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Microreaction Technology as a Novel Approach to Drug Design, Process Development and Reliability

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Abstract:

This paper focuses on the application of microreaction technology in the life science industry. Certain features of microreaction technology, for example, mixing, heat transfer, and residence time distribution, are discussed. Important advantages such as high operational safety and the possibility to transfer the experimental results directly from laboratory to the production of pilot-plant scales are mentioned. Potential application fields in the drug discovery and development processes, from research to production, by including chemical synthesis of different targets in the case of the quinoline acid derivative (ciprofloxacin) and the Paal−Knorr pyrrole synthesis are presented.

1. Introduction

The time and cost of developing drug compounds for the pharmaceutical industry have increased dramatically over the last three years.[1] Combinatorial chemistry and high throughput screening even speed up the identification of new lead compounds. However, the fast preparation of the first kilogram quantities of drug candidates and active ingredients represents an immense pressure to keep pace with developing processes for large amounts of drug substances. The increasing need to reduce cost and time consumption, improve process routes, and minimise environmental impact leads to an enormous interest in developing new technologies to be used as an alternative to or combined with conventional batch processes. In the past decades, a wide variety of methods have been developed for the realization of "state of the art" chemical synthesis. One strategic approach is to simplify the synthetic route by employing unique reactions such as "domino" or cascade transformation. Another strategic approach uses innovative technologies to improve the quality of synthetic reactions. Microreaction technology belongs to the latter one. Because of their reduced hold-up, high throughput potential, and the elimination of the scale-up process, microdevices have become of interest in chemistry, particularly for hazardous reactions in the early 1970s.[2] Microreactor devices are generally defined as miniaturised reaction systems fabricated by microtechnology and precision engineering. They are available today in different models and designs, and most of these are meant for research or have been designed for precisely defined applications.[3] The development of these microreactors was focused either on a specific process or simply on demonstration of the feasibility for a particular task. The emphasis in any case was not on creating a universal system that could be used for different applications such as development as well as production of pharmaceuticals and chemicals under manufacturing conditions. Providing scientists with an integrated and "ready to use" operating system has now been realized by CPC-Cellular Process Chemistry Systems, an innovative company involved in the design and fabrication of integrated microreaction systems and their application to a wide range of chemical reactions.

2. Definition and Features of Microreaction Technology

At least two basic functions can be assigned to the microreactor: initiate and facilitate a reaction through mixing of the reactants, to provide or remove reaction heat (heat transfer).

Microreactors usually consist of several stacked plates containing the microstructures in the submillimeter range **(**Figures 1 and 2). Because of flow structures with submillimeter dimensions in which the chemical processes occur, excellent heat transfer and improved mixing of the reactants compared to those for conventional systems can be achieved. These features provide the system with an exact control of the reaction temperature which significantly affects the quality of chemistry and the reproducibility of syntheses.

2.1. Mixing. Provided the most common case—the mixing of two miscible liquids in a macroscopic reactor, mixing occurs mainly due to the action of the following: (1) rather large fluid aggregates are coarsely spread over the reactor volume and (2) mixing proceeds via shear stress induced by vortexes. These decay under the action of turbulent eddy diffusion into smaller and smaller ones, which dissipate energy primarily through viscous shear and influence chemical reactions strongly if they show reaction time constants in the order of milliseconds. Examples are crystal nucleation and growth or in reactions which are sensitive with respect to stoichiometric ratio. To measure and characterise the micromixing in chemical reactors, fast and stoichiometrically sensitive reactions, such as described by Bourne et al.[4] as well as by Villermaux,[5] have to be employed. This type of reaction can be also used to optimise the mixer design as reported by Hessel et al.[6]

(1) Littlehales, C. The Price of a Pill. *Mod. Drug Discovery* **1999**, *2*, 21.
(2) U.S. Patent 3,701,619, 1970 and U.S. Patent 5,534,328, 1993.
(3) *Top. Curr. Chem*. **1998**, 194.
(4) Bourne, J. R,; Oemer, M. K.; Lenzner, J. *Ind. Eng. Chem. Res*. **1992**, *31*, 949−958.
(5) Fournier, M.-C.; Falk, L.; Villermaux, J. *Chem. Eng. Sci*. **1996**, *51*(23), 5187−5192.
(6) Ehrfeld, W.; Golbig, K.; Hessel, V.; Löwe, H.; Richter, T. *Ind. Eng. Chem. Res*. **1999**, *38*, 1075−1082.

