The hybrid approach seems to be the more pragmatic procedure and its time has come already. It allows one to analyze the advantages of micro reactors without delay, especially facing today's industrial time demands. The impressive results gathered so far, especially on the industrial side, substantiate that this – and so far only this – concept is not lacking in innovative character besides pragmatism [11, 28]. Set-ups with many micro-reactor components, pointing to a monolithic concept, will find use when each of these components on their own or the interplay between all of them gives advantages. This needs more time for development, but can be built on the progress achieved so far.

1.5.5.3 **Methodology of Micro/Mini-plant Conception**

Rinard dedicated his research to a detailed analysis of methodological aspects of a micro-reactor plant concept which he also termed mini-plant production [85] (see also [4, 9, 10] for a commented, short description). Important criteria in this concept are JIT (*j*ust-*i*n-*t*ime) production, zero holdup, inherent safety, modularity and the KISS (*k*eep *i*t *s*imple, *s*tupid) principle. Based on this conceptual definition, Rinard describes different phases in plant development. Essential for his entire work is the pragmatic way of finding process solutions, truly of hybrid character [149] (miniaturization only where really needed). Recent investigations are concerned with the scalability of hybrid micro-reactor plants and the limits thereof [149]. Explicitly he recommends jointly using micro- and meso-scale components.

1.5.5.4 **Highly Integrated Systems**

Jensen emphasizes the potential of system integration to combine many functions on one chip [101] (see Section 1.5.1.5). Chemical detection is often the rate-limiting step in many chemistry investigations for gathering product information. Macroscopic test systems may be replaced by PC card-sized micro-chemical systems consisting of integrated microfluidic, sensor, control, and reaction components. The advantages are obvious: namely less space requirements, less utilities, and less waste production. This is seen as the step towards high-throughput screening of process chemistries under controlled conditions.

Jensen gives several examples for his present highly integrated chip systems [101], including a gas-phase reactor, a liquid-phase reactor, a catalyst-testing reactor, and a packed-bed multi-phase reactor. In addition, he provides the vision of a multiple micro-reactor test station (see Section 1.5.5.2).

1.6
Impact on Process Results

1.6.1
Selection Criteria for Chemical Reactions for Micro Reactors

Lerou et al. mention the following criteria that render reactions suitable for investigations in micro reactors [74]:

Chemical Micro Process Engineering: Fundamentals, Modelling and Reactions
Volker Hessel, Steffen Hardt, Holger Löwe

ISBN: 3-527-30741-9

- fast
- homogeneous
- catalytic
- photochemical
- high temperature
- hazardous

1.6.2 Conversion, Selectivity, Yield

1.6.2.1 Conversion

Owing to increased mass transfer and the use of aggressive reaction conditions (e.g. increase in temperature), high conversions can be achieved in micro reactors.

Such improvements in conversion were reported for the oxidation of ethanol by hydrogen peroxide to acetic acid. This is a well-studied reaction, carried out in a continuous stirred-tank reactor (CSTR). Near-complete conversion (> 99%) at near-complete selectivity (> 99%) was found in a micro-reaction system [150]. Processing in a CSTR resulted in 30–95% conversion at > 99% selectivity.

For the Michael addition of 2,4-pentanedione enolate to ethyl propiolate, improvements in conversion were determined. This example serves also to demonstrate that proper process conditions are mandatory to have success with micro-reactor processing. A conversion of only 56% was achieved when using electroosmotically driven flow with a two-fold injection, the first for forming the enolate and the second for its addition to the triple bond (batch synthesis: 89%) [151]. Using instead a stopped-flow technique to enhance mixing, a conversion of 95% was determined.

1.6.2.2 Selectivity

Wörz et al. stress a gain in reaction selectivity as one main chemical benefits of micro-reactor operation [110] (see also [5]). They define criteria that allow one to select particularly suitable reactions for this – fast, exothermic (endothermic), complex and especially multi-phase. They even state that by reaching regimes so far not accessible, maximum selectivity can be obtained [110]. Although not explicitly said, 'maximum' refers to the intrinsic possibilities provided by the elemental reactions of a process under conditions defined as ideal; this means exhibiting isothermicity and high mass transport.

Consecutive reactions can reduce selectivity. Among them, partial oxidations or partial hydrogenations undergo several consecutive reaction steps during the course of the reaction. Usually, an intermediate, rather than the final product is the value target product. In this context, it was proven that micro reactors can exhibit high selectivity to such intermediates. For the hydrogenation of *cis*,*trans*,*trans*-1,5,9-cyclododecatriene to cyclododecene, the performance of the micro reactor was benchmarked against three types of fixed beds, two of them being composed of the same catalyst as employed for the micro reactor. Monitoring cyclododecene yield versus selectivity, it was found that the yield decreases from 62–64% within the range of conversions investigated when using the conventional granules. For the

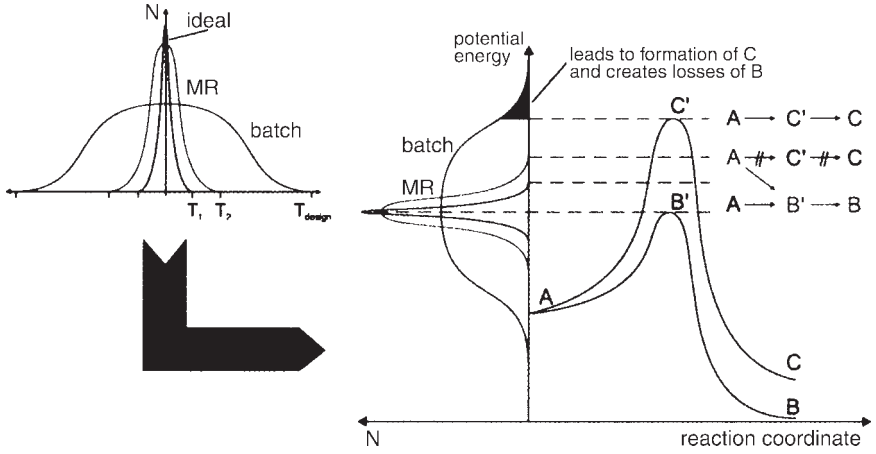


Figure 1.30 Temperature/energy distributions correlated to a generic potential energy curve [81].

foil fragments, a nearly constant selectivity of 73% was found. Wire pieces and the micro-channel reactor both give notably better results than the foils; the micro-channel reactor is slightly better than the wires.

Similar findings were made for liquid-phase reactions such as the naphthalene nitration in micro reactors. The nitro group can be introduced only once per naphthalene molecule or multiple times; up to four nitro groups can ultimately be attached to the aromatic core. For micro-reactor processing, mainly mono- and dinitro products were obtained [152]. For batch processing of naphthalene, a wider range of products are found containing many isomers of the above-mentioned species, but also tri- or tetranitrated products. In the micro reactor, even at 50 °C and using a large excess of nitrating agent, high selectivity was maintained, as revealed by the high degree of mononitronaphthalenes in the product mixture [152].

Side reaction can reduce selectivity as well. In this context, Schwalbe et al. gave the first insight into the relationship between potential-energy profiles of the reaction course and setting proper micro-reactor operation, particularly to enhance selectivity [81]. Using generic, known profiles under kinetic and thermodynamic control, a first mechanistic analysis is presented on how selectivity will be affected on changing the temperature. Normal distributions of temperatures within a micro reactor and a batch are given, the first being much smaller. These temperatures can be related to energy values, thereby revealing the respective energy distributions for the batch and the micro reactor. Two such curves were superimposed on a potential energy curve under kinetic control with a main and a side reaction (Figure 1.30). In this way, it becomes evident that a high-energy energy fraction given in the batch can induce the side reaction (having a higher value of activation energy). In contrast, the micro reactor is virtually only supplying the energy needed for passing the transition state, related to the activation-energy curve. Hence the micro reactor does not induce side reactions to any great extent.

The main achievement of Schwalbe et al. is to have initiated such considerations in micro-reaction technology, known in conventional chemistry for decades, and to have pointed out the theoretical value of such reaction mechanism-based organic micro-reactor processing [81].

Selectivity may also come from reducing the contribution of a side reaction, e.g. the reaction of a labile moiety on a molecule which itself undergoes a reaction. Here, control over the temperature, i.e. the avoidance of hot spots, is the key to increasing selectivity. In this respect, the oxidative dehydrogenation of an undisclosed methanol derivative to the corresponding aldehyde was investigated in the framework of the development of a large-scale chemical production process. A selectivity of 96% at 55% conversion was found for the micro reactor (390 °C), which exceeds the performance of laboratory pan-like (40%; 50%; 550 °C) and short shell-and-tube (85%; 50%; 450 °C) reactors [73, 110, 112, 153, 154].

1.6.2.3 Yield

As it was shown before that conversions and selectivities can be increased, usually not at the expense of each other, it stand to reason that micro reactors provide high yields. For example, the Suzuki coupling of 4-bromobenzonitrile and phenylboronic acid gives a yield of 62% for micro-flow processing which is about six times higher than with batch processing (10%) at comparable process conditions [155].

As a second example, several Hantzsch syntheses using diverse ring-substituted 2-bromoacetophenones and 1-substituted-2-thioureas are given. For these reactions, comparative and better yields were achieved when using a micro-mixing tee chip reactor as compared with conventional laboratory batch technology. The increase in yield amounted to about 10–20% [156, 157].

Finally, yield improvements were also reported for industrial process developments. For the Merck Grignard process, a yield of 95% was obtained by a micro mixer-based process, while the industrial batch process (6 m^3 stirred vessel) had only a 72% yield (5 h, at –20 °C) [11]. The laboratory-scale batch process (0.5 l flask; 0.5 h, at –40 °C) gave an 88% yield.

1.6.3 Reaction Time – Reaction Rate

1.6.3.1 Reaction Time

Many reports confirm notable reductions in reaction times when carrying out reactions under micro flow conditions. Concerning β-dipeptide synthesis, for example, a comparison between batch and micro-reactor processing was made for the reaction of Dmab-β-alanine and Fmoc-L-β-homophenylalanine [158]. While the micro reactor gave a 100% yield in 20 min, only about 5% was reached with the batch method. Even after 400 h, only 70% conversion was achieved.

Most often, such enormous improvements are discussed in a classical way following conventional organic chemistry descriptions, e.g. providing the experimental protocol and briefly giving the results. This is usually not followed by a chemical-engineering explanation. Thus it remains unclear to what extent the batch

protocols relied on actually providing much more residence time than kinetically needed. Everyone knows the expression 'stirring overnight' to complete reactions. In the future, we need real kinetic data to compare batch and micro-reactor performance. However, 'stirring overnight' is common practice and organic reactions are typically conducted over hours, if not for days. There is a lot of evidence that micro-reactor processing is definitely faster in most cases (see [29] for an overview). One just does not know which share of this has to be attributed to improvements of mass and heat transfer and how much of the reactions were simply processed too long, in a kind of chemist's tradition.

1.6.3.2 **Reaction Rate**

Often the micro-reactor data were able to confirm literature values for true reaction rates. For ethylene oxide synthesis, a reaction rate of $4.8 \cdot 10^{-5}$ mol s^{-1} m^{-2} was observed [159]. This figure, when corrected to compensate different experimental conditions, compares with a literature value of $1.7 \cdot 10^{-6}$ mol s^{-1} m^{-2}; then, a value of $1.9 \cdot 10^{-6}$ mol s^{-1} m^{-2} is obtained for the micro-reactor processing.

In some cases, higher effective reaction rate constants were reported for micro-reactor processing, usually without giving a chemical-engineering explanation for this fact. Often, this is associated with somehow suboptimal processing at the macro scale. Accordingly, not all improvements reported really refer to a generic advantage of the micro reactor; sometimes, the latter just facilitates processing improvements which in principle are achievable also with conventional equipment (but, in fact, were not achieved so far). An example of this type is the Kumada–Corriu reaction between 4-bromoanisole and phenylmagnesium bromide. For this reaction, observed rate constants were determined [160]. For high-flow-rate processing (33.3 µl min^{-1}), an observed rate constant of 0.033 1 s^{-1} was obtained. This amounts to a rate enhancement of 3300-fold compared with the value for batch processing. This was explained by being able to feed the reaction solution inside the pores of a Merrifield resin, thereby dramatically increasing the available reaction surface in comparison with traditional processing, relying on the outer surface only.

