

3-D microfabricated reactor devices are typically made by fabrication techniques other than stemming from microelectronics, e.g. by modern precision engineering techniques, laser ablation, wet-chemical steel etching or µEDM techniques. Besides having this origin only, these devices may also be of hybrid nature, containing parts made by the above-mentioned techniques and by microelectronic methods. Typical materials are metals, stainless steel, ceramics and polymers or, in the hybrid case, combinations of these materials.

3-D devices have complex requirements on assembly and, in particular, sealing. Integration of sensing is not as facile as for chip micro reactors. In turn, 3-D devices are robust and comprise the classical materials for chemical engineering apparatus.

4.1.5.1 **Reactor 18 [R 18]: Interdigital Micro Mixers**

Interdigital micro mixers (see [R 20]) are devices with an alternate feed micro-channel arrangement, connected to two feed reservoirs [39–42]. On introducing two liquids, a set of multi-laminated lamellae is created. This set may flow without any change in cross-section as long as needed for completion of mixing by diffusion. The corresponding micro mixer is then termed *rectangular interdigital mixer* (Figure 4.17). The multi-lamellae flow may be geometrically compressed by constantly reducing the micro-channel cross-section. By compressing the overall lamellae set, the individual lamella becomes thinner, speeding mixing by diffusion. The corresponding micro mixer is then termed a *triangular interdigital mixer*. When such geometric focusing is put at its extreme and a subsequent wider flow-through chamber (so-called focusing–expansion approach [43]) is added, secondary flow patterns rise to give eddies which speed up mixing. By this means, jet mixing of the multi-laminated incoming stream is established. The corresponding micro mixer is then termed a *slit-type interdigital mixer*, owing to the first such realized geometry in a stainless steel micro mixer.

The interdigital micro mixers are typically realized as 3-D microfab reactors having a micro structured inlay with the interdigital feed structure and the subsequent flow-through chamber in the top part of a housing [39, 41, 42]. The interdigital feed is realized by guiding multiple flows within overlapping micro channels in the counter-flow direction. The inlay is placed in a recess of the bottom housing part. A characteristic section of the flow-through chamber is the so-called slit, a shallow, but initially wide conduit which becomes much narrower in the direction of the flow (Figure 4.18). This slit, a section of an arc when given in 2-D projection, is connected to a tubing of small inner diameter which feds an outlet. Three such connectors of multiple origin (e.g. HPLC) are connected to the top part of the housing.

The interdigital feed can be fed in a counter-flow or co-flow orientation; the first principle is realized in metal/stainless steel or silicon/stainless steel devices [39, 41], the latter in glass chip devices [40, 44–46].

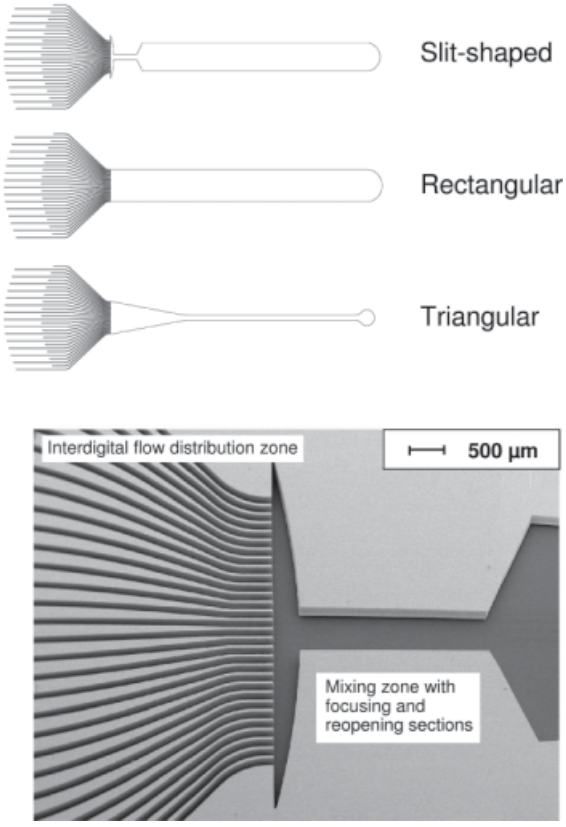

Figure 4.17 Schematic of the central part of interdigital micro mixers, the interdigital feed element and the flow-through chamber as mixing element. Different shapes of flow-through chambers allow one to perform micro mixing in different ways. Three different designs for interdigital 2-D micro mixers (top). SEM-image of the interdigital feed zone and part of the mxing chamber of the slit interdigital 2-D micro mixer [40].

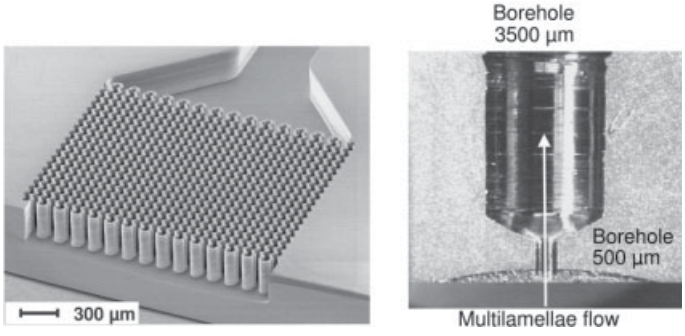

Figure 4.18 Left: interdigitated micro channels made by ASE (inlay for 3-D device). Right: cut through the top part of the housing of the slit interdigital 3-D micro mixer comprising the slit-type focusing zone and the subsequent small channel to the outlet [40, 41].

The inlay of the first sort of interdigital mixers is typically a metal part manufactured by the LIGA process, relying on synchrotron irradiation and electroforming [39, 41]. The slit is made by a die-sinking process, a variant of μEDM. The small bore attached to the slit is prepared by special drilling of the top housing part. Alternatively to LIGA, the inlay can be fabricated by ASE, μEDM and laser ablation. By this means, other materials can be used for the inlay such as stainless steel (including high-grade alloys such as Hastelloy), metals not consistent with LIGA (e.g. titanium), conductive ceramics, and polymers.

As a second sort of interdigital micro mixers, chip micro devices, based on thin microstructured plates, were developed [40, 44–46]. Here, the flow conduit has to be arranged in several plates to avoid cross-over of streams. Conduits in the plates serve for interconnection of streams where desired. Finally, all streams are directed to one plate comprising the interdigital feed structure (now in co-flow orientation) and the subsequent mixing chamber (Figure 4.19). The inlet and outlet feed is achieved directly via holes leading to the two feed reservoirs and the end of the mixing chamber, respectively.

This chip version is typically made in glass and has the great advantage that the flow can be directly visualized [40, 44–46]. Fabrication is achieved by photolithography and wet-chemical etching followed by thermal bonding of the plates covered with a thin layer of solder [47].

For the application referred to, the interdgital micro mixers were used on their own, without tubing attached, as reactors. Especially at low flow rates, the internal flow-through chamber acts as delay loop for providing a sufficient residence time.