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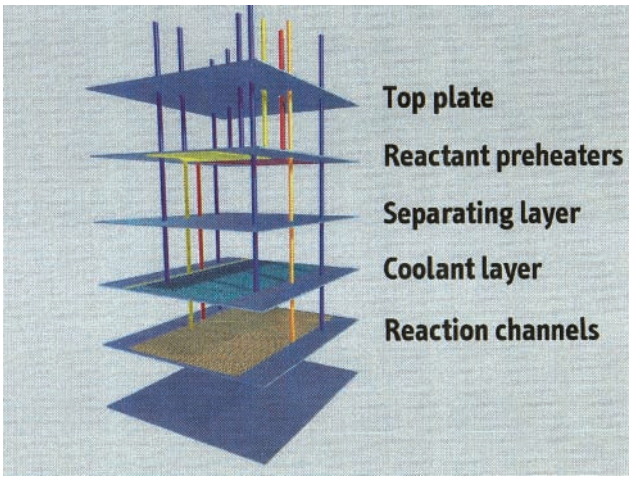

Figure 1. **Stacked plates architecture of microreactor (dimensions: 95 mm × 95 mm).**

Contrary to conventional vessel equipment, where mixing is provided by turbulence, microreactors are operating at much lower Reynolds-numbers, in the range of 2−200 (cf. Table 1). In this regime laminar flow conditions prevail, and the mass transfer is only dominated by molecular diffusion. From the molecular point of view, the mixing process can be then regarded as an in-stationary transient process that is described by a dimensionless diffusion time or Fourier-number Fo_d. This dimensionless number expresses the ratio between mean residence time to the diffusion time constant.[7]

$$Fo_d = \frac{t_{mean} D}{d^2}$$

where t_{mean} is mean residence time, D is diffusivity, d is tube diameter.

The same dimensionless number can be used to characterise the residence time behaviour of microfluidic elements. The majority of today's micromixers utilises the principle of *multilamination*, which is usually generated by division of the feed flows to several substreams and subsequent transformation into a layered arrangement. By applying multilamination, fast mixing of reagents via diffusion, in the range of a few seconds, can be achieved. Multilamination exhibits a smaller clogging risk of the channels in comparison to other miniaturisation concepts such as repeated splitting and recombining of liquid flows or collision of two high-energy substreams, termed microjet reactor, mentioned in ref 8.[8]

2.2. Heat Transfer and Temperature Control. The most important parameter influencing kinetics and product quality is the temperature at which the reaction takes place. This theoretical reaction temperature is not automatically identical to the measured temperature. Increasing a reaction temperature usually increases the reaction rate, but in most cases, with decreasing product selectivity. Therefore, exact temperature control is an essential factor to gain optimal process conditions. Efficient heat management is one of the most important advantages of microreactors. Removal of the reaction heat, particularly in fast or highly exothermic reactions, is the struggle while scaling up. The rate of heat transfer is directly proportional to the heat-transferring surface area, and for externally temperature-controlled vessels the specific rate of heat transfer decreases with larger volumes. Therefore, the surface-to-volume ratio represents a key parameter for temperature control via external heat transfer. For a flat microchannel with a width of 100 μm the specific surface-to-volume ratio is 200 cm^2/cm^3, whereas it is about 1 cm^2/cm^3 for a 100 mL flask, 0.084 cm^2/cm^3 for a 50-gal reactor and only about 0.06 cm^2/cm^3 for a 1 m^3 vessel. As demonstrated by these numbers, microreactors have, caused by the remarkable surface-to-volume ratio, a heat-exchange capability that is orders of magnitudes better than with conventional vessels. Hot spots, which lead to unfavorable selectivities and the formation of by-products, can be avoided. Thermal conditions even in laboratory glassware are not comparable to those in microreactors.

The diagram in Figure 3 illustrates the steady-state temperature profile in a 70 μm high microchannel fed with acid and base solutions from the left. This neutralisation reaction is combined with a high specific heat release (reaction enthalpy −55 kJ/mol). The hot spot of just 3 K is fairly low compared to 60 K in conventional glass equipment, measured by thermographic camera. In addition short contacting times of the reagents can be realised in a continuously running microreactor system which leads to less by-product formation.

Due to the efficient heat transfer in microreactors, the reaction can be carried out at the *actual reaction temperature* that is in most of cases much higher compared to those for conventional processing. At first glance this appears to be difficult to understand. The diagram in Figure 4 explains this phenomenon. According to the fact that main part of chemical reactions is exothermic and because of poor heat transfer in macroscopic equipment, there is often a significant hot spot at the feed location. This affects yield and selectivity of the reaction, whereas the measured temperature is some measure of the mean reactor temperature. A microreaction system producing the same quality operates at a temperature that is identical to the that of the hot spot of the macroscopic equipment. This indicates that the reaction can be run at higher temperature than its mean temperature. Contact times of the reagents as well as the time period where the reactants are subjected to higher temperature have to be considered. On the right side of Figure 4 the transient temperature behaviour is plotted. In many highly exothermic reactions the reaction control is performed by slow dosing of the reagents. On the other hand, the reactants in a microreactor can be added simultaneously, which leads to much shorter residence times and favors reduced by-product generation. Also beneficial is that in some cases the reaction temperature can be increased without violating the conventional quality limits such as selectivity and yield.