1.6.4 **Space–Time Yield**

Given large conversions and sufficiently short contact times, space–time yields can be very high in micro reactors, in particular since the 'space' itself, i.e. the micro-flow-through chamber, inevitably is small. It stands to reason that improvements in space–time yields may be obtained for any fast organic reaction which conventionally is carried out in batch very slowly, e.g. for reasons of control over heat release, and now is performed at high throughput in a micro mixer/heat exchanger system.

When the space–time yield is referred to the total reactor volume (and not only to the micro-channel volume), the large share of 'inactive' construction material has to be taken into account. Consequently, the space–time yields per micro-channel volume have to differ by orders of magnitude, e.g. more than a factor of 1000, from

those of conventional reactors, to have a gross result. So far, only a few data have been provided in the open literature, although many such processes, also from the industrial side, have been developed subsequently.

By an industrial investigation of a gas-phase reaction, the chlorination of alkanes, thermal management (faster temperature ramping, avoidance of overshoots) was improved and, hence, control over radical formation was exerted. As a result, a significant increase in space–time yield to about 430 g h^{-} l^{-1} was achieved using a hybrid micro-reactor plant compared with the conventional performance of 240 g h^{-1} l^{-1} [127, 161].

Even for the well-known ethylene oxide formation, improvements in space–time yield were reported. A value of 0.78 t/(h m^3) using an oxidative modified silver was obtained, which exceeds considerably the industrial performance of 0.13–0.26 t h^{-1} m^{-3} [159].

However, these investigations also point out that we need a proper definition of space–time yields for micro reactors. This refers to defining what essentially the reaction volume of a micro reactor is. Here, different definitions lead to varying values of the respective space–time yields. Following another definition of this parameter for ethylene oxide formation, a value of only 0.13 t h^{-1} m^{-3} is obtained – still within the industrial window [159, 162, 163].

Data are also available for space–time yields of reactions where completely new reaction paths or regimes were followed. In some cases, this was associated with operation in the explosion regime. An example of this type is the direct fluorination of aromatics using elemental fluorine. For toluene fluorination, space–time yields higher by an order of magnitude were found for the falling film micro reactor and the micro bubble column compared with the laboratory bubble column [164]. The space–time yields for the micro reactors ranged from about 20 000 to 110 000 mol of monofluorinated product h^{-1} m^{-3}. The ratio with respect to this quantity between the falling film micro reactor and the micro bubble column was about 2. The performance of the laboratory bubble column was in the order of 40–60 mol of mono-fluorinated product h^{-1} m^{-3}.

1.6.5 Isomerism

1.6.5.1 Cis–Trans Isomerism of Double Bonds

The products of reactions generating double bonds can exhibit positional isomerism, as rotation of the moieties, given before the reaction, is now prevented. This is usually referred to as cis/trans or, as a complementary description, Z/E isomerism. There are first hints that cis/trans or Z/E ratios of the products with micro-reactor processing differ from the corresponding data for conventional processing.

An example of such an impact is the Wittig reaction. For the formation of double bonds from 2-nitrobenzyltriphenylphosphonium bromide and methyl 4-formylbenzoate, it was determined that the ratio of cis and trans products (Z/E ratio) can be changed by simply adjusting the voltages in an electroosmotic-flow driven chip

[78]. The Z/E ratio is also strongly influenced by moving the reactants separately or as a pre-mixed solution. For a 1 : 1 ratio of the reactants, the Z/E ratio changed from 2.35–3.00 (pre-mixed) to 0.82–1.09 (not pre-mixed, separate movement) [165]. In a subsequent extended study it was found that relatively small voltage changes of the order of only 100 V were needed for large changes in the Z/E ratio. For instance, changing the voltage from 694 to 494 V for one channel decreased the Z/E ratio from 2.30 to 0.57.

For a Michael addition, however, the same isomeric ratio (99% trans : 1% cis) was observed for micro-reactor and batch operations [151].

The results clearly show that more results are needed to confirm the validity of the impact of micro reactors on the regioisomerism of substituted aromatics. Also, an explanation is needed of whether the effect can be confirmed.

1.6.5.2 **Regioisomerism in Condensed Aromatics**

The substitution of condensed aromatic rings is possible at various sites. This leads to regioisomerism, already when the first substituent is introduced. There are first hints that the distributions between regioisomers of condensed aromatics differ when conducted in a micro reactor as compared with conventional processing. The reason for this is not understood; even suggestions on this are lacking in the literature.

For the nitration of naphthalene a ratio of 1- to 2-mononitronaphthalene of about 20 : 1 is found in industrial processes. This ratio is dramatically increased to more than 30 by using micro reactors [166].

1.6.5.3 **Regioisomerism in Aromatics with One Substituent**

When aromatics, even single-ring compounds such as benzene, have one substituent already, the introduction of the next also gives rise to regioisomerism. In addition, the first one guides the introduction of the second by steric and electronic effects.

In this context, the second-stage nitration of 1-mononitronaphthalene was investigated. The isomeric ratio of the two regioisomers, 1,5-dinitro- to 1,8-dinitronaphthalene, was constant at 1 : 3.5 for macroscopic batch reactors, whereas it changes to 1 : 2.8 in micro reactors [166].

For toluene fluorination, the impact of micro-reactor processing on the ratio of ortho-, meta- and para-isomers for monofluorinated toluene could be deduced and explained by a change in the type of reaction mechanism. The ortho-, meta- and para-isomer ratio was 5 : 1 : 3 for fluorination in a falling film micro reactor and a micro bubble column at a temperature of –16 °C [164, 167]. This ratio is in accordance with an electrophilic substitution pathway. In contrast, radical mechanisms are strongly favored for conventional laboratory-scale processing, resulting in much more meta-substitution accompanied by uncontrolled multi-fluorination, addition and polymerization reactions.

1.6.5.4 **Keto–Enol Isomerism**

Hardly any work has been done on reactions that give both enol and keto forms of a product. One short note is given below, indicating possible changes in micro-

reactor operation by optimization of process parameters. Much more information is needed here and the first results have to be analyzed with care.

A Grignard reaction between cyclohex-2-enone and diisopropyl magnesium chloride was carried out in a micro reactor yielding a keto and enol product each [168]. In this context, 14 different reaction conditions were investigated in 14 hours. By software-supported process optimization (factorial design), the initial yield of 49% could be improved to 78% with a simultaneous increase in keto/enol isomer ratio (A : B) of 65 : 35 to 95 : 5.

1.6.6 Optical Purity

1.6.6.1 Enantiomeric Excess (*ee*)

The very first investigations on this topic pointed out that a similar degree of optical purity is achievable for some reactions in microreactor as compared to conventional processing. Hence there is no reason not to investigate a chiral reaction in a micro reactor; the feasibility has been proven.

For example, the hydrogenation of methyl (*Z*)-α-acetamidocinnamate gives a chiral product when conducted in the presence of a chiral diphosphine catalyst. The enantiomeric excess data for micro-reactor and batch operation are in line when performed under similar conditions [169]. A very high reproducibility of determining data on enantiomeric excess was reported [170]. In addition, the *ee* distribution was quite narrow; 90% of all *ee* data were within 40–48% [170].

1.6.6.2 Racemization

The very first investigations on this topic indicated that racemization can be monitored in micro reactors and that the degree of racemization seems not to be higher than in conventional organic synthesis. For dipeptide formation from the pentafluorophenyl ester of (*R*)-2-phenylbutyric acid and (*S*)-α-methylbenzylamine, racemization of 4.2% was found [158]. At higher concentration (0.5 M instead of 0.1 M), a higher degree of racemization was found (7.8%).

1.6.7 Reaction Mechanism

From all that we know, reactions in micro reactors still have to be considered as bulk reactions, i.e. they follow all the whole known rules which we know for conventional synthesis. In particular, we expect the same reaction mechanisms to occur. However, there may be exceptions to this rule.

1.6.7.1 Preferring One Mechanism Among a Multitude

Micro reactors can have a distinct influence on which reaction path is undergone, if there is close competition between several reaction mechanisms, which may be steered by, e.g., temperature control. This is nothing else than the selectivity impact already mentioned above (see Section 1.6.2). As one example for this impact,

the electrophilic path could be favored for direct fluorination using elemental fluorine at the expense of the undesired radical path by providing better temperature control and decreasing residence times [164, 167].

1.6.7.2 Tuning Bulk Reactions to Surface Control

Another exception to the known mechanisms of conventional chemistry may arise when dominance of surface reactions is achieved in micro reactors. This holds for all catalytic reactions on solid contacts. Beyond that, it was shown that some formerly homogeneous bulk reactions may become heterogeneous when carried out in a micro reactor owing to the very large surface-to-volume ratio [155, 171, 172].

1.6.8 Experimental Protocols

Experimental protocols are amenable to change by using micro-flow conditions.

1.6.8.1 Residence Time

One commonly found feature is a reduction in process times, simply because flow conditions allow a faster sequence of all necessary processing steps such as mixing and completion of reaction and promote reaction by optimized transport properties.

1.6.8.2 Reaction Temperature

Another feature often reported is an increase in reaction temperature from cryogenic conditions below or to ambient temperature, without losing selectivity. Sometimes even selectivity is increased in this way. Most often, such improved performance was found for fast organometallic reactions, probably the most prominent example being the Grignard reaction of Merck which was transferred to industrial production in the final stage.

The industrial Merck process had to use equipment with a surface-to-volume ratio of 4 $m^2\ m^{-3}$; the corresponding figure for the laboratory-scale process was 80 $m^2\ m^{-3}$ and that for the micro reactor was 10 000 $m^2\ m^{-3}$. Accordingly, the residence time had to be increased from 0.5 to 5 h to allow less heat generation per unit time for the large-scale process. As a consequence, the contribution of side and follow-up reactions is larger. In addition, micro-channel operation at –10 °C causes lower energy expenditure and costs than the former batch processing at –20 °C.

This is, at a first sight, against chemists' intuition, since the extent of side reactions is usually the larger, the higher the temperature is set, as they have higher activation energies. However, by going to room-temperature operation, simultaneously the residence time is considerably reduced. There is definitely a need for more in-depth analyses to understand better the chemical-engineering background of the favorable room-temperature processing.

1.6.8.3 Type of Reactants and Auxiliary Agents

Among the most striking changes reported is that auxiliary agents such as bases may no longer be needed, since functional groups on the surface of the micro channels may take this role. As the specific surface area is much increased in micro channels, effects that are not visible on a macro scale may become important upon miniaturization. Hence, the addition of aggressive reactants may be superfluous, i.e. milder reaction conditions may be applied elegantly, since the species they create are made at the channel surface in high local concentration, even though the total amount is very low compared with the bulk reaction material.

In this context, the esterification of 4-(1-pyrenyl)butyric acid with an alcohol to the corresponding ester was investigated [171]. Without the presence of sulfuric acid no reaction to the ester was found in the micro reactor. On activating the surface by a sulfuric acid/hydrogen peroxide mixture, however, a yield of 9% was achieved after 40 min at 50 °C. On making the surface hydrophobic by exposure to octadecyltrichlorosilane, no product formation was observed. Using silica gel in a laboratory-scale batch experiment resulted in conversion, but substantially lower than in the case of the micro reactor. The yield was no higher than 15% (40 min; 0.1 μl min^{-1}), while the best micro reactor result was 83% (40 min; 0.1 μl min^{-1}).

In a similar way, elimination of the need to add a base was reported for Suzuki couplings. Conventionally, such base addition is needed for Suzuki couplings to activate the boronic acid group. Surprisingly, there is no need for addition of a base when performing Suzuki coupling in a glass chip micro reactor [155, 172]. This was explained as being due to the local generation of a base at a heterogeneous site of the micro-channel wall. Under the action of the voltage for electroosmotic micro-flow processing, water can be converted to hydroxide ions. The high specific surface area in the micro reactor probably accelerates this process. Although the corresponding hydroxide concentrations may be low in bulk, they potentially can be large at the catalyst surface where these species enrich. As a consequence, the Suzuki coupling can be performed without a base in micro reactors. Testing with the same process parameters does not lead to any conversion in a batch reactor. Here, the addition of a base is essential.

1.6.9 Safety Profits

1.6.9.1 Share of Safety-relevant Industrial Processes

Approaching the subject from a practical point of view, how many plants actually are performing safety-relevant chemical processes? In an older study, the share of safety-relevant plants in the German state of Rhineland-Palatinate are listed [173]. It is assumed here that the trend given there still is valid.