Reactor type	Interdigital micro mixer	Triangular chamber: initial width; focused width; depth; focusing length; mixing length; focusing angle	3.25 mm; 500 μm; 150 μm; 8 mm; 19.4 mm; 20°
Mixer material	Metal/stainless steel; silicon/stainless steel; glass	Slit-type chamber: initial width; focused width; depth; focusing length; expansion width; expansion length; expansion angle	4.30 mm; 500 μm; 150 μm; 300 μm; 2.8 mm, 24 mm; 126.7°
Metal/silicon mixer feed channel width; depth	40 μm; 300 μm	Slit depth in steel housing	60 μm
Glass mixer feed channel width; depth	60 μm; 150 μm	Tubing attached to slit: diameter	500 μm
Type of flow-through chamber	Rectangular; triangular; slit-type	Device outer dimensions: diameter; height	20 mm; 16.5 mm
Rectangular chamber: width; depth; length	3250 μm; 150 μm; 27.4 mm		

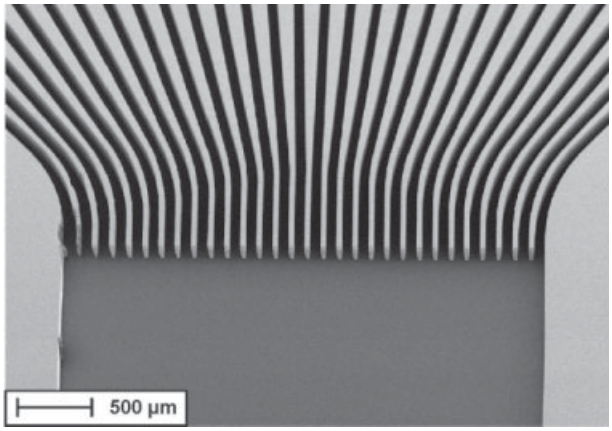

Figure 4.19 SEM of the feed part of a 2-D rectangular interdigital micro mixer [44].

4.1.6 3-D Microfab Mixer–Tube Reactors

3-D microfabricated micro mixers (see Section 4.1.5) may be connected to tubes for reasons of residence time prolongation, similar to chip–tube micro reactors (see Section 4.1.4). The tube may also have the function of creating distinct hydrodynamic features (see Section 4.1.4).

4.1.6.1 Reactor 19 [R 19]: Slit-Type Interdigital Micro Mixer–Tube Reactor

Interdigital micro mixers comprise feed channel arrays which lead to an alternating arrangement of feed streams generating multi-lamellae flows [39–42]. If processes have to be carried out with extended residence times (> 1 s) and/or at a temperature level different from the mixing step, tubes have to be attached to the interdigital micro mixers. Their internals comprise millimeter dimensions or below, if necessary.

One version of such a reactor concept is the combination of a slit-type interdigital metal/steel micro mixer (for a detailed description see [R 18]) with a conventional tube. In [37], PTFE tubing was applied (Figure 4.20).

Reactor type	Slit-type interdigial micro mixer–tube reactor	Mixer material	Stainless steel, nickel
		Tube material	PTFE
		Tube diameter	Not reported
Mixer channel: width, depth; slit width	40 µm; 300 µm; 60 µm	Tube length	Up to 150 cm

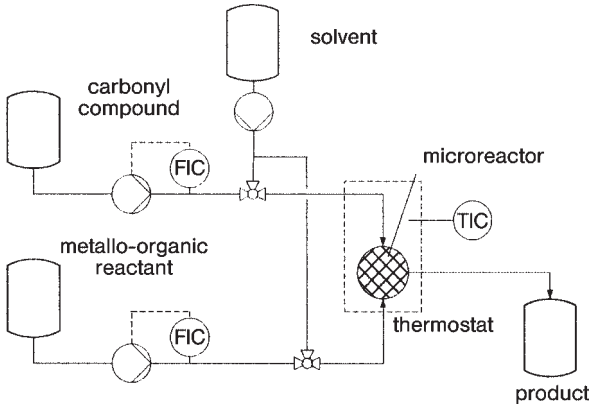

Figure 4.20 Schematic of laboratory-scale reaction system with a slit-type interdigital micro mixer as central element, used at Merck site [134].

4.1.6.2 Reactor 20 [R 20]: Triangular Interdigital Micro Mixer–Tube Reactor

One version of this reactor concept is the combination of the triangular interdigital metal/steel micro mixer (for a detailed description, see [R 18]) with conventional PTFE tubing (Figure 4.21) [46, 48].

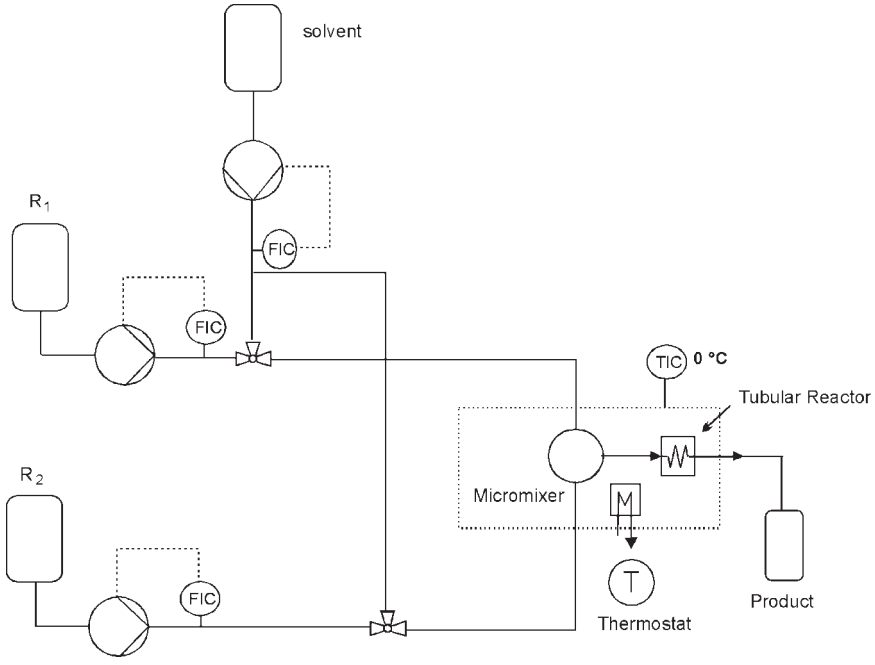

Figure 4.21 Flow sheet of a laboratory triangular interdigital micro mixer–tube reactor set-up, used for an industrial application, the so-called Clariant process [48].

Reactor type	Triangular interdigital micro mixer–tube reactor	Mixer material	Specialty glass (Foturan™)
		Tube material	PTFE
		Tube diameter	2 mm
Mixer channel: width, depth; slit width	60 μm; 150 μm	Tube length	6 m

4.1.6.3 **Reactor 21 [R 21]: Caterpillar Mini Mixer–Tube Reactor**

A caterpillar steel mini mixer is connected to conventional tubing, either stainless steel or polymeric. The caterpillar mixer acts by distributive mixing using the split–recombine approach which performs multiple splitting and recombination of liquid compartments [41, 42, 48, 49]. A ramp-like micro structure splits the incoming flow into two parts which are lifted up and down. Thereafter, the two new streams are reshaped separately in such a way that the two new cross-sections combined restore the original one. Then, the streams are recombined, again by the lifting up and down procedure using ramps. This procedure is repeated multiple times, yielding a multi-lamellae flow configuration – in the ideal case.

For a first-generation device, real-case deviations from this ideal pattern were found when experimentally visualizing the flow [50]. Splitting did not give identical compartments so that more stages may actually be needed than according to ideal-case simulations. At large volume flows, even no lamellae at all are formed, but rather twisted and intersegmented patterns. These induce secondary flows and turbulences which speed up mixing (however, not in the way the in which mixer actually is intended to do). For this reason, a second-generation device was made containing a splitting plate in the middle of the mixer (Figure 4.22).