Furthermore, as a consequence, the *dosing time*, which is a significant part of the reaction time, becomes unneces-

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(8) Löwe, H.; Ehrfeld, W.; Hessel, V.; Richter, Th.; Schiewe, J. *IMRET 4*, 4th International Conference on Microreaction Technology, 2000; pp 31−45.

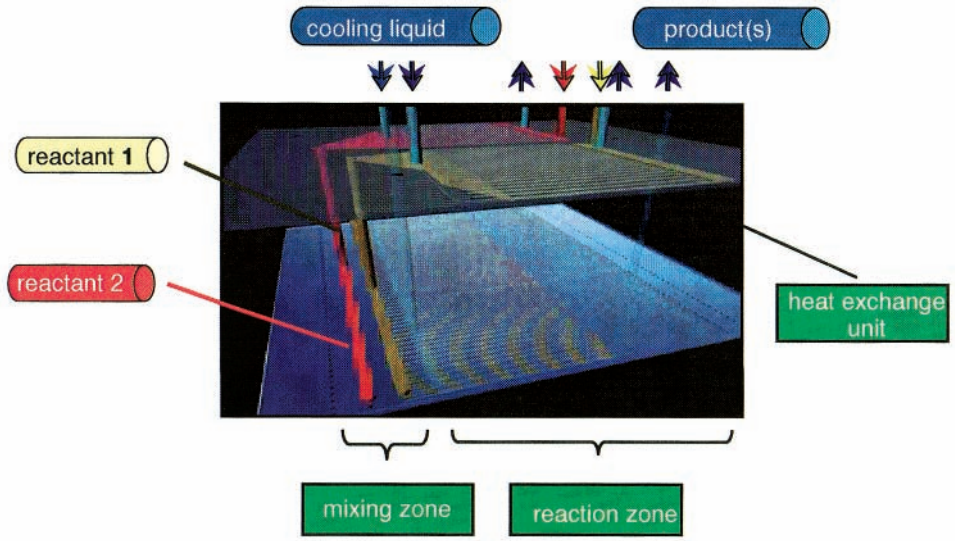

Figure 2. **Inside a microreactor (dimensions of reaction channels: 0.5 mm× 0.5 mm).**

Table 1. **Reynolds numbers for different channel arrangements at different flow rates**[a]

flow rate (mL/min)[b]	1.0	3.0	6.0	10.0
8 × 4 mm × 200 μm	0.99	3.0	5.9	9.9
16 × 4 mm × 100 μm	0.51	1.5	3.2	5.1
32 × 4 mm × 50 μm	0.26	0.77	1.5	2.6

[a] Constants: viscosity and density of water at ambient conditions, kinematic viscosity of 10^{-6} m^2/s. [b] Channel data: number × width × height.

sary. As an example, low-temperature reactions, as required for organometallic reactions, can gain new perspectives for reaction engineering. *Real reaction time*, without any dosing time, and the *actual reaction temperature* of conventional processes become considerable process parameters. Due to the high heat conduction rate, caused by microscopic wall thickness, the material of the reactor does not play a significant role for the heat management which gives chemical engineers more flexibility with respect to unusual materials such as ceramics or polymers—particularly from corrosion considerations—an important alternative.

2.3. Residence Time Behaviour. Usually, continuous processing is assigned for reactions that need rapid heat transfer, for preparing unstable compounds, and for reactions which are more complex, like heterogeneous reactions or catalytic conversions. Whereas continuous operations are generally used for large-volume products, batch processing operations are more commonly used for making drug substances and intermediates. CPC-Systems' technology has realised in its miroreactor, *CYTOS*, an appropriate combination of the advantages of a continuously operating system and the benefits of microreaction technology, predominantly with respect to constant product quality and flexible product quantity which are important issues in drug development. However, the residence time behaviour in a continuously running system is a considerable factor in terms of quality control. The residence time distribution should be as narrow as possible to have the same "history" for each reactant volume element and to be able to run reactions in sequences within a short time.