From 1980 to 1993, the number of safety-relevant plants increased from 65 to 772 [173]. They constituted slightly more than a quarter of all plants (3472) at that time. Concerning big chemical plants, selected as falling into the category of a special law [173], 230 out of 346 plants were safety-relevant; 163 of them, in addition, had special obligations.

1.6.9.2 Safe Micro-reactor Operations in the Explosive Regime or for Otherwise Hazardous Processes

Many examples of safe processing in micro reactors have been reported. Among them, the formation of the poisonous hydrogen cyanide is often mentioned [5]. Rinard and Saha refer to the non-oxidative Degussa variant [174] of this synthesis [85], while a micro reactor has performed the oxidative formation of hydrogen cyanide [175] via the Andrussov process [176, 177].

Another reaction with hazardous potential is the synthesis of methyl isocyanate from methylformamide, which was investigated using a micro reactor in industry [74].

Many examples of the use of safe micro-reactor operation in the explosive regime have been given, including ethylene oxide [159, 162, 163, 178] and maleic anhydride [179] formations, the oxyhydrogen reaction [180, 181], the synthesis of explosive endoperoxides [182] and the Hock phenol process [183]. Concerning the prominent oxyhydrogen reaction, inherent safety was ascribed to hydrogen/oxygen mixtures in the explosive regime when guided through channels of submillimeter dimensions under ambient-pressure conditions, based on an analysis of the thermal and kinetic explosion limits [18]. This was confirmed by experiments in a quartz micro reactor [18] and other measurements in steel micro reactors [180, 181]. The reason for safe operation is seen in improved thermal control (better removal of reaction heat; avoidance of hot spots) and in a wall-induced quenching of radical chains (flame-arrestor effect).

An impressive example of the impact of miniaturization on the explosion limit has been given for the oxyhydrogen reaction [18]. For a conventional reactor of 1 m diameter, explosive behavior sets in at 420 °C at ambient pressure (10^5 Pa). An explosion occurs at about 750 °C, when the reactor diameter is decreased to about 1 mm. A further reduction to 100 μm shifts the explosive regime further to higher pressures and temperatures.

1.6.10 New Process Regimes

Micro reactors can open up new process regimes [5, 18, 70, 147, 180, 184–186]. Actually, the term 'new' is used in this respect in the micro-reactor literature with ambiguous meanings. There are at least three types of 'new' processes:

- essentially novel processes that were not known before realization in a micro reactor [187–192];
- processes that were principally known before, but behaved much worse or otherwise differently when carried out in conventional equipment [164, 167, 193–197];
- processes that are known, but bear threat to equipment and life when being carried out in conventional equipment or are otherwise considered as prohibitive [18, 147, 180, 184–186].

1.6.10.1 Essentially Novel Processes

Keeping in mind the controversial discussion on 'new physics' in micro reactors [198], we certainly have to be at least as careful when introducing or claiming essentially novel chemical processes. A thorough scientific consideration is required for an exact definition and differentiation here that is beyond the scope of this book. So far, no deep-rooted scientific work has been published analyzing the origin of the novelty of chemistry under micro-channel processing conditions.

1.6.10.2 Known Processes that Become Entirely Better or Otherwise Different

It is certainly more philosophical question as to whether a known process that becomes entirely better or otherwise different is to be called new or old with a new complexion. It is – chemically speaking – even more difficult when 'better' or 'otherwise different' refer to undertaking a new elemental pathway, i.e. to following a different reaction mechanism.

Some authors even speak of 'inaccessible regimes' when processes are operated with maximum selectivity [110]. As pointed out above, there is no clear definition of what a new process regime is and what just a change of process parameters is. Hence the definitions given here may be taken as a guideline until there are better ones.

An example of operation in new process regimes is ammonia oxidation which was carried out in membrane-carrying micro reactors [188]. Dependent on triggering heat removal via change of membrane properties such as heat conduction and thickness, the ignition–extinction behavior is completely different from the normal process. Hysteresis-type behavior, typical of conventional operation, vanishes for certain specifications of the membrane reactor. Not only does the processing itself change, it is accompanied by a difference in product spectra. Operation without hysteresis ('no-loop') gives mainly dinitrogen oxide (N_2O) as product, whereas in operation with hysteresis ('loop'), the 'conventional' products nitrogen and nitrogen oxide (NO_2) are obtained instead.

1.6.10.3 Processes Known, but not Used for Safety Reasons

Some processes have been known and investigated for a long time, even over decades, but are not used for industrial production or even for common laboratory-scale practice. Although promising, safety reasons may restrict widespread permission to use them or render them inconvenient. The processes are investigated but at extreme dilution or in complex special apparatus.

For example, direct fluorinations with elemental fluorine are kept under control in this way, at very low conversion and by entrapping the molecules in a molecular-sieve reactor. As with some other aromatic substitutions they can proceed by either radical or electrophilic paths, if not even more mechanisms. The products are different then; this may involve position isomerism, arising from different substitution patterns, when the aromatic core already has a primary substituent; further, there may be changed selectivity for undefined addition and polymeric side products (Figure 1.31). It is justified to term this and other similar reactions 'new', as the reaction follows new elemental paths and creates new products or at least new

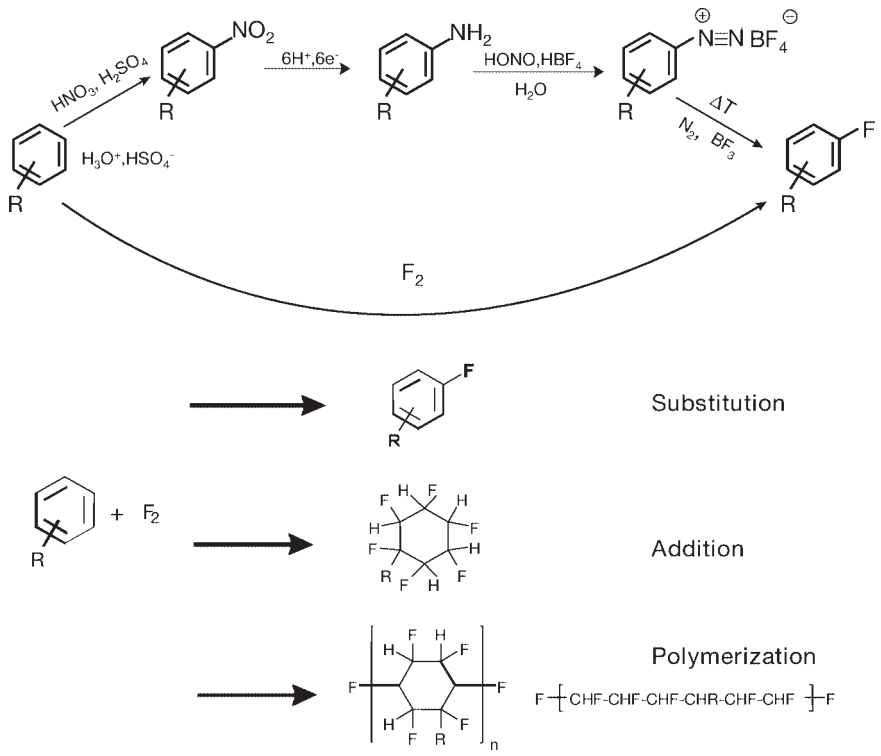


Figure 1.31 Electrophilic and radical paths in direct-fluorination chemistry leading to substitutions, additions and polymerizations with the example of toluene as substrate. The aromatic substitutions give rise to defined, characteristic substitution patterns.

product mixtures; however, the reactants used are the same and so are (some of the) products.

Other well-known examples of processes that fall into the category discussed in this chapter are many oxidation reactions that have extended explosive regimes. Among them, the reaction between oxygen and hydrogen is renowned to be particularly dangerous, as is evident from the extremely large explosion range of oxygen contents from 4 to 96%. The reported explosions for this process were more than vigorous and hindered not only any use of this process, but even most scientific investigations on this topic. Recently, some micro-reactor processing was reported to exert control over this reaction. For instance, even up to 1200 °C safe operation was achieved at relatively large volume flows [18, 147, 180, 184–186]. Somehow, 'the beast was tamed' [199] and acquired a completely new appearance.

According to the information given above, several reasons exist for why promising processes actually do not find application. Literature descriptions refer especially to the following reasons:

- safety precautions [124]
- insufficient turnover rates [124].

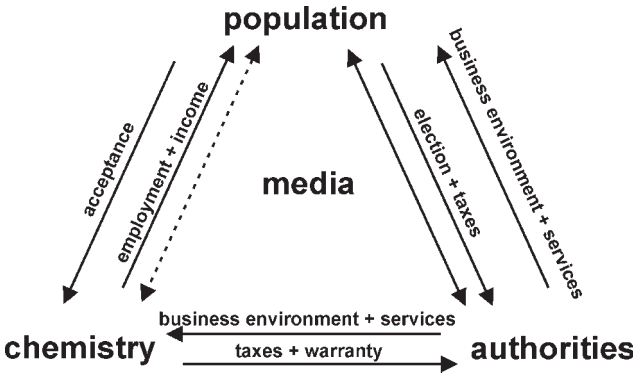


Figure 1.32 'Control circuit' with three cornerstones, creating the socio-economic perception of chemistry (redrawn from [200]).

1.7
Impact on Society and Ecology

The awareness of chemistry in general and its socio-ecologic perception is characterised by some kind of 'control circuit' having three parts, namely population, public authorities, and chemistry itself (Figure 1.32) [200] (see also the same three-cornered relationship between technology push, market pull, and social demands given by Felcht [137]). As a type of information exchange and creating platform, media serve between these parts. There are mutual relationships between each of the cornerstones with the other of the control circuit. As a result, a state is reached that is stable for a time, but gradually amenable to changes, i.e. the socio-ecologic perception of chemistry as a technology for mankind. This view has an influence on the technology itself, besides economics and margins. Hence it is worthwhile to look for changes that especially a technology as innovative as micro reactors may induce here.

1.7.1
The 'Control Circuit' for Chemical Micro Processing

Micro-reaction technology has just left its infancy and started commercialization. Consequently, we do not know about the social response to micro reactors in general, i.e. the 'micro-reactor control circuit' in the sense outlined above has not yet developed, but we do know something of the response of chemical industry and customers to what the micro-reactor offers.

Hessel and Löwe try to take the view of the user [9, 10]. They conclude that micro reactors have long since become a constituent part of today's chemical R&D activities. For them it is not surprising that much news of successes is not disseminated in a branch that profits largely from patents and keeping knowledge secret. Hence all essays on this topic, such as this volume, can only provide a fraction of the information which is free to be communicated.

→ Themenblock 2

Auszug aus: Schulbuch TERRA der Gymnasien Baden-Württemberg, Abiturklassen

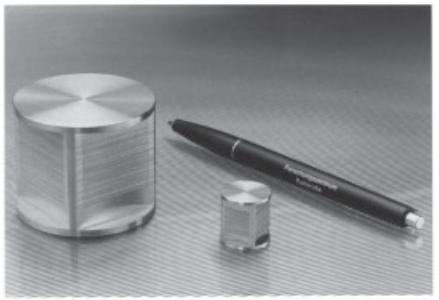
Wirtschaftliches Handeln und dessen Raumwirksamkeit

M1 *Schrägluftbild der Betriebsanlagen des Chemiekonzerns BASF in Ludwigshafen*

BASF (Badische Anilin- & Soda-Fabrik)
Werk Ludwigshafen in Zahlen (2000):
Beschäftigte: ca. 40 000
Werksfläche: 7,11 km²
Gebäude, Anlagen: ca. 2 000

Straßen: ca. 115 km
Bahngleise: ca. 211 km
oberirdische Rohrleitungen: ca. 2 000 km

BASF [Hrsg.]: BASF-Gruppe – Daten und Fakten – Chorin 2001. Ludwigshafen 2001, S. 27



M2 *Industrieanlagen der Zukunft? Minireaktor „Karlsruher Würfel" – Chemiefabrik im Schuhkarton*

Agilent Technologies
www.agilent.com

BASF
www.basf.com

Forschungszentrum Karlsruhe
www.fzk.de/imvt

Ein am Forschungszentrum Karlsruhe entwickelter Minireaktor – eine Innovation im Bereich der Mikrotechnik – bietet bei einem Rauminhalt von 1 cm³ Platz für 4 000 haarfeine Röhren. Durch „etwas größere" Würfel mit Kantenlängen von 3 cm können in einer Stunde 7 000 l Flüssigkeit gepumpt werden, was industriellen Anforderungen entspricht.
Aufgrund der außergewöhnlichen Eigenschaften der Minireaktoren lassen sich die verwendeten Rohstoffe besonders wirtschaftlich nutzen. Durch den Einsatz derartiger Anlagen schrumpfen die Mengen der miteinander reagierenden, oft giftigen Chemikalien. Das Risiko von Chemieunfällen reduziert sich ebenso wie der Verbrauch von Ressourcen sowie die Belastung der Umwelt.
Mikro- und Nanotechnologie könnten es ermöglichen, Teile industrieller Großanlagen zu miniaturisieren und den Flächenbedarf der Industrie zu verringern, auch wenn es in der Zukunft sicherlich keine Fabriken „in Postkartengröße" geben wird.
Für Analysezwecke sind daumengroße Chips in der Entwicklung, die vielleicht einmal ganze Großlabore ersetzen können. Die US-amerikanische Firma Agilent Technologies bietet bereits Chips an, die mit einem Milliardstel Milliliter Probenstoff auskommen. Werkstätten der Zukunft?