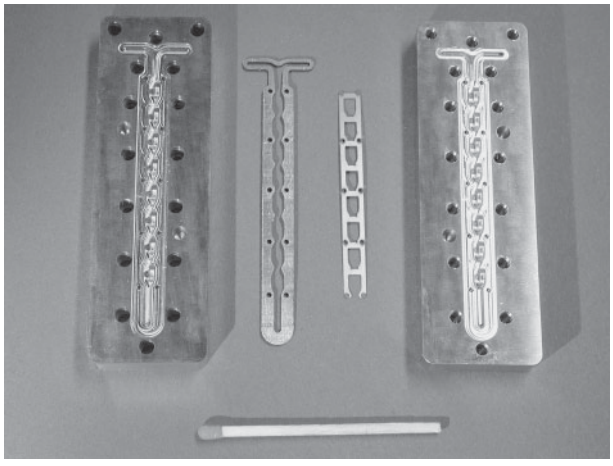

Figure 4.22 Second-generation caterpillar mini mixer with splitting plate and improved microstructure geometry [50].

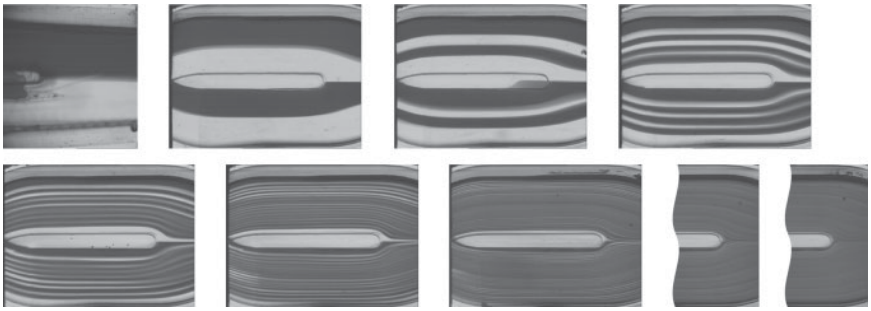

Figure 4.23 Near-ideal multi-lamination flow patterns in the second-generation caterpillar mini mixer as a result of introducing a splitting plate and improving micro structure geometry [50].

This plate cuts the flow into pieces which are better defined than the poorly defined ones obtained by the first-generation caterpillar mini mixer. In addition, the micro structure geometry was improved by means of simulation. As a result, near-ideal multi-lamination flow patterns were yielded (Figure 4.23), which showed excellent correspondence with simulation [50].

All types of split–recombine mixers generally have high volume flows (e.g. $100\,l\,h^{-1}$ and more at moderate pressure drops) at favorable pressure drops (not exceeding 5 bar) as their internal micro structures can be held large [41, 42, 48, 49].

Reactor type	Caterpillar mini mixer–tube reactor, 1st generation	Micro structure in one plate: initial depth; maximum depth	600 μm; 850 μm
Mini mixer material	Stainless steel	Mini mixer stage: length	2400 μm
Number of plates needed to form mini mixer channel	2	Number of mixing stages	8
Mini mixer channel: initial width; maximum width	1200 μm; 2400 μm	Total length of caterpillar mini mixer	19.2 mm
Mini mixer channel (both plates): initial depth; maximum depth	1200 μm; 1700 μm	Device outer dimensions	$50 \times 50 \times 10\ mm^3$

4.1.6.4 **Reactor 22 [R 22]: [Separation-layer Micro Mixer; Tube] – Reaction System**

Separation layer mixers use either a miscible or non-miscible layer between the reacting solutions, in the first case most often identical with the solvent used [48]. By this measure, mixing is 'postponed' to a further stage of process equipment. Accordingly, reactants are only fed to the reaction device, but in a defined, e.g. multi-lamination-pattern like, fluid-compartment architecture. A separation layer technique inevitably demands micro mixers, as it is only feasible in a laminar flow regime, otherwise turbulent convective flow will result in plugging close to the entrance of the mixer chamber.

Both concentric and stacked fluid layer arrangements, corresponding to different versions of separation mixers, were developed, allowing either a drop- or stream-like injection of liquids in a reaction tube attached to the micro mixer [48].

Concentric separation layer micro mixer

This separation layer mixer is constructed as an assembly of stacked stainless-steel plates having three tubes [48]. These tubes are placed into each other and are inserted into a fit. The plates contain three feeding lines for reactants 1 and 2 as well as the separating fluid.

The stacked steel plates were manufactured by milling [48]. The PTFE tubes were home-made by means of turning and milling.

Reactor type	Concentric separation-layer micro mixer–tube reactor	Tube outer diameters	2.0 mm; 3.0 mm; 4.0 mm
Material	PEEK (tubes); stainless steel (housing)	Tube lengths	28.50 mm; 21.75 mm; 15.00 mm
Tube inner diameters	1.5 mm; 2.5 mm; 3.4 mm	Device outer dimensions	$41 \times 41 \times 24$ mm^3

Stacked separation layer micro mixer

This separation layer mixer was fabricated as an assembly of stacked glass plates which were irreversibly bonded by a thermal process [48]. An interdigital feeding structure generates alternately arranged lamellae of the three liquids. The mixing chamber is rectangular from the feed inlet until close to the outlet and becomes then tapered. In a later version, the same design concept was transferred into stainless steel. The steel device version was made by thin-wire μEDM.

Reactor type		Number of lamellae created	9
Material		Mixing chamber: width; depth; length	2.15 mm 2 mm 5 mm
Micro channel: width; depth; total length; Straight (i.e. uncurved) length	150 μm; 2 mm; 4 mm; 1 mm	Outer dimensions: length; width; depth	$58 \times 26 \times 8$ mm^3
Fin width	100 μm		

4.1.6.5 Reactor 23 [R 23]: [Impinging-jet Micro Mixer; Tube] – Reaction System

Impinging-jet micro mixers rely on a similar fluid guidance as given for impinging jet contactors for gas/liquid processes, namely on collision of two liquid streams [48]. Different from the latter, they generate a liquid jet rather than an extended liquid film. Since the collision of the streams can be performed in either a gaseous or a non-miscible medium, wall contact can be strongly diminished, thereby strongly reducing fouling.

The impinging-jet micro mixers are constructed as a cylindrical block comprising two feed tubes which become smaller towards the outlet [48]. Accordingly, the main characteristics of these mixers are the diameter of the outlet bore, the interspaces between the bores and the angle defined by the orientation of bores (relative to the normal). For one experimental study [48], nine impinging jet micro mixers were made which differ in these specifications.

Reactor type	Impinging-jet micro mixer–tube reactor	Bore angles	45°; 60°; 90°
Material	Stainless steel	Interspaces between bores	2 mm; 3 mm; 4 mm
Bore diameters	500 μm; 1000 μm		

4.1.7 3-D Microfab Micro Mixer–Micro Heat Exchangers

3-D microfabricated micro mixers (see Section 4.1.5) may be connected to 3-D microfabricated micro heat exchangers and also other combinations of micro devices performing unit operations and reactions are possible. These are combinations of components, rather than presenting total system approaches. Flexibility of component connection is generally higher compared with modifying a system, but integration and in some sense functionality are tentatively lower. Compared with the multi-scale micro mixer–tube reactor concept (see Section 4.1.6), combining micro components represents more a mono-scale solution.

4.1.7.1 Reactor 24 [R 24]: System with Series of Micro Mixers–Cross-Flow Reactor Modules

Various micro mixers and reaction modules with heat transfer function were connected (Figure 4.24). Details on the micro mixers were not given; the reaction modules comprise cross-flow configurations in a micro-channel platelet architecture [51]. The micro mixers are also connected in a serial manner to allow sequential mixing of up to three reactant solutions. The heat exchange modules are connected in series, by using commercial flange technology.