Under the action of the pronounced parabolic velocity profile found in laminar flow a concentration peak injected at the inlet will be soon dispersed, yielding a broad residence time distribution at the outlet, in the case of capillary tubes used in microreaction systems. Nevertheless, the diffusion in the radial direction limits this peak-broadening. The technology group at CPC-Systems derived design rules that account for this effect and which can be used as a pre-optimisation tool in microreactor design. For more complex flow structures simulation tools, for example, CFD, have to be employed. However, a numerical approach has been developed to be more flexible with respect to geometry and boundary conditions. The model uses finite volume balances and makes some assumptions such as a fully developed velocity profile as well as neglecting diffusion in the axial direction.[9]

Similar to mixing behaviour, the resulting residence time curves are just dependent on one parameter, the dimensionless diffusion time or Fourier-number Fo_d. For a Dirac-pulse at the inlet the results can be summarised in terms of peak width at half of the peak height:

$$PW_{1/2} = 0.241 t_{mean} Fo_d^{-0.515}$$

Another, more complex simulation result based on this model is the temperature profile already presented in Figure 3.[7]

2.4. Operational Safety. Safe operation conditions include safe equipment, process operations, chemicals, and personal safety. Each chemical reaction should be considered for possible hazards, including reaction exotherms and safe handling of reagent, solvents, and product during a operation. Many time-consuming quantitative and semiquantitative assays, such as calorimetric determination of the reaction heat, have to be performed to ensure a safe process for production of a larger amount of a target compound. Due to their remarkably reduced hold-up, microreactors provide chemical reactions with an immense high operational safety. The hold-up in the microreactor is usually in the range of a

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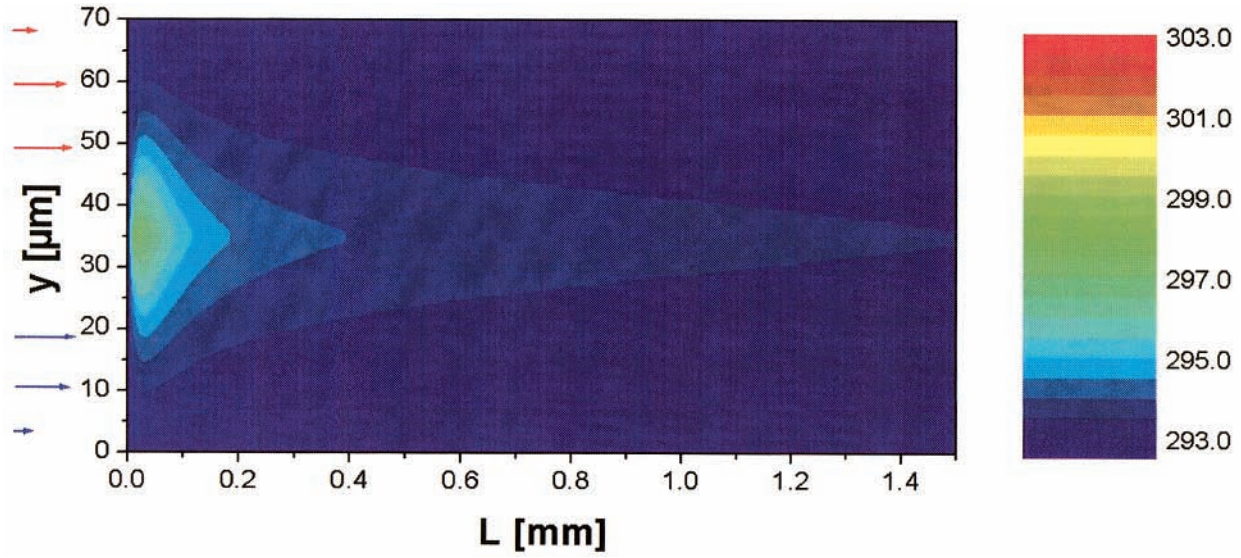


Figure 3. **Simulated temperature profile in a CPC-Systems microreactor. Isothermal boundaries (top and bottom). Parabolic velocity profile of 1.5 cm/s maximum. Reaction with high heat release (55 kJ/mol). Diffusion and thermal conduction in *y*-direction.**

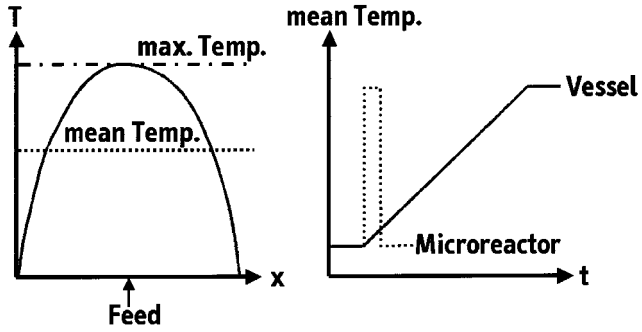
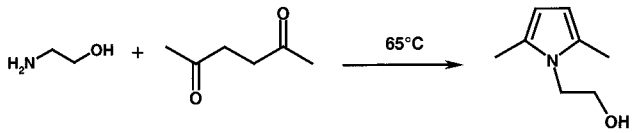