Figure 1.33 Micro-reactor images as teaching material in German school books.

Hessel and Löwe further comment that cautions optimism meanwhile has replaced the euphoria with which many developments in the 'hype 1990s' were associated [9, 10] (a description of the industrial standpoint was given, e.g., by Oroskar et al. [201]). The suppliers of micro reactors and their components have to comply with their promise to purchase in line with market requirements. Seriousness on the part of the customer is also required concerning the application targets when approaching the supplier. Large, often too large, expectations were aroused during the start phase or were waiting to be awoken. At present, it is very clear that micro reactors are not a panacea for processes that suffer from conversion or selectivity problems. On the contrary, really bad results may be obtained if the process does not fit their capability.

1.7.2
Social Acceptance via Education and Awareness

The fact that the 'control circuit' for micro chemical processing has not been established, as outlined in Section 1.7.1, can be seen as chance to have a deep, positive impact on society in a way not known before. Education and awareness of the technology can be used as one main driver for developing such circuit.

Micro-reaction technology is a classic example of a novel discipline generated at the interface of existing disciplines; hence this new discipline demands special teaching at universities, presented by specialized lecturers [57, 58]. It is the multidisciplinary merging of chemistry, physics, chemical engineering, and mechanical engineering, to name just a few. In this way, chemical micro processing may become a novel, individual branch of research and education organization within universities.

In fact, this movement has started. Some universities now provide training courses and give lectures on this aspect [202, 203]. Sooner or later, this will also be taught at schools. In the state of Baden-Württemberg in Germany, school books now show photographs of micro reactors (Figure 1.33) [204]. As a result, society may be much more aware of the 'revolutions' of miniature chemical equipment that it was in the past concerning the use of remote, large-scale chemical apparatus. This may be accompanied by a much increased social acceptance of chemistry in general as it can exhibit a modern, dynamic change in a similar way to microelectronics. Once we are using micro-reactor equipment for our household and personal needs, we will no longer feel reluctant about chemistry in general. This may even stimulate further interest in chemical developments in a way such as is given now only for selected scientific topics such as cancer or AIDS drug development and gene therapy.

1.7.3
Ecologic Acceptance via Environmental Acceptability

However, it is not only knowledge transfer on the technology itself which impacts on society; microchemical processing will have repercussions on our wealth, health, and environment. From the late 1960s (first prognoses on limits of production

increase, e.g. given by the Club of Rome) to the early 1980s (peace and ecology movement), the awareness of the environmental acceptability of new and existing production processes rose in society. This becomes more and more important when establishing new ways of production.

In this context, Benson and Ponton declare that while the chemical industry has made considerable achievements in reactor performance, safety and control, comparable to those in the microelectronics business, this success is by no means evident to the public, in deep contrast to the latter [139]. It is said that this is mainly and in a way simply due to the visual recognition of chemical production plants. From a distance and for somebody outside the field, the chemical plants of the late 1940s and the early 1990s look virtually similar, whereas one is able immediately to see the big differences in, e.g., television sets and automobiles. Hence it is not evident that notable improvements were made over the decades.

Following this, it stands to reason that micro reactors can aid in changing the perception of chemical plants. Usually their outer shape is small and compact, at least compared with most existing equipment. At best, the outer shape of the whole plant is visibly diminished. Even if this does not arise owing to employing multi-scale architecture of almost unchanged outer shape (see Section 1.1.7), one could accentuate the new tool in various ways, including the press and TV. If desired, micro reactors could stand for a paradigm change; more likely and realistically, they could visualize the enormous improvements in industry in recent years, particularly referring to process intensification.

Nonetheless, no change will happen without external stimuli. Benson and Ponton list the following:

- environmental pressures on the process industries
- electronic point-of-sale (EPOS) demands for just-in-time (JIT) production
- increased emphasis on product quality and consistency
- expansion of plants into the Asian and African regions leading to a demand for smaller distributed plants, also with a high degree of reliable automation
- economics of scale will be 'disproved' if significant technology improvements and computer control are achieved. This especially holds for directly converting raw material into valuable products.

Benson and Ponton propose, based on this analysis, the concept of distributed manufacturing [139, 145], which will be referred to in detail in Volume 2 of this book series. Basically, they refer to small, transportable plants which are fed with reactants 'over the fence', hence using only non-hazardous, generally available materials by normal piping or standard transport. If an aggressive chemical is needed, it has to be made from environmentally friendly base materials as an intermediate on-site. Needless to say, effluents have to be completely harmless, plant operation has to be intrinsically safe, and the plant should be clean and quiet.

The scenario of Benson and Ponton seems to be for the remote future. However, this is no quality rating at all, since we all need such long-term views for new innovations. Moreover, parts of the predictions certainly have already been addressed

in the work published so far. It should be a guideline or an ideal for promoting chemical micro-process engineering.

1.7.4 Environmental Restoration

While the discussion give above was more generically oriented, this will be underlined here by a practical example.

Wegeng mentions the use of micro reactors for the cleanup of environmental contamination [1]. In particular, he refers to downwell groundwater cleanup by micro-chemical separations and conversions such as destruction of organics.

In a further paper, Wegeng and Drost give several examples of distributed processing applications, which refer to the fields of energy generation and environmental restoration [106]. Concerning the latter, compact cleanup units for waste treatment are mentioned, mainly in consideration of the numerous radioactive sites, stemming from cold-war military developments [106] (see Section 1.5.4.5 for more information). As another example, the use of distributed systems for global carbon dioxide management aimed at reducing the greenhouse effect [106] (see Section 1.5.4.5) is mentioned.

1.7.5 The Micro-reactor Echo in Trade Press and Journal Cover Stories

Micro reactors have attracted the attention of the press and journals (Figure 1.34). This 'echo' reflects the perception of how the technology is seen by journalists and experts in the field, thereby influencing the opinion of the interested society. It is worth – not only from a marketing perspective – having a closer look at this and attempting to draw some conclusions concerning one's own future developments.

Before showing some examples of press releases and their content, we shall briefly shortly sum up all the information given. Most frequently the relationship of micro-reaction technology to the development of microelectronics is cited, suggesting a similar success story. Expectations are created that some day micro reactors will be mass fabricated at low cost in a similar way. In addition, it is believed that compactness can be achieved as for the integration of functions in the microelectronics world. In this context, often the vision of a shoebox-sized plant or a plant on a desk is given.

Micro reactors have also frequently been compared with nature and nature's reactors such as cells, organelles, organisms, etc. In turn, the cell is often taken as a model for micro reactors. It is stated that nature decided to not change the size of the cells throughout evolution, e.g. when comparing the small animal the mouse with the very large elephant; both have cells of the same size range, the elephant just has much more than the mouse. This 'numbering-up concept of nature' is seen to resemble the approach of parallelizing micro reactors. From this, it is analyzed if a similar numbering-up concept can be provided for technical reactors. In this context, it is often questioned if there will be a production supplying huge quantities of micro reactors. On this and other topics typically a number of expert

science/technology

DOWNSIZING CHEMISTRY

Chemical analysis and synthesis on microchips promise a variety of potential benefits

Michael Freemantle
C&EN London

The notion of putting a conventional, general-purpose chemistry laboratory onto a single microchip is possibly fanciful. But the miniaturization of chemical and physical processes and their integration onto such a chip for a specific application are a definite reality.

The development of microscale devices that can process and analyze minuscule amounts of samples and reagents is exciting the interest of increasing numbers of chemists. According to some, it could revolutionize chemical analysis and synthesis in the same way that microchips have revolutionized computers and electronics.

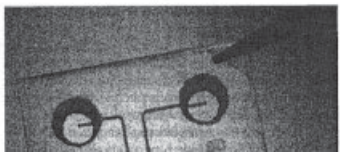
"The field is one that is growing very rapidly," says George M. Whitesides, a chemistry professor at Harvard University. "The first real applications will very probably be in analytical systems."

Many companies are racing to

that fact has significant implications for instrument companies, which will have to go from a business of a few expensive sales to bulk sales of inexpensive systems."

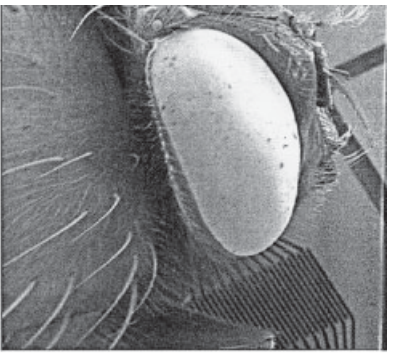
According to Richard D. Kniss, vice president of Hewlett-Packard and general manager of its Chemical Analysis Group, the emerging lab-on-a-chip technology will revolutionize the drug discovery process in the same way that the processes of miniaturization and integration have recast the microelectronics industry.

The pharmaceutical industry is the main driver for developing this technology right now, observes J. Michael Ramsey, a corporate fellow and group leader



NEWSFRONT
EDITED BY AGNES SHANLEY

Tiny reactors and ancillary devices may work where large equipment would be too risky or costly



This static mixer, right, shown near a fly's eye, is of truly microscopic dimensions. Such devices are being developed for use with 'downsized' reactors, for highly exothermic or flammable reactions, where conventionally sized equipment would prove too dangerous

MICROREACTORS FIND NEW NICHES

Normally, chemical engineers take bench chemists' concepts, and devices handling liters of reagents, and scale them up to tons-per-year industrial plants. Today, a

lists low manufacturing, operating, and maintenance costs, and low power consumption, among the advantages. The report was published by Technical Insights, Englewood, N.J., a unit of John Wiley & Sons.

To the list of potential benefits, Ramsey adds automation, reduced

tiny systems into commercially available products should take about five to ten years, says Wolfgang Ehrfeld, managing director of the Institute of Mi-

to date to commit publicly to the new technology, while, in Europe, BASF AG (Ludwigshafen) is most visible.

However, industrial interest is grow-

Figure 1.34 Title pages of two trade-press articles on micro reactors [45, 226].

opinions are quoted. The question concerning production is ultimately related to the marketability of the technology. Start-up enterprises selling micro reactors and market studies/prognoses are hence also in the focus of the press articles.

Finally, the topic of standardization ('plug-and-play') has gained interest. Will there be modular flexible plants in the future, for multi-purpose and on-site production? Concerning the latter, the chemical manufacture of hazardous and explosive substances has attracted readership over many years.

Besides all these comparisons, press releases cite and explain the technological benefits of micro reactors, which were described in Section 1.3, often in a vivid description. This includes the following items:

- safety gains
- process intensification
- the on-site production of, e.g., dangerous materials
- use of new process regimes
- general advantages of micro reactors such as enhancing transport
- highly parallel screening.

In the following, selected trade-press and cover-story releases (mostly from German sources, but not exclusively) are presented. These releases are given by the headline, the source (name of journal), the time of release, and a list of key contents, completed by a citation. The citations are listed in the sequence of their appearance.

Bulk chemicals on the drop, The Economist, June 2003
Better chemistry through confinement; economy of scale; limits and expenditure of scale-up; micro reactors origin from microfabrication; expert opinions; general advantages of micro flow; hybrid construction; industry's efforts; chip micro reactors; numbering-up; vision of computer-like chemical workstation [205].