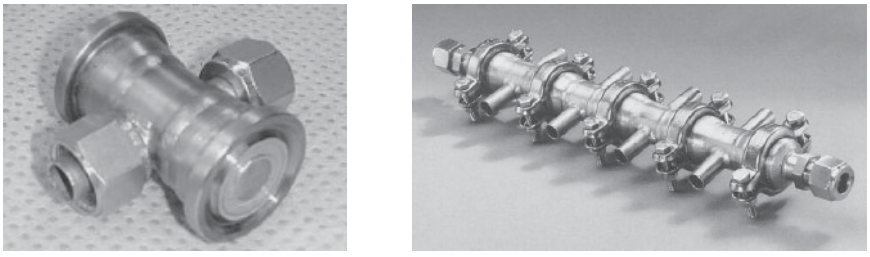

Figure 4.24 Modular micro-reactor system. Left: single reactor module with (length 60 mm). Right: mounted system of four single reactors (overall length 24 cm) [51].

Each of the reactor modules is fed by a heat transfer liquid, either water or a heat transfer fluid. The inlet temperatures of the reactor modules are set by these liquids; the outlet temperatures may be higher owing to release of reaction heat. By varying the inlet temperatures per module, a temperature profile along the reaction passage is created. Thereby, a series of operations, ignition/reaction/quenching is initiated, with the two inner modules performing a reaction. The cross-flow heat exchangers have so-called highly asymmetric passages, i.e. comprise much more (e.g. by an order of magnitude) micro channels on the heat transfer flow side than on the reaction side.

Reactor type	System with series of micro mixers–cross-flow reactor moldules	Number of reaction channels	169
Details on micro mixer	Not given in [51]	Number of heat transfer channels	1960
Reaction platelet material	Hastelloy C	Flange connection	Sandvik™ type L
Reaction channel width; depth; length	300 μm; 150 μm; 60 mm	Heat transfer fluid	Marlotherm™ SH

4.1.8
2-D Integrated Total Systems with Micro Mixing and Micro Heat Exchange Functions

Different from sole combinations of micro devices, this refers to a total system with many functional elements and flow-distribution and, recollecting zones, typically composed of 2-D plate-type architecture. Each of these plates usually has a separate function, comprising unit operations and reaction. Frequently, micro mixing and micro heat exchange functions and corresponding elements are employed. Often, the system can be composed of different elements resulting in different process flow combinations. Such an approach may be termed a construction kit.

Compared with the multi-scale micro mixer–tube concept (see Section 4.1.6), the total-system approach is a true mono-scale solution, and may be even termed monolithic. Integration of sensing and controlling is facile owing to the high order and repetition of construction units (plates).

4.1.8.1 **Reactor 25 [R 25]: CPC Micro Reaction System CYTOS™**

This is a commercial system comprising mixing and reaction/heat exchange functions [52] (see also [53, 54]). The system is constructed from various modules, typically caving stacked-plate units (Figure 4.25). The modules can be easily connected by a special interface. The plates are mounted together by metallic bonding. Numerous parallel channels fulfil functions of dividing reactants into substreams, performing reaction, maintaining the reaction temperature and collecting product substreams [55] The system is equipped with pumps and other fluidic peripherals so that it can be considered as a whole plant.

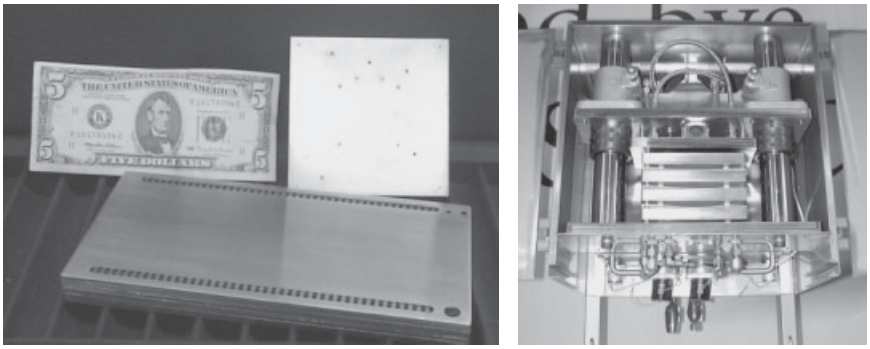

Figure 4.25 Specialty plates for laboratory and pilot plant micro reactor modules of modified CYTOS™ systems (left). Standard off-the-shelf CYTOS™ system (right) [55].

Details on microfabrication and on the internals in the stacked plates have not been substantially disclosed so far. Accordingly, no information on the mechanisms of mass and heat transfer was reported. In one version, geometrically focused multi-lamination is used for mixing liquid streams [55].

4.1.8.2 Reactor 26 [R 26]: Chip Micro Reaction System with Parallel Mixer–Reaction Channels

A chip-type micro reactor array comprises parallel mixer units composed of inverse mixing tees, each followed by a micro channel that it is surrounded by heat exchange micro channels (so called 'channel-by-channel' approach similar to the 'tube-in-tube' concept). Such an integrated device was developed as a stack of microstructured plates made of a special glass, termed Foturan™ (Figure 4.26). The integrated device was attached to PTFE tubes of various lengths.

Figure 4.26 Chip reaction system with 20 parallel mixer–reaction channels, made of glass [with courtesy from mgt mikroglass AG, Germany].

Reactor type	Chip micro reaction system with parallel mixer–reaction channels	Plate thicknesses	2 × 0.2 mm; 5 × 0.7 mm; 1 × 1 mm
System material	Specialty glass (Foturan™)	System outer dimensions	90 × 50 × 4.9 mm^3
Mixer micro channels: width; depth	350 µm; 200 µm	Total number of plates	8
Reaction micro channels: width; depth; length	700 µm; 200 µm; 31.15 mm		

4.1.8.3 Reactor 27 [R 27]: [Bi-layer Contactor; High-aspect-ratio Heat Exchanger] – Reaction System

This micro reaction system is constructed as a stack of five machined plates [56] (see also [57–60] and further [61–63]). Between the first two plates, four parallel reaction platelets are laid. The first two plates serve for feeding one reactant each. Both feed streams are distributed to the four platelets which comprise an array of eight micro structured channels on both sides. First, the two streams, typically immiscible liquids, are contacted in a bi-layer configuration. This bi-layer may, under certain flow conditions, decompose to a dispersion, further enlarging the specific interface for mass transfer. Attached to the micro contactor is a micro heat exchanger formed by a reaction channel of large aspect ratio surrounded by cooling liquid channels of similar aspect ratio. The latter channels are structured on the back side of the platelet. Owing to the channels' large aspect ratio and the thinness of the platelet, the channels overlap, although they are not cross-linked. After passage to the heat transfer channel, the single flows are collected from the eight channels in an inverse bifurcation unit. A schematic of the bi-layer configuration platelet comprising reaction area, heat exchange area and collecting channels is shown in (Figure 4.27).

From there, the reaction flow either leaves the total system to be quenched or, more commonly, enters the next plate which contains a delay loop, a spiral channel [56]. Leaving that plate, the streams flow to the last structured plate containing a bifurcation–mini mixer unit. The streams are distributed in multiple streams and contacted with a likewise split water stream. This leads to fast dilution, e.g., of a concentrated sulfuric acid stream, and rapidly cools the reaction stream. The reaction is quenched more or less initially. The final plate is unstructured and acts as a cover plate with holes for liquid withdrawal (Figure 4.28).