Figure 4. **Schematic of the axial temperature profile in a batch reaction vessel and temperature plot in case of gradual dosing.**



Process Specification	
Throughput	136 g/h
Running time	7.8 h (460 min)
Reaction temperature	65°C
Simultanous Working-Up	8 h
Isolated Yield	1064 g (98 %)

Figure 5. **Paal−Knorr pyrrole synthesis as an example for a neat (solvent free) reaction in CYTOS.**

few milliliters. Combined with the flame-arrestor effect in microchannels and their excellent pressure resistance, microreactors are inherently safe tools for lab-, pilot-plant, and production-site operation. The necessity for process safety studies becomes smaller, potentially dangerous and runaway reactions can be handled more safely, and the invested time in process development can be reduced considerably.

2.5. Environmental Assessment, "Green Chemistry". The political importance of minimizing environmental impacts is rising with enhanced appreciation of our finite environmental resources. Optimal use of material, energy, and consequent waste management can be recognized as important methods for environmental protection.[10] In the case of minimizing waste there are two approaches: the traditional approach aims at reducing waste "*at the end of pipeline*", for example, decreasing emission by catalytic incineration of exhaust fumes, and so forth. The second approach is based on minimizing waste "*at the source*". In this case innovative methods and procedures have to be employed to change the usual production way right from the beginning. Alternative synthetic routes with enhanced selectivity as well as neat (solvent-free) reactions belong to the latter approach.

Due to the unique heat transfer ability of microreactors, many chemical reactions employing liquid reactants can be achieved without using a solvent (neat reaction). Paal−Knorr pyrrole synthesis,[11] presented in Figure 5, is an example of the first kilogram synthesis of an exothermic reaction under solvent-free conditions in one microreactor.

Application of microreactors in parallelised arrays (numbering-up) enable fast switching to pilot-plant production quantities, a tremendous potential for time and investment savings compared to scale-up procedures. A further environmental benefit results from (potential) improvements in selectivity and yield because of the higher quality of temperature and concentration control only possible when using microreactors.

3. Proof of Principles

Microreactors do not provide new chemistry. However, according to the previous chapters, they open up the opportunity for better chemistry. Limited reaction control or disturbances, respectively, caused by poor heat management (hot spots) or concentration gradients, can prevent optimal results in conventional vessels. Applications of microreaction technology in chemical synthesis urge the

(10) Glauser, M.; Müller, P. *Chimia* **1997**, *51*, 201.

(11) Buu-Hoi Ng, P.; Xuong Ng, D.; Gazave J. M. *J. Org. Chem.* **1955**, *20*, 639−642.