'Numbering up' small reactors, Chemical Engineering News, June 2003
Expert opinions; general advantages of micro flow; market situation; modular construction; time-to-market; industrial implementation and experience; off-the-shelf catalogue sales; numbering-up; problem hurdles; filament reactors; state of knowledge acquisition [206].

Chemieküche für Zwerge, VDI Nachrichten, April 2003
Safety; risk of incidents; miniature plants; novel process routes; industrial and academic examples of use; HTE; standardization; LEGO-type plants [207].

Tausend Kanäle für eine Reaktion, Chemische Rundschau, February 2003
Industrial and institutional expert opinions; general advantages of micro flow; safety; work of institutes; particle precipitation; pilot-scale operation; challenges; process control; plugging; miniature sensing and controlling; emulsification; market situation [204].

Vor dem Sprung in die Produktion, Chemie Produktion, December 2002
Prognoses on speed of implementation; PAMIR market study; industry's demands; numbering-up risks; expert opinions; Clariant pigment micro-reactor production; smallness not an end in itself; general advantages of micro flow; industrial process development and optimization; share of reactions suited for micro reactors; hybrid approach; standardized interfaces; start of industrial mass production of micro reactors?; unit construction kit [208].

Die Fabrik auf dem Chip, Spektrum der Wissenschaft, October 2002
Miniaturization and modularization of parts of future chemical apparatus; general advantages of micro flow; expert opinions; specialty and fine chemical applications; leading position of German technology; flexible manufacture; large-capacity micro reactors; reformers for small-capacity applications; compatible and automated micro-reaction systems; process-control systems; temperature and pressure sensors [209].

Chemiefabrik im Schuhkarton, Handelsblatt, June 2002
Shoebox-sized lab-on-a-chip laboratories; personal drug manufacture; general advantages of micro flow; Merck's production; nitrations; HTS; parallel catalyst testing; turnkey bench-scale test station; standardization; cube-like modules [210].

Kleine Reaktoren mit großer Zukunft, Chemische Rundschau, April 2002
PAMIR study; large commercial potential; large industrial interest; market volume; standardization; strategic cooperations; time horizon; potential for pharmaceuticals and fine chemistry; Clariant pilot with caterpillar mixer [211].

Les premiers pas des microréacteurs, Industries et Techniques, October 2001
Numbering-up; use for analytics and screening; faster and improved production; smart processes; process intensification; 'intelligent' reactor and new process regimes; dominance of surface over gravity forces; precise control of process conditions; control over selectivity; direct fluorination; distribution problems during numbering-up; CFD modeling; interdisciplinary field; onset of industrialization of micro reactors; market considerations; selected devices for combustion, power-generation (reforming); outer-space applications [212].

IMRET 3: 3rd International Conference on Microreaction Technology, CIT, 2000
This article gives a summary on the topics and selected presentations of the 3rd International Conference on Microreaction Technology and draws conclusions. Among the topics of the conference were design and production of micro-flow devices and microfluidics. Further topics of major concern are micro reactors for production processes, for energy generation and storage, and for biotechnology. In addition, a conference section was devoted to commercialization of the technology [213] (see also [214]).

Mikroreaktoren für die chemische Synthese, Nachrichten aus der Chemie, May 2000
Chip technology initiates quest for small structures; better temperature control on the small scale; fast mixing by diffusion; several kg productivity per day; no novel, but better chemistry; perfect control over process parameters; corresponding increase in selectivity; basic micro-reactor functions; selected examples of use; micro reactors as routine tools in the laboratory; first start-up companies [113].

Gezähmte Chemie im Mikroreaktor, VDI Nachrichten, June 2000
Micro-reactor enterprises; shape and material variety of micro reactors; selectivity gains and new project regimes; direct fluorination; faster process development; BASF investigations; safety increase; speed-up of catalyst development; production for fine chemistry and pharmacy; numbering-up; first industrial examples for micro-reactor production [215].

Wozu Mikroreaktoren?, Chemie in Unserer Zeit, April 2000
Innovation – advocates and opponents; origin from microtechnology; list of microfabrication techniques; selectivity and efficiency as main driver for industrial implementation; special properties and general advantages of micro reactors; process-development issues; BASF investigations on liquid/liquid and gas-phase reactions; micro reactors as ideal measuring tools; production in micro reactors as exception, the rule will be transfer to mm-sized channels [111].

Herrscher über die Temperatur, Chemie Technik, 1999
Interview with Wörz/BASF in a special on heat exchangers giving expert opinion on: compact heat exchangers, feasibility and problems of large-scale implementation of micro reactors; measuring tool for process optimization; exotic status?; scale-up; unit-construction kit; industrial implementation in 5 years [216].

Chemical reduction, Chemist, 1999
Situation like microelectronics decades ago; impetus by analytical chemistry; lab-on-a-chip – biological applications; microfabrication and micro devices; scale out; input–output board; fast and hazardous reactions; plug-and-play modules; interconnects; non-linear synthesis; growth of scientific community; industry's response; selected key players and their activities [217].

Microchemical systems:
status, challenges, and opportunities, AIChE Journal – Perspective, October 1999
Advances in microelectronics; reduction in size and integration of multiple functions; MEMS development as base; not only reaction, but also separation and analytics based on μTAS advances; general advantages of micro reactors; more aggressive reaction conditions and novel process regimes; monitoring for replacement of failed reactor unit; numbering-up; scheduled, gradual investment; biological screening, DNA amplification; manipulating processing, in particular steering thermal control; mixing by novel means; many innovative reactor designs in parallel; more focusing on separation and surface forces; fabrica-

tion beyond classical MEMS; multiple packaged reactors with integrated sensing [75].

Chemie im Kleinen, VDI Nachrichten, May 1999
Smallness of micro-flow components; safety gains; tool for kinetics evaluation; process development for large-scale processes; polymerization; combinatorial catalyst screening; hydrogen via reforming [218].

Downsizing chemistry, Chemical Engineering News, February 1999
Miniaturization of processes is reality, that of complete laboratories not; revolution as in microelectronics possible; joint development of Caliper and Hewlett-Packard; revolutionizing drug discovery; combinatorial screening; huge gains in throughput by vast numbers of analysis systems on one chip; DNA diagnostics; other advantages of μTAS; low-inventory process synthesis and other further uses; increase in performance at small scale; lab-on-a-chip definitions; materials discussion; microfabrication techniques; mixing demonstrating small-scale process intensification; electro-osmotic flow; surface-directed flow on patterned surfaces; miniaturized total analysis systems; selected μTAS devices and applications; electrophoresis-on-a-chip; selected examples for electrophoretic separations [45].

The world in figures: industries, The Economist, January 1999
Original citation: 'Miniature chemical reactors will pave the way for the future. These reactors will cut today's monster chemical plants down to the size of a car, with huge financial and environmental gains' [219].

Process Miniaturization Second International Conference, CATTECH, December 1998
Steep progress in microelectronics in the past; key players; topics of IMRET 2; general advantages of micro flow; energy, safety, process development, combinatorial catalyst testing, lab-on-a-chip biological applications; anodically oxidized catalyst supports as alternatives to non-porous supports [220].

Process miniaturization: 2nd Second International Conference on Microreaction Technology, Chemie-Ingenieur-Technik, October 1998
Number of participants of IMRET 2; steering organizations and initiators of IMRET 2; excellent resonance on IMRET 2 in the framework of AIChE spring meeting; topics of IMRET 2; summary of selected presentations; investigations beyond feasibility and laboratory stage [221].

Sicherer, effizienter, flexibler, Verfahrenstechnik, 1998
Today's use of microtechnical products; microfabrication techniques; general advantages of micro flow; parallelization for screening; steep transport gradients; plant safety; numbering-up; industrial response; outlook on market [222].

Das Chemielabor im Mikrochip, Blick durch die Wirtschaft, December 1997
Chemtel glass chip of Orchid Biocomputer, Princeton; 144 cells for parallel processing; matchbox-sized system with many devices; micro pumps with no movable parts; 10 nl internal volume; carrying out of different reactions in parallel fashion; complete chemistry laboratory en miniature; 10 000 cells as future-development task [223].

1st International Conference on Microreaction Technology, CIT, August 1997
This article gives a summary on the topics and selected presentations of the 1st International Conference on Microreaction Technology and draws conclusions [224].

Daumengroßes Labor aus Aluminium-Folie, Blick durch die Wirtschaft, June 1997
Heterogeneous gas-phase micro reactor; micro-fabrication of this device; anodic oxidation of aluminum to porous catalyst support; vision of complete small laboratory; numbering-up; development of new silicon device [225].

Microreactors find new niches, Achema Daily/Chemical Engineering, June 1997
Conclusions on IMRET1; micro-reactor exhibitors at ACHEMA 1997; expert opinions; industry's commitment; general advantages of micro flow; views on commercialization; extended list of leading institutes' and companies' activities; topological approach; numbering-up [226].

Chemielabor auf dem Mikrochip, Blick durch die Wirtschaft, May 1997
Lab-on-a-chip; protein separation; DuPont's investigations; general advantages of μTAS; DARPA foundation of military biological sensor development; MEMS components [223].

Teufelszeug im Griff, Wirtschaftswoche, April 1997
DuPont's phosgene synthesis in a micro reactor; BASF's vitamin precursor synthesis; developments in the bio field; prognosis on market volume in 2000 [227].

Microreactors find new niches, Chemical Engineering, March 1997
Leading players; expert opinions; conclusions on IMRET1; general advantages of micro flow; views on commercialization; extended list of leading institutes' and companies' activities; topological approach; numbering-up [228].

Die Natur der Chemie, FUTURE (Hoechst Magazin), August 1996
Vision of large-scale production in shoebox-sized plants; nature and plant cells as model for micro reactors; sustainable development; central role of catalysis; general advantages of micro flow; use of clean raw materials; minimization of waste; the next step in the sequence acetylene-to-ethylene chemistry: ethane chemistry; renewable resources; combinatorial chemistry; intelligent and creative solutions [229].

Chemie in neuen Dimensionen, Chemie Produktion, August 1996
Plant cells as model for micro reactors; hidden process regimes opened by micro reactors; general advantages of micro flow; intelligent chemo chip as vision; DuPont's and BASF's pioneering efforts; μTAS; safe processing; distributed manufacture; need for knowledge base [230].

Mikrotechnik – Anwendungsmöglichkeiten in der chemischen Industrie, CHEManager, November 1995
Interview with Jäckel/BASF: general advantages of micro flow; safety expenditure; multi-phase processing; analytics; process development; heat release of exothermic reactions – hot spot; limits of industrial tube-bundle, single-tube, and short-bundle reactors; micro reactors can overcome these limits; high heat-transfer coefficients; analytics of small volumes; combinatorial testing; mobile sensing systems for inspection of tubes; formulations for agricultural chemistry; production feasible? [72].

Ätzende Wolken, Wirtschaftswoche, June 1995
Nature as model for micro-reactor development; general advantages of micro flow; onset of industrial interest; micro heat exchanger; vision of methanol-fuel reforming; costs still too prohibitive [231].

Small but environmentally friendly, The Chemical Engineer, March 1993
Huge increases in technology in the past; distributed manufacturing in small-scale plants; miniaturization of processes; domestic methanol plant; point-of-sale chlorine; simpler and cheaper plants; economy of plant manufacture; process control and automation; start-up and shut-down; sensor demand [145].

1.7.6
The Micro-reactor Echo in Newspaper Press and Magazines

Chemiker sind der Zelle auf der Spur, Handelsblatt, August 2000
Plant cells as model for micro-reactor development; availability of micro-flow devices; German leadership; first production applications; BASF's motivation; spotting for DNA arrays; materials for micro reactors; Merck production plant; smallness for efficiency, but not an end in itself [232].

Ultra-Hochdurchfluss-Tests in der Arzneimittelforschung unverzichtbar, Frankfurter Allgemeine Zeitung, June 2000
Miniaturization and parallelization key approaches for drug development; apparatus for combinatorial chemistry; UHTS; 1536 titer-plate format; modular construction of apparatus; applications of UHTS; fine-chemical synthesis by micro reactors; numbering-up; nature as model; general advantages of micro flow; vision of 'plants-on-a-desk' [233].