The outer shape of the plates was made by thin-wire erosion [56]. Annealing processes served for improving flatness and eliminating stress. Thereafter, the microchannels were introduced by die sinking. A special variant was used here, based on rotating disk electrodes, enabling high-aspect-ratio micro structuring by facilitating withdrawal of material [60]. In a later development, a normal die sinking process was employed [56]. Tungsten carbide electrodes, having a negative shape of the microstructure to be manufactured, were made by wire erosion using a brass core wire-

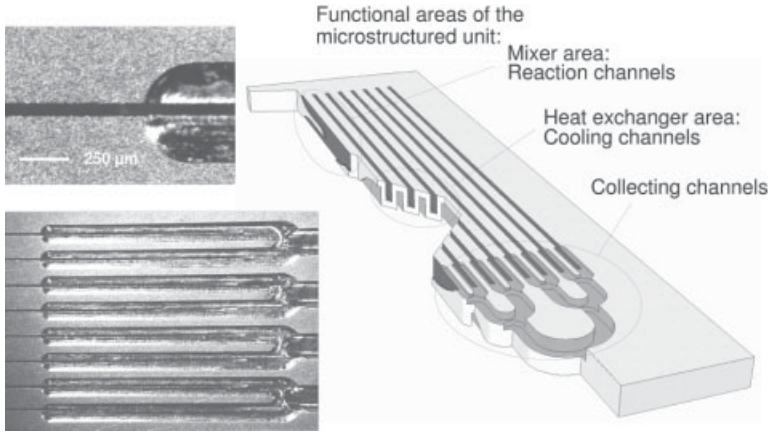

Figure 4.27 Schematic of the bi-layer contacting reaction platelet and photographs of details of the transfer region micro channel-collecting channel (left top) and of the array of the collecting channels (left bottom) [56].

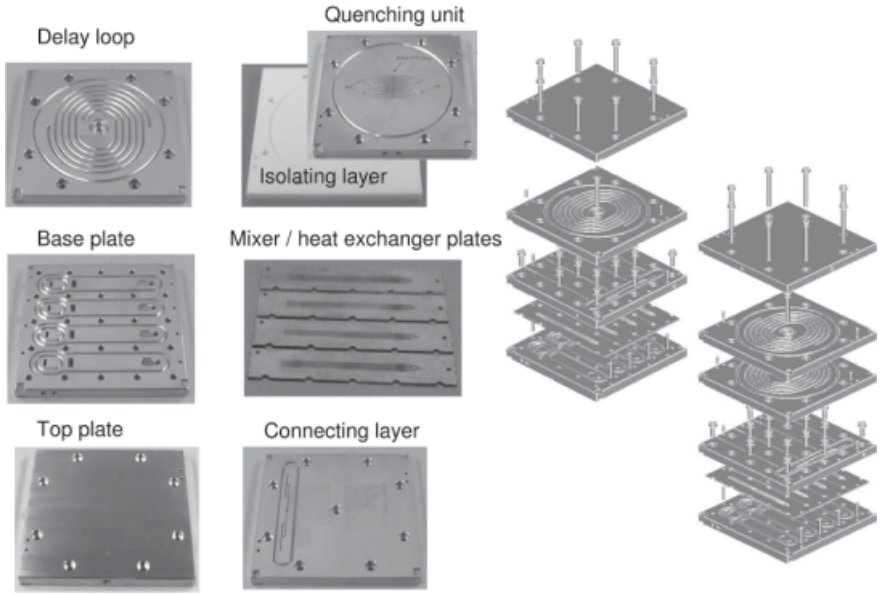

Figure 4.28 Overview of the five machined stainless steel plates. Two possible arrangements of all these system parts are given as well; many other are possible due to a flexible interconnection concept [56].

electrode 150 µm in diameter and coated with zinc. Using a special multi-clamping device, as many as five roughing and five finishing electrodes were employed in a single fabrication run without the need for any intervention by an operator. After electrode manufacturing, transfer to the die sinking machine was effected using the same clamping mechanism. The feeding plates, the delay-loop plate and the mini-mixer plate were made by conventional machining, drilling and milling.

Reactor type	[Bi-layer contactor; high-aspect-ratio heat exchanger]–reaction system	Residence times at 750 ml h^{-1}; 1 ml h^{-1} for different combinations of plates	1–10 s; 14 min – 2 h
Plate and platelet material	Stainless steel, grade 1.4539	Total number of plates; total number of platelets	5; 4
Sealing	Polymer O-rings	Reaction platelet thickness	1.2 mm
Reaction micro channel width; depth; length	70 μm; 900 μm; 61.4 mm	Total number of reaction channels; number on platelet	32; 8
Heat transfer micro channel width; depth; length	70 μm; 900 μm; 61.4 mm	Volume of total number of reaction channels	0.12 ml
Material thickness between reaction and heat transfer channels	100 μm	Volume of system without, with one and with two delay loops	< 1 ml; < 3 ml; < 5 ml
Volume flow at 1 bar pressure drop	~3 l h^{-1} (depending on plate combination)		

4.1.8.4 **Reactor 28 [R 28]: Multi-channel Integrated Mixer-Heat Exchanger**

This concept relies on integrated mixing and heat exchange functions, i.e. when mixing is initiated, cooling of the reaction mixture can be performed directly [64]. Both reactant streams are split into a multitude of reaction channels. One set of redirected channels merges with another set of straight channels so that one channel of one type joins with another without having contact with a third channel. After a certain reaction passage, the parallel channels are combined to one channel. Thin liquid layers are achieved by having reaction and cooling micro channels of small depth at large width. The former have typically larger hydraulic diameters than the latter. The separating wall is kept thin to reduce resistance by heat conduction.

Reactor type	Multi-channel integrated mixer–heat exchanger	Hydraulic diameter of cooling channel	900 μm
Reactor material	Stainless steel	Surface-to-volume ratio of reaction micro channels	10 000 m^2 m^{-3}
Reaction micro channel width; depth; length	100 μm; 5000 μm	Heat transfer coefficient (cooling liquid not moving)	2000 W m^2 K^{-1}
Hydraulic diameter of reaction channel	200 μm	Thickness of wall separating reaction and cooling channels	1 mm
Cooling micro channel width; depth; length	500 μm; 5000 μm		

4.1.9
Electrochemical Micro Reactors

These devices have a special function which allows them to perform electro-organic synthesis. Typically, they contain electrode structures to generate electrons as tunable 'reactants'. Often, these electrodes are constructed as plate-type structures, sometimes also being the construction material for the channels themselves.

4.1.9.1 Reactor 29 [R 29]: Multi-sectioned Electrochemical Micro Reactor

The multi-sectioned electrochemical micro reactor comprises a multitude of alternating conducting and insulating layers [65]. Each conducting section is combined with independent current generators (Figure 4.29). This ensures that each section receives the planned average current density. In order to reach optimum reactor performance the layers have to be made sufficiently thin (micro-scale approach) and their number sufficiently large (parallel operation).

This new design is sought to overcome the limits of conventional porous fixed-bed reactors using an electrode phase flowing through the pores [65]. The latter systems suffer from the low conductivity of the electrolyte phase. This generates electrical resistance and leads to accumulation of the electrical current in certain reactor zones and hence results in a spatially inhomogeneous reaction. This means poor exploitation of the catalyst and possible reductions in selectivity.

Accordingly, the multi-sectioned reactor has advantages in terms of process refinement in the space domain by appropriate positioning of micro fabricated insulating and conducting surfaces [65]. However, it is said also to have advantages for process control in the time domain. By rapid and precise time-varying control of the electrical current in the microsecond range, steady-state and pulse operation can be improved. Concerning the latter, a concept of raster-pulse electrolysis was proposed [65]. Here, a steady-state baseline distribution of the current density, spatially uniform or non-uniform, is superimposed by a cleaning pulse. This pulse is applied periodically to each of the electrode sections in a programmed manner. By this means, both kinetics and catalyst poisoning can be taken into account.

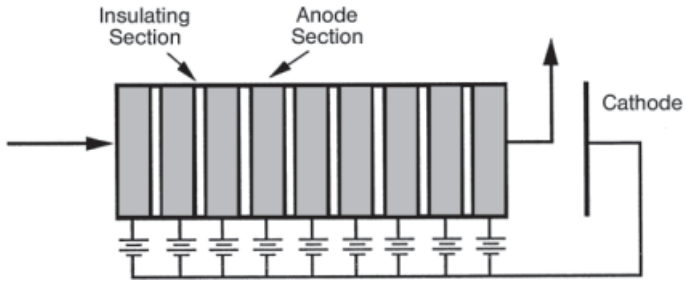

Figure 4.29 Electrochemical reactor with alternating conducting and insolating porous sections each connected to separate power supplies [65].