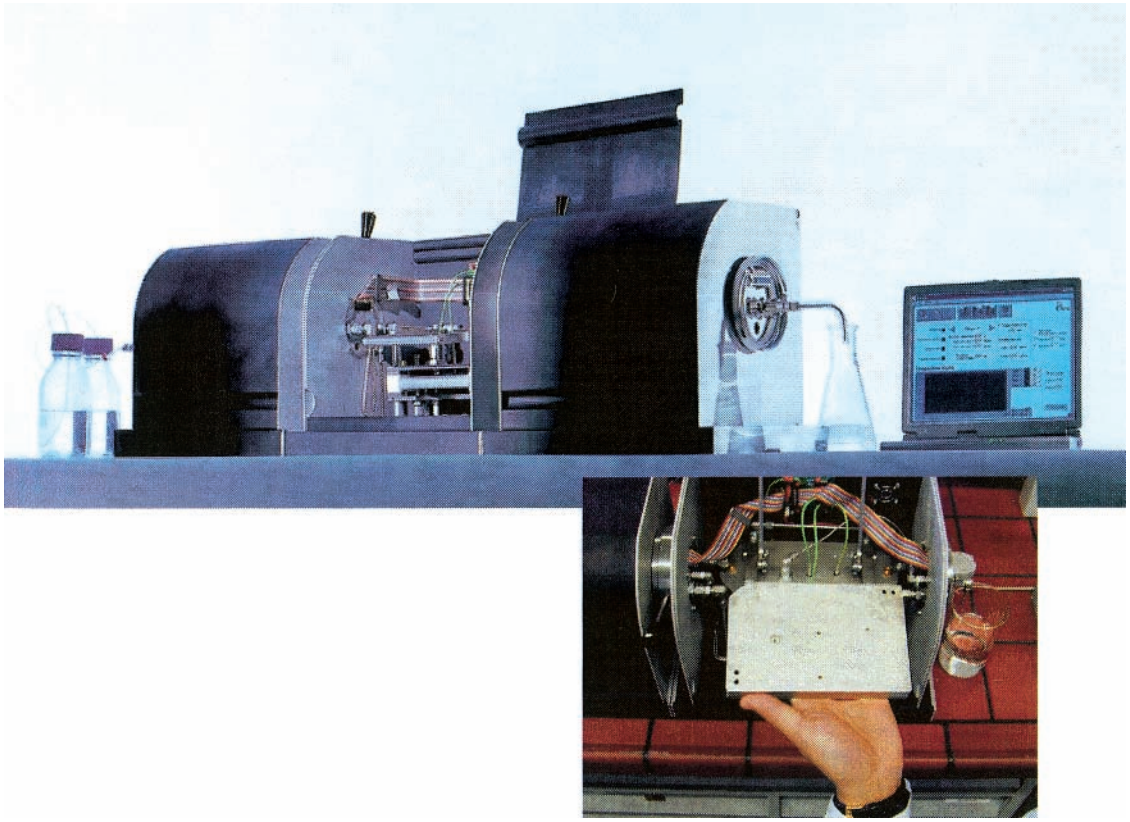


Figure 6. **CYTOS-Microreaction System, the world's first modular microreactor system. "micro" only where "micro" is required, in the exchangeable reaction unit, CYTOS (dimensions: 100 mm × 150 mm).**

incorporation of microreactors in an integrated system that offers maximum flexibility toward the different reaction types and various reaction conditions. The availability of a standard microreactor system for a wide range of applications is of a great benefit for progress of microreaction technology. Focusing on this purpose, CPC-Systems has developed the world's first modular microreaction system based on an easily exchangeable microreactor, called *CYTOS* **(**Figure 6), the unique heart of CPC-Systems' advanced technology. It has the size of a videotape with a hold-up of 1.8 mL. The high surface-to-volume ratio for the mixing section as well as for the temperature controlled reaction channels allows heat transfer coefficients up to 2000 W/m^2 K.

3.1. Chemical Synthesis. Numerous applications are stated in the literature which can be considered as proof of principle for microreaction technology in general. Microreactors have been used in commodity synthesis, that is, ethylene oxide[12] and HCN,[13] and have also been used in polymerisations. CPC-Systems' microreactor, CYTOS, was designed for broad applicability in organic synthesis. More than 50 reactions from different reaction classifications have been performed successfully in CYTOS-based modular standard systems.[14] Examples include different reaction classes such as:

- organometallic reactions such as Grignard-, BuLi-reactions
- nucleophilic substitutions
- nucleophilic additions
- electrophilic substitution to aromatic
- oxidations and reductions
- rearrangements
- condensations
- radical substitutions, etc.

In most cases, a positive effect in terms of yield and selectivity could be detected. The suitability of the CYTOS passed the test, in which a multistep blockbuster pharmaceutical (ciprofloxacin) synthesis had been successfully adapted for running in the microreactor (Figure 7). This synthesis has been applied for process patent by CPC-Systems and has demonstrated the potential for faster development, particularly in the preparation of relevant quantities for development studies, that is, clinical trials.

3.2. Chemistry of Highly Energetic Materials. "The investigation of energetic material is emerging from a field primarily directed toward practical interest to an advanced area of fundamental research, where state-of-the-art methods and modern synthetic procedure are used side by side".[15]

Microreactors open a new perspective in study of energetic materials. As already mentioned, fast mixing of the

(12) Richter, Th.; Ehrfeld, W.; Gebauer, K.; Golbig, K.; Hessel, V.; Löwe, H.; Wolf, A. *Topical Conference Preprints*; Process Miniaturization: 2nd International Conference on Microreaction Technology, March 9−12, 1998, New Orleans, LA; The American Institute of Chemical Engineers: New York, 1998; pp 146−151.

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(17) Noland, W. E.; Smith, L. R.; Johnson, D. C. *J. Org. Chem*. **1963**, *28*, 2262.