Chemische Technik findet im Fingerhut statt, Handelsblatt, November 1999
Nature as model; pharmaceutical industry as pathfinder; foxglove-sized micro-flow components; general advantages of micro reactors; direct fluorination; transport

intensification; BASF process development; Merck and Aventis production; production in micro reactors for niche applications, if problems are solved; micro sensors for monitoring of industry's processes; household applications; chemical 'micro nose'; integrated vision needs unit construction kits [234].

Winzige Reaktoren mit Höchstleistung, Handelsblatt, November 1998
General advantages of micro reactors; pioneering efforts of Forschungszentrum Karlsruhe (KfK); development of micro heat exchangers/reactors; micro only where needed – hybrid approach; good temperature control enhances yield and safety and reduces waste; details on cube-like device; details on power capacity (200 kW) and throughput (7000 l h^{-1}); 300 000 t yr^{-1} in shoebox-sized reactor; materials and fabrication; flame arresting effect; new process regimes; boom in micro-reaction technology; KfK as pathfinder [235].

Mikroreaktoren sind so klein wie ein Fingerhut, Handelsblatt, May 1998
Steep progress in microelectronics, sensor and analytical techniques in the past; transport intensification for catalysis; first catalytic micro reactors available; partial oxidation to acrolein; partial hydrogenation to cyclododecene; anodically oxidized catalyst supports as alternatives to non-porous supports; study group on micro reactors at Dechema; safety, selectivity, high pressure; exclusion of using particle solutions; limited experience with lifetime of micro reactors [236].

Chemiefabrik in der Größe eines Chips, Handelsblatt, May 1996
Vision of shoe box-sized micro reactors; plant cells as model for micro-reactor development; cost, performance, and safety advantages; LIGA process; numbering-up; safety processing of hazardous substances [237].

Sichere Chemie in Mikroreaktoren, Frankfurter Allgemeine Zeitung, December 1995
Plant cells as model for micro-reactor development; micro-fabrication techniques; DuPont's investigations; DECHEMA's initiation of micro-reactor platform; BASF's investigations; general advantages of micro flow [238].

1.8 Impact on Economy

1.8.1 Market Development/Commercial Implementation

1.8.1.1 A Historical Description of the Interplay between Technology Push and Market Pull

Hessel et al. describe the state of the market implementation of micro reactors, as opposed to the scientific development (Figure 1.35) [239].

The development of chemical micro processing was, among other influences, strongly promoted by continuing manufacturing and offering of micro devices, as

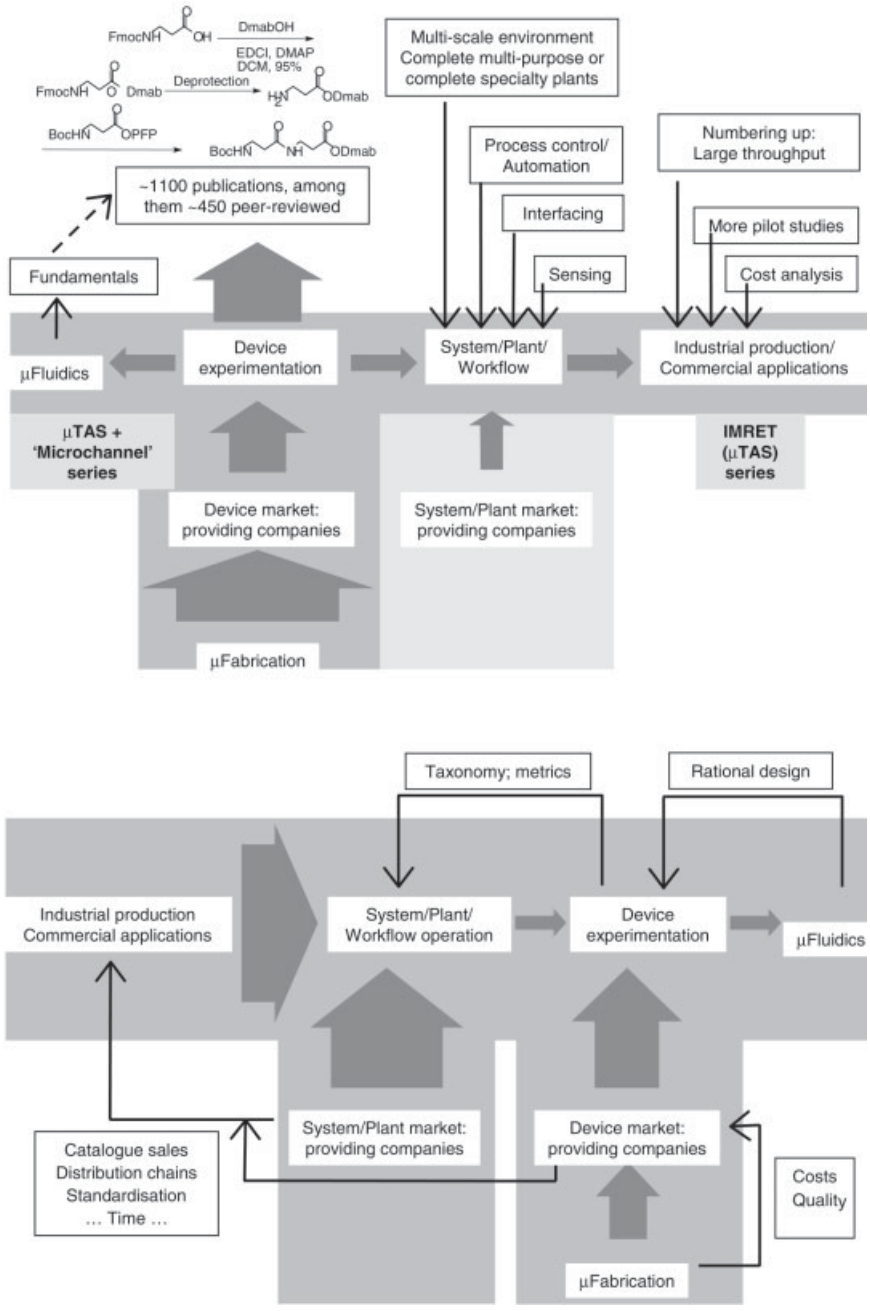


Figure 1.35 Current state of scientific and market implementation of micro reactors and optimistic future scenario. Micro reactors are today a device market and are technology driven (top). The future scenario is under market pull and will ask for more plant/total-system solutions (bottom).

a consequence of emerging microfabrication capabilities [239]. The rising, now even commercial provision of micro devices and their plants allowed a much larger scientific community to test predictions which were made in the early phase of the development, claiming several characteristic means of process intensification by chemical micro processing. Consequently, more and more journal articles report on scientific results in this field and often benchmark it to conventional equipment. By this means, a number of improvements over existing technology were indeed identified. Thus, this first phase of development with chemical processing micro devices was pushed, and so guided, by technology and the growing possibilities for its use.

Meanwhile, the chemical industry, in particular specialty and functional chemical producers, regard the technology to be mature enough to perform extensive industrial laboratory-scale testing and the first few reports on a transfer to pilot or production scale have appeared [239]. Recognizing the industrial demand, a market emerges. Institutes and companies, mostly spin-offs of the institutes, sell a range of chemical micro-processing devices off-the-shelf, for use in organic synthesis and heterogeneous catalysis, and also for various types of mixing and heat exchange. This offer is complemented by the supply of turn-key and application-specific plants, experimentation services, simulation/modeling services, and consulting.

In view of the technology push stated above, one can recognize, particularly in the last 2 years, a promising pull by the market in terms of increasing inquiries [239]. However, these requests are still partly motivated by the scientific success of the technology, gaining attraction, and only to a smaller extent by real business drivers, i.e. business units of the companies that profit from the use of micro devices. Technical obstacles due to the radical change in the way of chemical processing. It will also take some time to establish the new skills needed, to provide the investment, and to change habits that have been exercised for decades. Thus, penetration of micro devices into chemical production lines is a slow process, needing several more years.

1.8.1.2 **PAMIR – A Market Study Giving First Insight**

Prognoses on the amount and the volume of micro-structured devices are published regularly within the framework of a NEXUS study (see, e.g., [240]). It is, however, striking that in none of these studies do micro-structured reactors appear. Such information is given in a separate market study, named PAMIR ('*P*otential and *A*pplications of *MI*cro*R*eaction technology') and dedicated solely to micro-reactor technology, which was carried out by Yole Developpement (Lyon, France) and IMM (Mainz, Germany) [211, 241]. The study claims that the present market volume related to the sales of micro-structured reactors and services for their application are at approximately US $ 35 million per year (Figure 1.36). The study confirms that small- and medium-sized enterprises (SMEs) can make a turnover entirely or in parts of their organization already with their technology today. This also corresponds to the fact that a small number of medium-sized enterprises define micro-structured reactors as their core business, while bigger companies and

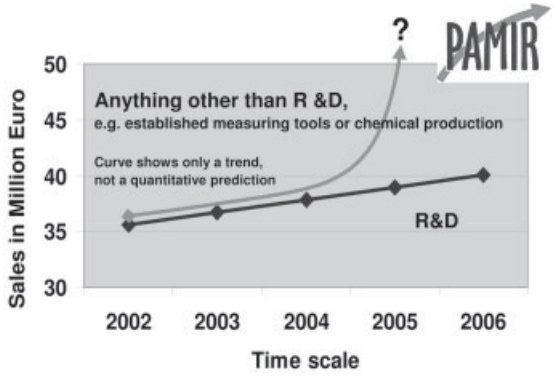


Figure 1.36 Sales-volume forecast for the field of micro-reaction technology for the next few years. A projection is given on when industrial production will set in [241].

also chemical plant manufacturers do not have them in their portfolio yet, but instead observe the market segment intensely. It is interesting to point out that the current suppliers of micro-structured reactors are nearly exclusively situated in Germany.

The study is based on interviews with about 100 selected companies and institutes/universities. Representatives from companies made up 70% of all interviewees. The study initially predicted a small increase in worldwide turnover according to general economic development. It predicts at the same time, however, that an interaction of an increasing acceptance and a significant improvement of the technical suitability of micro-structured reactors (e.g. for chemical production) could lead to an amplified steep increase of the market turnover also in the short term.

1.8.1.3 **Market Evaluation**

Some concrete conclusions on market evaluation for micro reactors are given by the PAMIR study, described above (see Section 1.8.1.2). In this context, it is worth reviewing general essays on the market evaluation of microsystems technology, since in a broader view they follow the same analysis and come to the same conclusions.

It is a general phenomenon of developments in microtechnology in the 1990s that they were rather technology-driven, hence a proper market evaluation was much behind the first technical breakthroughs [242]. As a result, unsuited market segments were often addressed and, more important, unsaleable products were released; in turn, real markets and their products were sometimes overlooked. This was accompanied by estimating the market potential too large and, in a sense, too euphoric.

Staudt and Krause commented in 1998, based on the results of a study by the Institut für Angewandte Innovationsforschung, Bochum (Institute for Applied Innovation Research), that many micro-systems technical companies still have prob-

lems in the analysis and evaluation of application changes and markets for microsystems technology [242]. The marketing problems also refer to bringing their own developments to an end and to establishing a manufacturing line for real products, once a prototype has been made. The causes lie partly in deficits in the competence of the acting personnel, but are also related to the complexity of the interdisciplinary topic microsystems technology. In this context, Steg mentions the term 'system innovation', describing a competence (of a country, society, industry, etc.) to bring new innovative technologies rapidly into many existing market sectors [243]. In the same reference, the different market-implementation strategies and the competitiveness of microsystems technology developments in Europe, Japan and the USA are described.

The technological revolution which microsystem technology brings is fascinating for those who develop; however, it is more frightening for those who are potential users, since it creates fears that the systems are too far from the well-known, marketable products of our daily experience and more generally it does not reach our common perception [242]. Consequently, a lot of future markets have not been identified as possible customers have not expressed interest and possible suppliers have not provided corresponding offers. Government funding tends more and more to select those projects which work on market implementation and thus search for potential needs of the technology.

At the turn of the century, this situation partly changed. By economic selection, only those developments that were market-oriented survived. In addition, most commentators in the field such as the trade press realized that they had to change their attitude on reporting a proper outlook, i.e. what can be realistically expected in the coming years; hence, euphoria changed to (sober) realism [242].