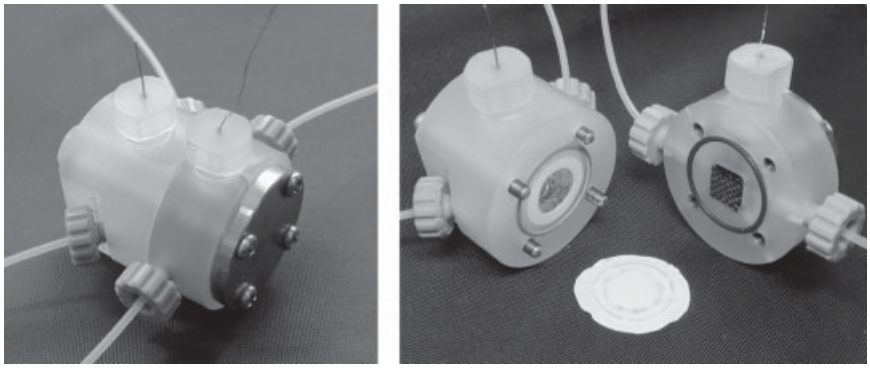

Figure 4.30 Electrochemical micro reactor, a diaphragm micro flow cell, applied to perform the 'cation flow' method. Assembled device (left). Disassembled device showing the two compartments of the cell within the housings and the diaphragm (right) [67].

4.1.9.2 **Reactor 30 [R 30]: Electrochemical Diaphragm Micro Flow Cell**

This type of electrochemical reactor is composed of two bodies by mechanical manufacturing [66, 67]. It contains a two-compartment cell with an anodic and cathodic chamber separated by a membrane as diaphragm. The anodic chamber is equipped with a carbon felt anode made of carbon fibers; a platinum wire is inserted in the cathodic chamber (Figure 4.30).

Reactor type	Electrochemical micro flow cell	Diaphragm material	PTFE
Reactor body materials	Diflone™; stainless steel	Carbon fibers: diameter	10 μm

4.1.9.3 **Reactor 31 [R 31]: Electrochemical Capillary Micro Flow Reactor**

This capillary micro flow reactor (Figure 4.31) is used for investigating spatially one-dimensional effects induced by electric fields which propagate parallel to the flow direction [68]. A rectangular cuvette with a rectangular capillary channel is fixed on both sides by filling chambers. These are attached by packing to larger electrode cells containing planar (plate) electrodes. The packing encompasses a microporous membrane. The whole system is tightened by screws and placed in a thermostatically controlled water bath. The cuvette is filled with a solution through openings in the filling chambers. The electrode cells are filled with the same solution. Thereby, electric current flows from electrode to electrode. The microporous membrane serves to separate the products of the electrode reactions from the reaction products in the capillary and thus to prevent intermixing.

By external stimulus at the plate electrode, migration of the ions in the solvent is induced, which changes the spatial concentration and so the local course of reactions [68]. By this means, weak electrical fields change the propagation velocity of the reaction zone through the capillary; strong electrical fields ('supercritical') further affect the global feature of the reaction in the capillary.

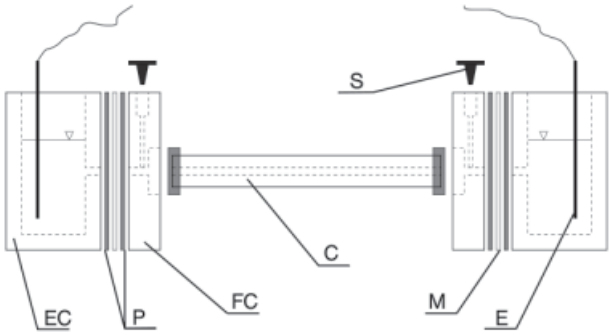

Figure 4.31 Electrochemical capillary micro flow reactor.
EC, electrode cells; FC, filling chambers; SP, silicon packings; C, rectangular capillary; M, microporous PTFE membranes; E, platinum planar electrodes; S, stoppers [68].

Reactor type	Electrochemical capillary micro flow reactor	Electrode dimensions	$30 \times 30 \times 3$ mm^3
Cuvette material	Optically clean glass	Electrode cell material	Organic glass
Cuvette outer dimensions	$9 \times 9 \times 84$ mm^3	Electrode cell dimensions	$45 \times 85 \times 60$ mm^3
Capillary material	Optically clean glass	Electrode cell volume	15 ml
Capillary cross-sections	1×1 mm; 0.7×0.7 mm; 0.5×0.5 mm;	Microporous membrane material	Teflon™
Filling chamber material	Organic glass	Packing material	Silicon

4.1.9.4 **Reactor 32 [R 32]: Electrochemical Sheet Micro Flow Reactor**

This sheet micro flow reactor (Figure 4.32) was used for investigating spatially two-dimensional effects in reaction media using agar gel induced by electric fields [68]. This device utilizes an adapted Petri dish which comprises a rectangular channel

Reactor type	Electrochemical sheet micro flow reactor	Reaction medium layer depth	600 µm
Polymer packing material	Lukopren™	Excess mixture depth	14 mm
Rectangular channel cross-section	4.5×2 mm^2	Center hole diameter	300 µm
Shaped seal material	Optically clean glass	Wire electrode material	Plantinum

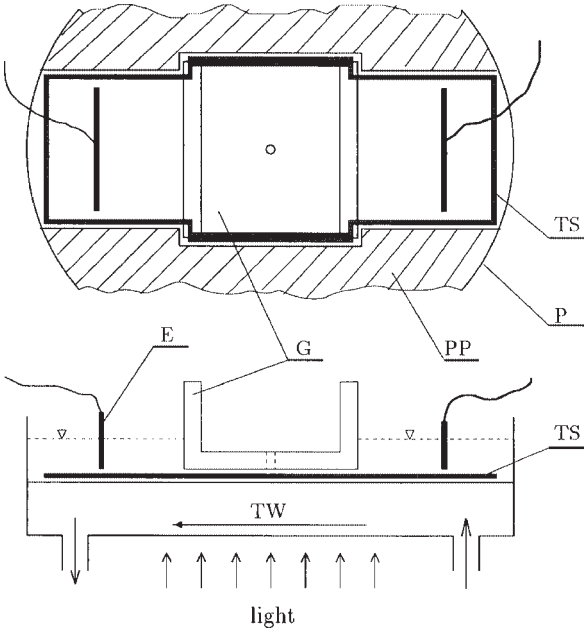

Figure 4.32 Electrochemical sheet micro flow reactor.
P, Petri dish; TS, PTFE supports; PP, polymerized packing (Lukopren™); G, glass seal, E, platinum planar electrodes; TW, thermostated water [68].

after filling with polymerized packing. A specially shaped seal is placed on supports to create a thin layer of the reaction medium. The excess which is removed by this seal yields a layer in which the plate electrodes are inserted. In a small hole in the center of the glass seal a wire electrode is placed.

By external stimulus at the wire electrode, a reaction is initiated which propagates from the center in all directions evenly and so forms an expanding ring [68].

4.1.9.5 **Reactor 33 [R 33]: Electrochemical Plate-to-Plate Micro Flow Reactor**

This electrochemical micro reactor concept was based on the utilization of micro structuring techniques for electrochemical thin-layer cell technology, so far being applied in analytics [69]. The main component of the stacked-platelet-type micro reactor is a micro channel layer embedded between a working and a counter-electrode, referred to as a plate-to-plate configuration. Furthermore, an integrated cooling element serves for control of reaction temperature (Figure 4.33).