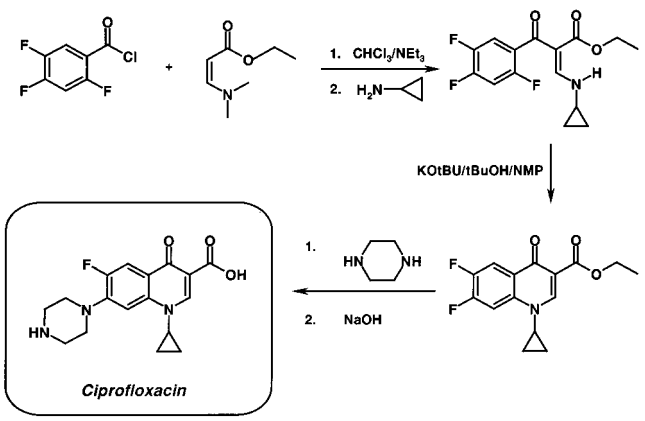

Figure 7. **Ciprofloxacin synthesis performed in CYTOS.**

reagent, exact control of reaction conditions, short contacting time, and high operational safety are beneficial features of microreactors which offer an appropriate facility to investigate and to produce energetic materials. Electrophilic nitration of aromatics has to be considered as a fundamental reaction with a great industrial importance for preparation of key organic intermediates belonging to highly energetic materials. Several nitration reactions with different nitration agents such as highly explosive acetyl nitrate, have been successfully performed in CPC-Systems' standard microreactor, CYTOS. In extremely short investigation time the selectivity and the yield of the reaction can be optimised, and the resulting reaction conditions can be applied to the production of the first kilogram amounts of the compound. The most of nitration reactions are inhibited reactions where the adding of the nitration reagent has to be maintained at much lower temperature compared to the actual reaction temperature. By applying a microreactor, nitration reactions can be run at the actual reaction temperature, the reaction heat can be removed immediately, and the contact time at the high temperature as well as the thermal stress of the product can be reduced. This is of great benefit, particularly for the nitration of heterocyclic compounds where in many cases even the first step, the protonation of the heterocyclic nucleus, is a highly exothermic reaction. In a two-step system arrangement the reaction medium can be quenched directly in a second CYTOS under exact temperature control to suppress multiple substitutions.

Examples in Figure 8 demonstrate the feasibilities of microreactors for carrying out reactions containing highly energetic materials. These assigned reactions have potential to be optimised toward yield and throughput.

3.3. Avoiding Scale-Up. As one progresses to larger and larger reactors, micromixing can become a greater concern, and tight temperature control gets more difficult, particularly with fast and exothermic reactions. Heterogeneous reactions, particularly gas−liquid or gas−liquid−solid reactions often create scale-up challenges due to the difficulties posed by mixing and intimate contact of components on scale. Conventional process R&D, scale-up and batch processing of organic reactions in tank reactors are usually a tedious and time-consuming procedure. Several process limitations such as: (1) reaction control, (2) mass transfer and agitation, (3) temperature range, (4) safety (high exotherms, runaways, and other hazards) have to be considered. The process often has to be adapted to available equipment, or if not, significant investments might evolve by implementation of special equipment. By using a continuous process instead of batch processing, microreactors can be used to synthesise kilogram- or even ton-amounts, particularly in parallelized arrays.

Numbering-Up Replaces Scale-Up! The same process developed in a microreactor can be used to produce pilot-plant quantities in an identical quality. In process development, no time is needed for the transfer of synthesis from lab-scale to a pilot reactor. This advantage cannot be overestimated since time to market as well as labour costs are very important issues for the pharmaceutical industry. The target compounds can be produced significantly faster and more efficiently. In several customised projects CPC-Systems has demonstrated the feasibility of this concept. First pilot plants and production modules for the preparation of ton quantities have already been installed at customer's sites by CPC-Systems. One example is shown in Figure 9. On the photograph the microreactor stack is displayed in front of its peripheric pumps. The system is tailored to the spe-

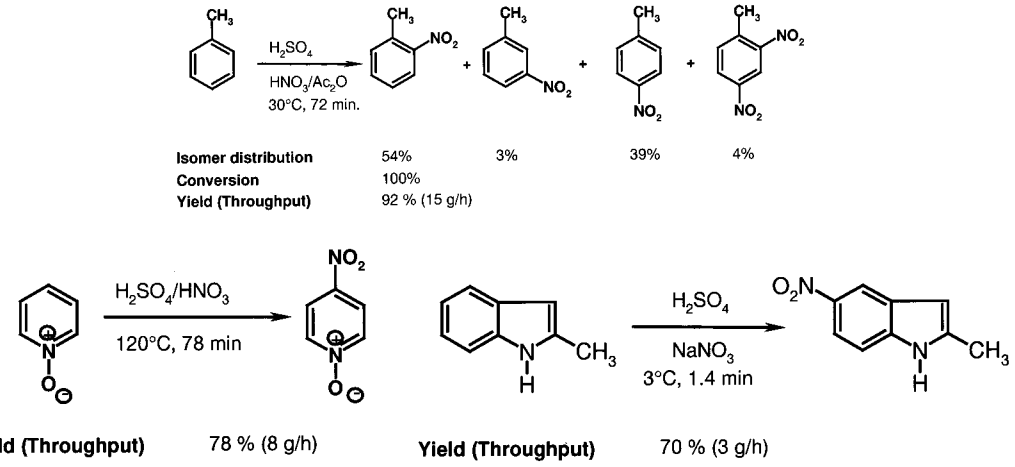

Figure 8. **Nitration of aromatic compounds by consideration of microreaction technology feasibilities. (a) Nitration of toluene[15] with highly explosive acetyl nitrate, *enhanced operational safety.* (b) Nitration of pyridine-*N*-oxide[16] at high temperature, *safe and ease of handling.* (c) Nitration of 2-methylindole,[17] *short contact time.***