1.8.1.4 **Start-up Companies and User–Supplier Platforms**

The development of start-up companies in the field of micro-systems technology, including microfluidics, has been reviewed by Wicht et al. [244]. Different types of business models are presented as well as the corresponding growth models. The development of start-ups in Germany in the last 10 years is presented and the product offer is discussed. This is compared with the situation in other European countries. Finally, information on problems and opportunities for the start-ups is provided.

Within the NEXUS activity, aimed at strengthening the interaction of European industry and institutes in microsystems technology, user–supplier clubs (USC) are formed as one means for joint developments (for the USC for CAD tools see [240]; for the MikroWebFab see [245]). This should serve to promote the industrial uptake, by bridging the gap also to new potential users.

Concerning such user–supplier relationships, see also [102] for IMM's view on the role of strategic alliances in the field of micro-reaction technology.

1.8.2 Device Fabrication and Quality Control

1.8.2.1 Cost Estimation from Mass-manufacture Scenarios for Chip-based Microfabrication

Schlaak gives a description of the choice of fabrication technologies suited for a basic function – electronic, mechanical, and optical – and provides an equation for calculating costs for multi-level wafer stacks and hybrid integrated devices [239]. The conclusions drawn hold for classical chip manufacture and can certainly be applied to micro reactors fabricated via this route. They give a first estimate of how costs develop when, e.g., the device area is enlarged or the construction material is changed (which usually involves changing the fabrication route). It is a mass-manufacture scenario and will not hold when only a few micro reactors are made. Naturally, it also cannot take into account design development costs and testing for proper functioning such as leak tightness.

Wegeng et al. refer to the low-cost, mass production of microstructures from metals, ceramics, and plastics as a crucial element for widespread application [1]. Micro technologies, they say, are generally conducive for mass production; however, this has so far only been proven for the field of microelectronics.

1.8.2.2 Quality Control

Off-the-shelf catalogue sales of micro reactors have just started [15]. With an increasing number of commercial products, quality control will become more important. Brandner et al. describe quality control for micro heat exchangers/reactors at the Forschungszentrum Karlsruhe [23]. All manufacturing steps are accompanied by quality control and documentation. Leak rates (down to 10^{-10} mbar l s^{-1} for He) and overpressure resistance (up to 1000 bar at ambient temperature) are measured. Under standardized conditions, the mean hydraulic diameter is determined. Dynamic tests supplement this quality control.

1.8.3 Cost Savings for the Chemical Industry

So far, no scientific extrapolation has been published on the cost savings for the chemical industry when using micro reactors. Industrial experience is also not known; at least, it has not been communicated. Thus, one is bound to rely on expert opinions given in the press and trade press. Mostly these come from suppliers of the technology, aiming to convince industry of the benefits of their systems, by prognosis of a return on investment. Considering the pharmaceutical R&D efforts of the order of US $ 50 billion worldwide, CPC/Mainz sees a potential for an increase in profit of more than US $ 15 billion if micro reactors are implemented consequently [246].

1.9
Application Fields and Markets for Micro Reactors

1.9.1
Transportation/Energy

Many authors mention the use of micro reactors for fuel processing as one of the most promising fields [1, 104]. Wegeng et al. point at using this micro-fuel processing for transportation [1]. The placement of reformers under the hood of an automobile for converting liquid hydrocarbons to hydrogen is explicitly mentioned.

Accordingly, serious commercially oriented attempts are currently being made to develop special gas-phase micro and mini reactors for reformer technology [91, 247–259]. This is a complex task since the reaction step itself, hydrogen formation, covers several individual processes. Additionally, heat exchangers are required to optimize the energy balance and the use of liquid reactants demands micro evaporators [254, 260, 261]. Moreover, further systems are required to reduce the CO content to a level that is no longer poisonous for a fuel cell. Overall, three to six micro-reactor components are typically needed to construct a complete, ready-to-use micro-reformer system.

Since space and weight savings are essential technical goals in reformer development, it is not sufficient to manufacture only one or a few components in miniature. Long and extensive research was carried out especially by research groups at Forschungszentrum Karlsruhe [248], Battelle (Richland, USA) [262], and PNNL (Richland, USA) [247, 250–256, 260, 263]. The PNNL work is governed by the strategy of employing micro reactors for mobile tasks concerned with energy supply and temperature control [255, 264], in particular focusing on outer space and military applications [90, 91]. As an example of outer space research, fuel generation in micro reactors was tested, e.g. by using Sabatier and reverse water-gas shift reactions for future Mars missions [265, 266].

Mini reformers undoubtedly are of interest for the automobile industry and have attracted considerable attention despite the considerable technical problems to be solved. Enlarging the scope of possible applications, mini reformers with a power supply notably higher or lower than needed for car use are currently being evaluated. This includes battery replacement, e.g. as an energy source for laptop computers (see also [262]) or energy supply for households without mains connection (stand-alone supply). Among the components developed are a micro evaporator (volume 0.3 l) for a 50 kW fuel cell [260], a micro heater (weight 200 g) for 30 W power and 85% efficiency [267], and portable energy sources with 10–100 W power (base unit of 21 cm length) [255, 268]. A compact steam reforming reactor (total size 4 l) for automobile applications achieves a conversion of 90% concerning isooctane and serves for the supply of a 50 kW fuel cell [247] (see also [269] for an industrial description of a micro-flow reformer development and testing for the automotive industry).

Fuel processing is not discussed in a separate, detailed chapter within this book; this will be done in Volume 2.

1.9.1.1 How Far is the Development? A Critical Review

Already in 1996, Wegeng et al. admonished that for the development of miniaturized reformers, e.g. especially facing the provision of hydrogen as fuel for transportation, several main issues have to be solved which probably will need a considerable time; among them are the reduction of the CO level, the high energy intensity of conventional reforming processes, the need for thermal integration, and the slow dynamic response of the reformers [1]. Within the last 7 years, after this first comprehensive analysis in 1996, there have been considerable scientific achievements concerning reformer and catalyst development. However, these investigations still appear to cover mainly one or a few aspects only, rather than providing a complete system approach. No flow sheets have been published on the total micro-channel reforming process, making evident the advantageous integration or reaction and heat transfer features [1]. However, with regard to a total-system approach for mobile applications, a conceptual design for a fuel cell-based portable power system of size 8–10 cm^3 was proposed [255] (see also [5]).

A growing number of research groups are active in the field. The activity of reforming catalysts has been improved and a number of test reactors for fuel partial oxidation, reforming, water-gas shift, and selective oxidation reactions were described; however, hardly any commercial micro-channel reformers have been reported. Obviously, the developments are still inhibited by a multitude of technical problems, before coming to commercialization. Concerning reformer developments with small-scale, but not micro-channel-based reformers, the first companies have been formed in the meantime (see, e.g., <www.hyradix.com>) and reformers of large capacity for non-stationary household applications are on the market.

1.9.2 Petrochemistry

Wegeng et al. mention the use of efficient, compact reactors for the conversion of methane to syngas, making natural gas an alternative to petroleum [1]. They see more potential in using the high-temperature partial oxidation of methane as a fast process than the slow steam reforming. In the latter case, short residence times may be utilized due to the speed of the reaction, permitting high productivity for compact reactor sizes. An estimative calculation of the capacity of a 1 m^3 reactor for the partial oxidation of methane predicts a capacity of 1 000 000 ft^3 of hydrogen per day.

1.9.2.1 How Far is the Development? A Critical Review

Petrochemistry has always been a topic in the discussion of possible micro-reactor applications. However, reported micro-reactor developments have not yet entered the field. This may be due to the large gap between the size of current micro reactors and that required for petrochemistry. Already the first demonstrators probably need to be of considerable size. It would not be surprising if an industry that is used to handling very large-scale equipment was the latest to enter such a new emerging field as micro-chemical processing.

1.9.3 Catalyst Discovery and Optimization via High-throughput Screening

Micro reactors can be used as part of the equipment for high-throughput screening [5, 104]. Schouten et al. even say, 'Microreactors are the natural platform for parallel screening and high-throughput testing ... of new catalysts ...' [104]. Micro reactors are also regarded as perfect tools for investigating intrinsic kinetics [104, 270]. Generally, a specific workflow for micro reactors needs to be developed on the basis of combinatorial methodologies to exploit its potential fully (see [271] for an example focusing on minimizing signal dispersion for a serial HTE apparatus).

Several reports underline the ability of micro reactors to perform catalyst testing for process development [187, 272–274] and for high-throughput screening [275–279]. Kinetic data have been extracted and the capability of both fast serial [272, 273], and parallel [275–279] screening has been demonstrated. The range of reactions investigated is large, covering, e.g., hydrogenations of double bonds [272, 273], ammonia oxidation [187, 280–282], and phosgene generation [274].

In-depth knowledge on the catalysts themselves, in addition to the reactions, could be gained, e.g. concerning turnover frequencies [280–282] or the internal composition, morphology, and microstructure of the catalyst [283–285]. Catalyst coating processes are of a much higher standard than some years ago [283–285]. Specialized micro reactors are available for kinetic data acquisition, such as a cross-flow, mini-short-bed reactor [286, 287]. Criteria on judging mass- and heat-transfer limits have been proposed recently, allowing an in-depth analysis of the suitability of these tools and reaction conditions to give reliable kinetic data [181, 286, 287].

It should be noted that ultimately the methods developed for catalyst HTE testing can also be applied to the discovery of new process parameters and new materials.

1.9.3.1 How Far is the Development? A Critical Review

The above given conclusions make it very clear. The investigations concerning catalyst testing and screening are of a high standard today, at least from a scientific point of view. These developments are, besides the organic investigations (see Section 1.9.5), actually one of the major drivers pushing developments in micro-reaction technology.

Many high-ranked catalysis experts have opened their research to micro-reactor studies and have become active. Engineering and catalysis journals have their eye on the field. Thus, cross-border expertise is approaching chemical micro processing. Virtually all chemical-engineering conferences have a micro-reactor session. One can say that micro reactors are now accepted and in a positive sense being 'absorbed' by the catalysis community.

BASF activities have shown that one can make money by investigating gas-phase reactions for process development. If Degussa and Krupp-Uhde have built a very large micro reactor with outer dimensions of more than 1 m, obviously there must be an economic reason for that.

Not to raise too much euphoria, it should be remarked that still much more work has to be done to obtain real, well-founded achievements compared with conventional attempts. The known micro-reactor investigations are a nice piece of work, but still have some kind of feasibility character. However, there is so far no outstanding achievement that can really be regarded as a breakthrough. As an outstanding result, something similar to that achieved by developing the maleic anhydride process (Contractor process), as a selective oxidation in the gas phase, can be envisaged. Here, reactor engineering, catalyst development, heat recycling, phase separation, and many more go hand in hand.

1.9.4 Bulk Chemicals and Commodities

There is not much to be said about the use of micro reactors for bulk chemicals and commodities. Wörz et al. are so far the only ones who have disclosed their work on the potential of micro-structured reactors for the optimization of chemical processes performed on a large scale of industrial relevance [110, 112, 154, 288–290]. This included a fast exothermic liquid/liquid two-phase reaction, which was used for the industrial production of a vitamin intermediate product, and a selective oxidation reaction for an intermediate, a substituted formaldehyde derivative.

1.9.4.1 How Far is the Development? A Critical Review

Wörz has often stressed the importance of using micro reactors as information tools for large-scale production, giving precise information otherwise not achievable [28, 110, 112]. This information is transferred and applied at the production stage, without changing the equipment from conventional to micro, but only affecting the setting of process parameters. In written form, there has been not a very large response to these ideas, i.e. not many follow-up articles by other industrial authors from the major chemistry players have appeared. This stands in obvious contradiction to the large potential provided and the clear evidence given so far by Wörz et al. and others. Maybe it is done in a hidden way due to the secrecy needs of industry (see, e.g., a patent on the use of a micro reactor for one step of the large-scale Hock process [183]). Probably, the large cost pressure in the field of bulk chemicals and commodities does not allow a search for novel, innovative means in laboratory-scale development. Having in mind, however, that Wörz stated that BASF "... would have saved many years of production at low yields" [28]. Thus, considering that obviously his investigations led to enormous cost savings of BASF processes, one might dare to question if this attitude is really fully correct.