The micro structured platelets, hold in a non-conducting housing, were realized by etching of metal foils and laser cutting techniques [69]. Owing to the small Nernst diffusion layer thickness, fast mass transfer between the electrodes is achievable. The electrode surface area normalized by cell volume amounts to 40 000 $m^2\ m^{-3}$. This value clearly exceeds the specific surface areas of conventional mono- and bipolar cells of 10–100 $m^2\ m^{-3}$.

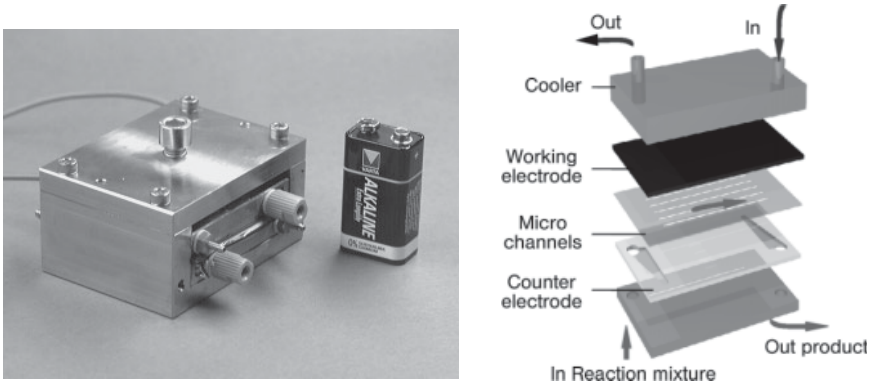

Figure 4.33 Electrochemical micro reactor with integrated electrode cooler. Left: overall view. Right: schematic of dismantled reactor [69].

Reactor type	Electrochemical plate-to-plate micro flow reactor	Reactor volume	35 µl
Micro channel width; depth; length	800 µm; 25 µm; 64 mm	Surface-to-volume ratio	400 cm^{-1}
Micro channel surface area	51.2 mm^2	Typical volume flow; Re number; pressure drop	6 ml h^{-1}; 0.2; 1.1 bar
Micro channel volume	1.3 µl	Typical residence time	21 s
Number of micro channels	27	Nernst diffusion layer	25 10^{-4} cm

4.1.9.6 **Reactor 34 [R 34]: Ceramic Micro Reactor with Interdigitated Electrodes**

This micro reactor consists of five ceramic layers [70, 71]. The top layer contains two bores for fluid feed and withdrawal. The second layer contains the flow distribution structures. The third comprises a micro channel array. The fourth carries the above-mentioned electrode structures. The last layer is an unstructured plate (Figure 4.34).

The ceramic micro reactor was fabricated in a three-step procedure, relying on screen printing, sintering and curing. Platinum interdigitated band electrodes were screen printed using a semi-automatic screen printer on a low-temperature co-fired ceramic soft tape [70, 71]. For gap widths exceeding 250 µm, the interdigital geometry was screen printed on the substrate via a patterned mask; direct writing with a laser beam on a printed platinum layer was applied when generating smaller gaps down to 30 µm. A dielectric layer was spread over the two connecting pads.

The micro channels were prepared with a cutter in a ceramic tape [70, 71]. Sealings served to ensure liquid tightness. Each end of the stack of five ceramic layers was clamped between two blocks, allowing a reversible interconnection.

Reactor type	Ceramic reactor with interdigitated electrodes	Number of electrodes	20 anodes + 20 cathodes
Ceramic tape material	Aluminum borosilicate and polymeric binders	Number of micro channels	7
Electrode material	Platinum	Micro channel width; depth; length	1000 μm; 254 μm; 50 mm
Anode–cathode gap	500 μm	Inlet and outlet hole diameter	2 mm
Pad width; length	5 mm; 80 mm	Seal material	PDMS
Working area	15 cm^2	Frame material	Polycarbonate

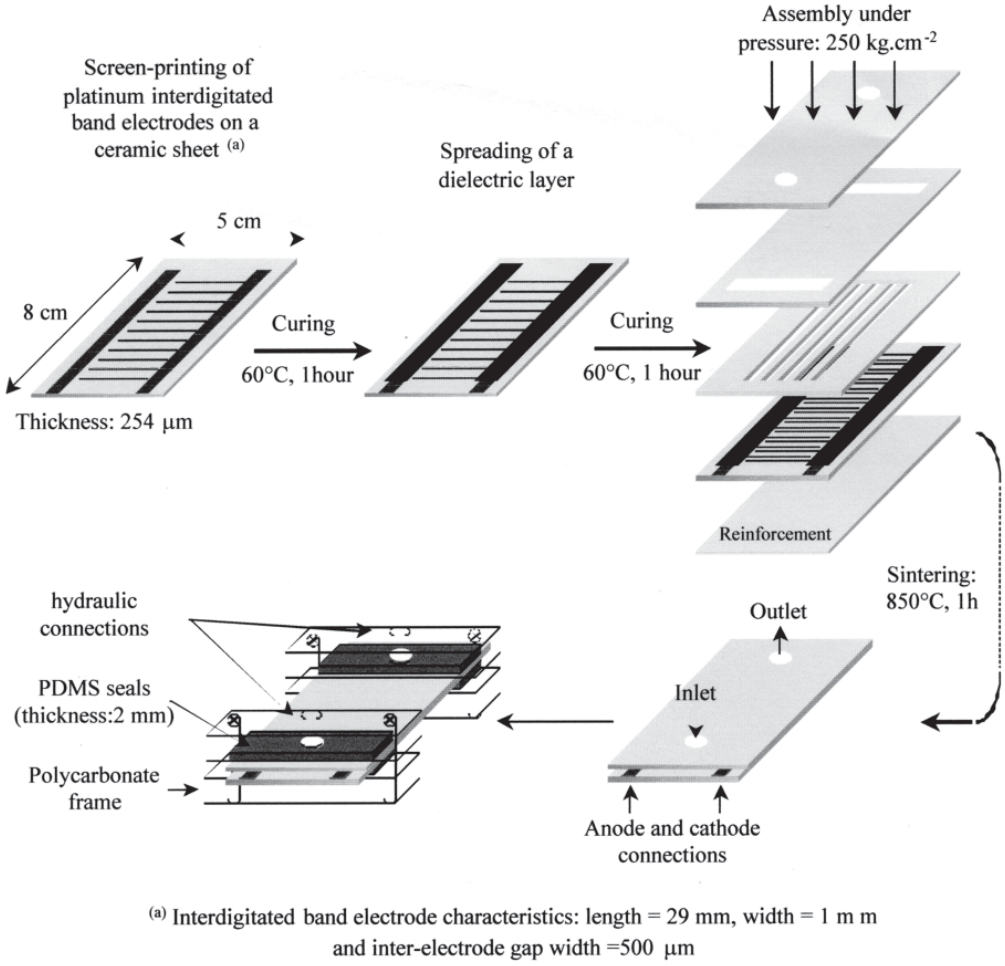

Figure 4.34 Schematic of the assembly for the ceramic micro reactor with interdigitated electrodes [70].

4.1.10
Photochemical Micro Reactors

These devices have special function, namely to irradiate the liquid phase with light to induce a photoreaction or photoinduced reaction. Hence the characteristic feature is a transparent section within the reactor, often in the visible or commonly in the UV spectral region. The devices may have integrated photo energy sources or on-line analysis units. Otherwise, this is performed by external instruments.

Reaction 35 [R 35]: Photochemical Serpentine Chip Micro Reactor
This chip micro reactor was designed to have transparent reaction sections, to provide a large specific surface area of the flowing liquid, and to minimize fouling by crystallization of insoluble photoproducts [72–74].