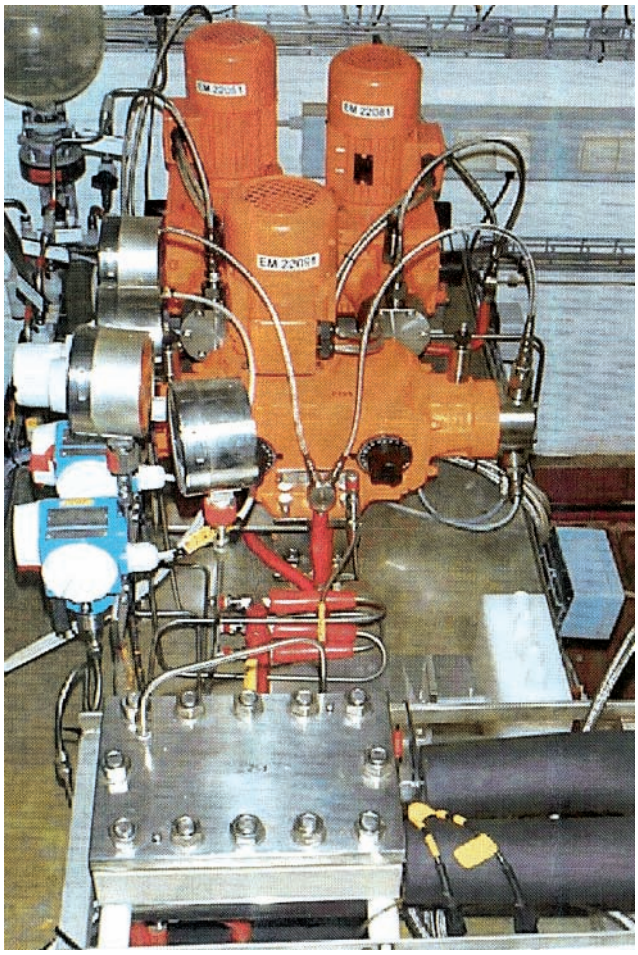

Figure 9. **CYTOS Plant (CPC-Systems' customised microreactor pilot-plant).**

cific demands of that precipitation process with a capacity of 30 t/a.

3.4. Process Optimisation. Microreactors are beneficial tools in the optimisation of chemical processes. Due to continuous processing, the modular microreactor system can be applied to the rapid screening of reaction parameters, such as temperature, time, relative concentration, and pH. In many cases it is possible to drive the reaction to the border of its inherent potential and then transfer this benchmark information to traditional scale-up studies. Reagent screening is an additional issue in process development, which is ensured by applying a microreactor system combined with manual

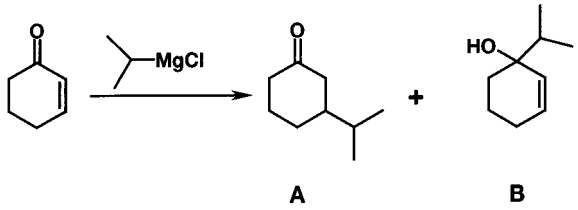

Figure 10. **Optimisation of a Grignard reaction toward regioselectivity.**

or automated feed sampling arrays. Obviously, online-analysis and software-supported optimisation of reaction variables can be adapted also to a modular microreactor system. In Figure 10 a Grignard reaction is shown as an example for a rapid process optimisation. The initial yield of 49% with a regioisomer ratio of 65:35 (A:B) could be improved to a yield of 78% with a regioisomer ratio of 95:5 (A:B) by investigating 14 different reaction conditions within 6 h.

4. Conclusions

Microreaction technology is inducing a paradigm shift by demonstrating the advantages of continuous processing over batch processing, from bench to production scale. The application of this technology to chemical synthesis is tied with the development of a new methodology which can generate the maximum increase in research and development throughput. CPC-Systems with its innovative technology, represents an interesting answer for the rationalisation of drug development processes. Microreactors will become a standard tool for chemists, not to replace, but to supplement existing technology. Its value for the life science and fine chemical industry is tremendous leading to a significant impact on R&D throughput and manufacturing quality. Today globalisation puts an immense pressure on margins and demands accelerated life cycles of chemical products. Therefore, time to market is of utmost importance. The shift from specific developments to standard systems has already started. CPC Systems' technology with its CYTOS microreactor centrepiece enables life science and fine chemical industries to achieve step-growth in chemical research and development throughput as well as in operational flexibility in manufacturing.

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