1.9.5 Fine Chemicals and Functional Chemicals

1.9.5.1 Fine Chemicals – Drivers and Trends

Specialty chemicals divide into fine and functional chemicals (Figure 1.37). Fine-chemicals manufacture today is undergoing a substantial change. Thus, before

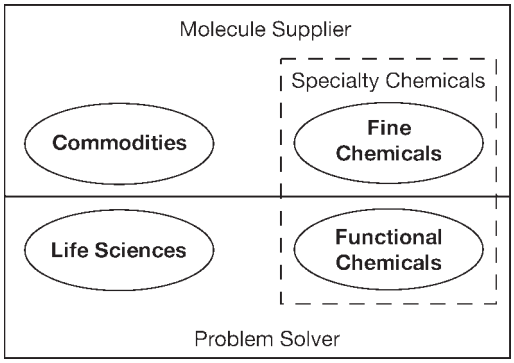


Figure 1.37 Diverse fields belonging to the class of specialty chemicals (redrawn from [137]).

having a look at the state-of-the-art of micro reactor use for fine chemicals, it is worth considering the changes that are occuring in the field. They will create – and already have created – a demand for using micro-reactor technology.

The classes of fine chemicals and functional chemicals are subsumed under the term specialty chemicals. This field is undergoing major changes at present and may need to employ micro-channel technology. ICI, for example, sees the following as current key trends and challenges for specialty chemicals [291]:

1. a move from molecule synthesis towards efficient delivery for the industry's products
2. requirements for sustainable products and services
3. trend to greatly increased regulation of chemicals
4. globalization of products, but at the same time growth in mass customization of products
5. multi-functionality of products as increasing requirement.

Points 1 and 5 refer to the increased importance of functional chemicals [291]. Owing to the wide parameter space determining functionality (not only molecular diversity), this demands much higher flexibility and speed in the preparation of new samples during the research phase. The behavior of complex molecular mixtures needs to be understood. In particular, product application, formulation, and blending skills need to be developed and acquired. In a more remote vision, this demands on-site distributed manufacture of functional chemicals such as paints and similar products.

Points 2–4 are related to green chemistry (see Section 1.1.6), sustainable development (see Section 1.1.6), and process intensification (see Section 1.1.9) which may need micro reactors as a preferred tool [291]. All these efforts are due to rising pressure from customers, regulators, and non-government organizations (NGOs). Once accepted as an unavoidable barrier, the only change for the chemical companies is to face this challenge and see it as an opportunity for profitable growth. One feature of sustainable development may be the upgrading of waste streams to first-quality products and high-efficiency processing of all raw materials.

Globalization creates a need to source complex products with a high degree of consistency across the world [291]. This, in turn, demands a well-defined and transferable process technology. A massive, local customization requires product availability in great variety close to the customer, demanding process intensification, modular operations, transportable plant, and fast response and product changeover. Multifunctionality demands a wider space in formulations and a chemistry set to deliver 'dial-in functionality', which needs assembly from a consistent set of basic materials.

1.9.5.2 Fine Chemicals – State of the Art of Micro-reactor Use

Fine chemicals are most commonly made using a large variety of organic (and inorganic) reactions. Hence the use of micro reactors for fine chemicals requires in-depth information about their performance with regard to several classes of (organic) reactions In this context, one should be aware of the huge steps forward that the performance of organic reactions in micro reactors has made in the past 5 years or so, which are summarized below.

Many of the known chemical syntheses such as Wittig [29, 165], Knoevenagel [29], aldol [292], Ugi [29, 293], Michael addition [29], Hantzsch [29, 156, 157], Diels–Alder [294], Azo coupling [136, 182], Suzuki coupling [29, 155] or enamine [29, 295] reactions (Table 1.8), to name but a few, have been carried out successfully in mi-

Table 1.8 Organic reactions conducted in a micro-chip reactor and details of the corresponding experimentation (redrawn from [29]).

Reaction	*Chip material*	*Solvent*	*Conversion (%)*	*Comments*
Suzuki	Glass	Aq. THF	67	EOF
Kumada coupling	Polypropylene	THF	60	Syringe pump
Aldol	Glass	THF	100	EOF
Nitration	Glass	Benzene	65	EOF
Wittig	Glass	MeOH	39–59	EOF
Enamine	Glass	MeOH	42	EOF
Ugi four-component coupling	Glass	MeOH		EOF
Peptide synthesis	Glass	DMF	100	EOF
Synthesis of pyridazinones	Glass	EtOH/AcOH	30	EOF
Synthesis of amides from amines and acid chlorides	Glass	DCM	77	EOF
Diazo coupling	Glass	MeOH, MeCN	37, 22	EOF
Aminothiazole synthesis	Glass	NMP	58–100	EOF
Knoevenagel	Glass	$MeOH/H_2O$	59–68	EOF
Hantzsch thiazole synthesis	Glass	NMP	58–100	EOF
Michael addition	Glass	EtOH	95–100	EOF
S_N2 alkyl halide	Glass	DMF/H_2O	25	EOF
Dehydration	Glass/PDMS	EtOH	85–95	EOF or syringe pump
Photochemical	Silicon/quartz	Me_2CHOH	60	Syringe pump
Phase transfer	Glass	EtOAc	100	Syringe pump
Fluorination	Ni or Cu	Nitrogen gas	90–99	Syringe pump
Fluorination	Silicon/Pyrex	MeOH	80	Syringe pump

cro-structured reactors and in most cases with improved results compared with macro-structured reactors (see also [29]). Fluorinations [164, 167, 193, 197, 296, 297], chlorinations [127], nitrations [152, 298–302], hydrogenations [303–306], and oxidations [18, 147, 150, 159, 162, 163, 178–180, 186, 307, 308] have been described in numerous examples. The range of chemical conversions includes many known chemical reaction mechanisms such as additions [151, 159, 162, 163, 307], eliminations [129, 304, 309–313], nucleophilic substitutions on aliphatics [314], electrophilic substitutions on aromatics [152, 164, 167, 298, 299], cycloadditions, radical polymerizations [21, 315] and more (see also a selection in [4, 316]).

The potential described above is not only of a scientific nature, as all these publications impressively prove. Indeed, it has been applied to bench-scale, pilot-scale and production-scale processing. Examples refer to the fields of Grignard reactions [11], polymerizations [21], boron chemistry [317], and azo pigment generation [136].

Fine-chemical companies have definitely shown interest in micro-reaction technology (see also the commitment in [137]) and have formed their own task forces for this purpose. The increasing number of patents is further proof of the beginning commercial use of micro reactors (see, e.g., [318–321]).

1.9.5.3 Functional Chemicals

Following a theoretical analysis of distributed small-plant manufacture, Benson and Ponton define assessment criteria for processes suitable for such processing [139]. Since micro reactors are one of the favorite and natural tools for distributed manufacture, this selection list also defines micro-reactor applications. In this context, the authors, probably in one of the first regular citations, emphasize that formulation processes, especially those with multiple ingredients, are particularly suited for distribution. The making of paint 'on-site' is referred to as an already existing way to do so. It stands to reason to augment the scope from formulations to functional chemicals.

Meanwhile, many investigations have paved the ground for the use of micro reactors with functional chemicals. Among these is work on emulsification [322–326], foaming [327, 328], creaming [329], and particle formation [17, 136, 330–332].

Noteable are recent studies on the generation of polymer particles as carriers for controlled drug release [333] and of cationic solid lipid micro-particles as synthetic carriers for the targeted delivery of macromolecules to phagocytic antigen-presenting cells [334]. The industrial interest, although rarely disclosed, is evident from the patents filed in the field (see, e.g., [335, 336]).

1.9.5.4 How far is the Development? A Critical Review

The PAMIR study predicts fine chemicals as one of the first fields where commercialization of micro-reactor technology will start [241, 337]. The small quantities, sometimes only in the kilogram range, and the large margins make the substitution of existing processes by micro reactors attractive. Currently, we can see the first signs of this, e.g. the work of Merck, Siemens-Axiva, Clariant and others.

The corresponding scientific investigations have advanced considerably in recent years. Together with the field of catalyst testing and screening (see Section

1.9.3), the conducting of organic reactions which could be applied to fine chemicals has made a huge step forward.

However, in contrast to the field of catalysis, not many high-ranked organic chemistry experts have so far opened their research to micro-reactor studies and have become active (for some exceptions see, e.g., [29, 47, 338–341]). Organic synthesis journals and conferences have yet not recognized to a great extent micro reactors, an exception being [82, 342]. This is, however, not true for researchers oriented towards analytical chemistry. In conjunction with μTAS developments, more and more work is being done in that area.

The organic chemists in academia still stick to their flask glassware. Here, certainly, some time is needed and education has to be provided. Micro-chemical engineering, as the name indicates, still remains a domain of the engineering society. Nonetheless, the fine-chemical companies have accepted micro reactors; the push will come from the industry side.

1.9.6 Cosmetics and Foods

There is one report on the use of micro reactors for cosmetics [323] and none for foods. Of all the topics mentioned, these have the smallest number of reports.

1.9.6.1 How Far is the Development? A Critical Review

In view of the prognoses of the PAMIR market study, predicting at least a certain interest for these fields, this is astonishing, in particular when compared with the great interest stimulated in the field of reaction engineering. The surprise becomes even larger when reviewing also the large potential forecast for functional chemicals (see Section 1.9.5), which is related to cosmetics and foods with regard to the type of processing. From the authors' own experience, it can be said that industrial investigations are being undertaken, but not being published.

1.9.7 Extra-terrestrial Processing

Gavriilidis et al. review the use of lightweight, compact chemical systems for application in the space sector [5], referring to original work done in this field [91]. The latter work was done for the NASA In Situ Resource Utilization (ISRU) program, designated for future missions to Mars. The investigations were aimed at the In Situ Propellant Production (ISPP) by converting the carbon dioxide of the Martian atmosphere to propellants and oxygen for the return trip using stored hydrogen, thereby decreasing the launch mass. Highly energy efficient micro-channel systems use extensive recuperation and energy cascading to minimize thermal and electrical wastage.

ISPP units are not the only micro device units of interest for space applications; micro fuel cells, compact cleanup units for water treatment, portable heating and cooling units and devices for chemical processing and mining are considered [91].

1.9.7.1 How Far is the Development? A Critical Review

Significant challenges exist when applying micro reactors to outer space; the latter will require adaptations, e.g. concerning fluid flow. Energy management has to be improved to yield the predicted major benefits for spacecraft size and payloads [91]. The investigations are long-term oriented, i.e. can profit from more funding in the coming years, as the first manned Mars mission will probably not come sooner than in 10 years. Nonetheless, at that time results will be demanded, as for such large, strategic developments no delays will be accepted.

1.9.8 Chemical Analysis, Analyte Separation, Assays and Further Diverse Applications in the Bio Field

μTAS components and systems exhibit sensor and analytical separation functions. DNA analysis, performance of polymerase chain reactions, clinical assays for pH, enzymes, proteins, oxygen etc., trace pollution monitoring and other sorts of biological analyzes are at the focus of recent developments [5]. Another reference lists environmental monitoring (including speciation), clinical monitoring, and quality control in production processes as applications of μTAS equipment in chemical analysis [30].

Since further reviewing μTAS could easily fill a separate book and is mostly concerned with biochemical applications, it was excluded from this book. Therefore, the description of these applications is beyond the scope of this chapter. The reader is referred to original reviews [31, 32].

Auroux et al. give an up-to-date description of the application of μTAS components and systems, including cell culture and cell handling, immunoassays, DNA separation and analysis, polymerase chain reactions, and sequencing [43] (see also [44] for a description of the μTAS components and systems).

Major drivers for using micro-channel chip systems for chemical analysis are low reagent consumption, low energy consumption, high reliability, good robustness also in the hands of personnel not trained in analytical chemistry, and low maintenance requirements [30].

Concrete applications of micro reactors for chemical analysis, albeit so far not a core application, have been described [5]. Among other uses in chemical analysis, micro devices for gas chromatography, infrared spectroscopy, and photoacoustic detection are mentioned.

1.9.8.1 How Far is the Development? A Critical Review

μTAS applications are very developed, at least from a scientific and technical point of view. For some of the applications given above, even commercial chips are available. A detailed description and a far-reaching analysis of these are not the topic of this book, as outlined earlier.

So far, micro-reactor developments apart from μTAS sector have not been used to a great extent for analytical purposes. Merging this technology base with that of μTAS devices, e.g. for hybrid assemblies, could have some potential.

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