(a) A first-generation micro device contained as main element a serpentine flow path, creating large surfaces at thin liquid layers [72–74]. Such a micro structured plate was covered by a transparent plate. One inlet and one outlet were used for solution feed and withdrawal.

A disadvantage of the first-generation device was that reaction and detection units were separated by HPLC tubing, which caused delay in analysis [72–74].

The device was realized by deep reactive ion etching (DRIE) using the SU-8™ technique, producing vertical side walls [72–74]. This fabrication route was chosen to avoid crystallization, which is known to occur at sharp channel edges. Using DRIE smooth, curved corners can be realized, unlike by conventional silicon wet etching.

Reactor type	Photochemical serpentine chip micro reactor, 1st generation	Reaction flow-through chamber: width; depth	500 μm; 50 μm
Channel material	Silicon	Device outer dimensions	20×25 mm^2
Cover plate material	Pyrex™	On-line analysis	Delayed

(b) A second-generation device had integrated reaction and detection units and, in addition, allowed light of shorter wavelength (down to 254 nm) to pass [72–74]. For this purpose, part of the reactor has to be transparent from the top to the bottom. A sandwich structure of a silicon wafer encased between two quartz wafers fulfilled this criterion. The fabrication was as described above, but using a special thermal bonding technique with special bonding material in addition.

As the second-generation device contains integrated reaction and detection units, virtually real-time analysis could be achieved (compare to the delay in analysis for the first generation device described above) [72–74].

For both types of micro devices, a stainless steel frame was used as holder and Viton gaskets were applied for sealing [72–74]. A clear PMMA cover plate was also used and served for compression. This cover plate provided housing for a mini UV lamp used for irradiation. The detection unit was packaged in a similar fashion. Optical fibers were also integrated.

Reactor type	Photochemical serpentine chip micro reactor, 2nd generation	Reaction flow-through chamber: width; depth	500 μm; 500 μm
Channel material	Silicon	Device outer dimensions	20 × 20 mm^2
Cover plate material	Pyrex™	On-line analysis	Not delayed

4.1.11
Complete Parallel-synthesis Apparatus

These are total systems or even plants made for parallel automated organic synthesis, typically in the liquid phase. In this section, no commercial devices (typically not relying on micro flow processing) are considered, but rather only specialty apparatus developed in the framework of chemical micro processing.

Whereas commercial systems usually employ stirred mini vessels, laboratory-developed apparatus may be operated in flow-through mode. For mini-vessels (vials, wells), the titer plate format is typical and widely accepted.

Reactor 36 [R 36]: Solid-phase Synthesis–Pneumatic Agitation–8-Reactor System
The design of a novel solid-phase parallel reaction system with 96 reactors in standard micro titer plate size, which is operated in semi-batch mode, is outlined in [75] (see also [76] and for microfabrication [77]). So far, a single-cell and an eight-cell prototype have been realized (Figure 4.35). Both comprise a stainless-steel housing with fluoropolymer plates containing the reactors and a membrane serving for mixing. The membrane is laser welded and the plates are compressed to tightness.

The reactors are cylindrical in shape and can carry up to 30 mg of resin. Polymer sieves at the top and bottom of the cylinders serve for liquid feed and withdrawal. The array of reactors is attached to a capillary system allowing feed to either columns or rows. This distribution system is said to provide uniform charges to the various reactors. A specific detail of the reaction system is that mixing is achieved by pneumatic actuation using a fluoropolymer membrane (Figure 4.36).

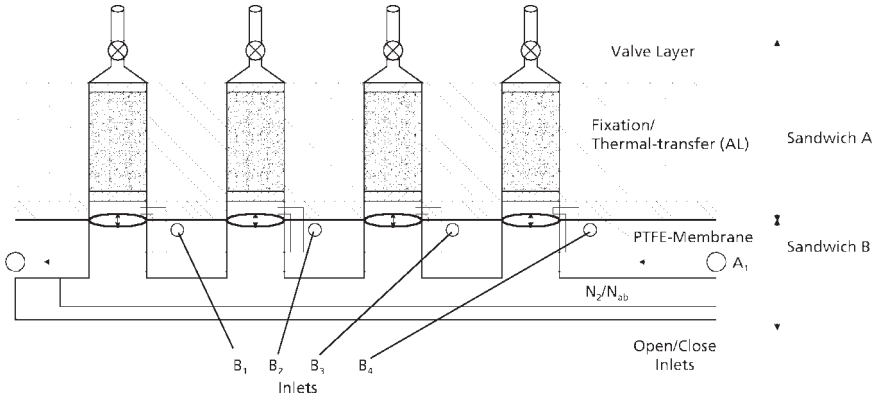

Figure 4.35 Schematic of the solid-phase synthesis–pneumatic agitation–8-reactor system [75].

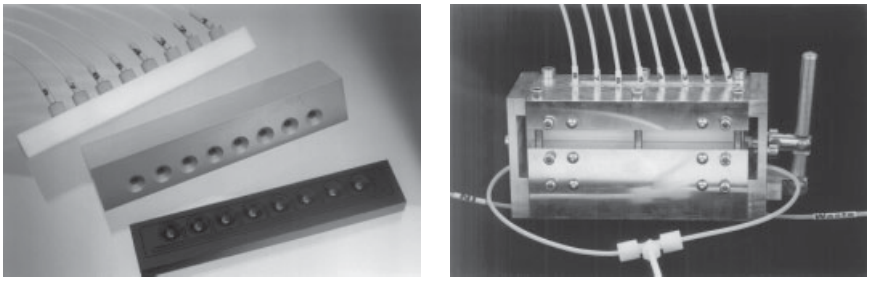

Figure 4.36 Solid-phase synthesis–pneumatic agitation–8-reactor system. Left: dismantled system. Right: same system, assembled [75].

4.2
Aliphatic Nucleophilic Substitution

4.2.1
Hydroxydehalogenation – Hydrolysis of Chlorides and Acid Chlorides

Proceedings: [46] (benzal chloride), [21] (acid chlorides).

4.2.1.1 Drivers for Performing Chloride Hydrolysis in Micro Reactors

The cleavage of two chloride groups on one C atom can be a very fast process. The hydrolysis of benzal chloride, for instance, is such a reaction between two immiscible media leading to huge heat release [46]. By uncontrolled mixing, the temperature can rise significantly accompanied by an increase in viscosity due to side reactions. For both reasons, the reaction can lead to a bursting of the whole processed sample. Therefore, the reaction is usually carried out by dropwise addition of one reactant and rigrous stirring. Accordingly, the driver for micro channel synthesis is to search for isothermal processing at high degrees of conversion and fast mixing.

Similar aggressive reaction conditions characterize the hydrolysis of acid chlorides, in particular when using short-chain alkyl-substituted acid chlorides such as propionic acid chloride. This fast reaction serves well as a model reaction for micro channel processing, especially for IR monitoring owing to the strong changes in the carbonyl peak absorption by reaction [21].

4.2.1.2 Beneficial Micro Reactor Properties for Chloride Hydrolysis

In the case of the above-mentioned dichloride hydrolysis, good mixing, i.e. emulsification, good heat transfer and restriction of residence time (to reduce side reactions) is demanded [46].

Concerning acid chloride hydrolysis, the advantage of micro chemical processing is that the micro reactor itself can be used as a flow-through cell for analysis, very unlike most large-scale conventional reactors [21]. For the case indicated, IR analysis is suitable and can be performed with silicon as encasing material, which is transparent for a wide range of the IR spectrum. In other cases, when reactions lead to color changes such as for the Wittig reaction [13], visible or UV detection may be required. Here, glass or quartz is the best micro-reactor construction material.