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Review

Development of microwave chemistry through a co-operation between a university and an equipment manufacturer

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Abstract

This mini-overview focuses on selected important details of reaction engineering in microwave chemistry and discusses the co-operation between the university working group "Alternative Energies" in Jena and the microwave plant MLS GmbH (Leutkirch/Germany).

Keywords: energy efficiency; microwave chemistry; MW-devices; overview; qualification; validation.

1. Introduction

The history survey of microwave chemistry informs that as early as 1973, the scientists Ponomarev and Tarasenko [1] reported on experiments which were focused on rubber vulcanization and the polymerization reaction of methyl methacrylate and styrene in benzene, in glass vessels or directly in the space of the metal microwave resonator. In the latter case, they observed a two-fold reaction acceleration at the beginning of the studied polymerization. This paper was predictive, cf. www.microwavetec.com/mwchem.php. This circumstance is not commonly known.

The use of high frequency waves as an alternative energy source for reactions and processes has been intensively investigated in laboratories and increasingly in scale-up versions over 25 years. It is well accepted that microwave-assisted chemistry was started about 1986 and with domestic microwave ovens by Gedye [2] and Giguere [3]. A plethora of scientific publications, monographs, and books [4–11] dedicated to microwave-assisted chemistry and technology is now available and useful for the solution of old and new synthetic challenges.

In the early days, reproducing reaction parameters such as conversion, yield, and selectivity, was often only possible with difficulty, or even impossible because of incomplete description of the experiments [12–14].

There are now commercial microwave setups with state-of-the-art techniques, sensors, and safety tools. Of note are: CEM (USA) [15], Biotage (Sweden) [16], Anton Paar (Austria) [17], and a number of smaller enterprises [18, 19]. The use of the microwave devices was/is realized by common acquisition or by intensive co-operation between the designer/manufacturer and a scientific institution. This article will, among other issues, discuss interactions between the plant "MLS GmbH (Leutkirch, Germany [20], and Milestone, Bergamo, Italy [21]) and the working group "Alternative Energies" at the Friedrich-Schiller-University (FSU) in Jena (www.ituc.uni-jena.de). All microwave producing enterprises have extended the possibilities of microwave-assisted reaction engineering by technical developments, e.g., tools for temperature and pressure measurement, continuous processes, and microwave leak sensors. With these new benefits, there is a growing interest in scaling-up microwave-based reactions and processes [22–24].

2. Principles of green chemistry and green engineering

Our present time is almost characterized by key words and/or time-relevant abbreviations, e.g., green, bio, micro, and nano. Everybody is informed on either sustainable or environmental or benign challenges. Chemists are (or should be) nowadays familiar with the 12 Principles of Green Chemistry. The definition of these was given firstly by Anastas and Warner [25]. Tang et al. condensed these principles into the mnemonic key word "Productively", cf. Scheme 1 [26]. One of the most important goals is to decrease the energy input of reactions and processes: "energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure." The development of energy sinks, here under microwave assistance, is an increasingly attractive important area of research.

A further mnemonic key word, also derived by Tang et al. [27], is "Improvements". This reflects a companion set of green engineering principles, cf. Scheme 2. Both sets of principles are well used in discussions, lectures, and presentations.

Green Chemistry and Green Engineering need to be combined with more environmentally friendly technologies, if step-change improvements are necessary in chemical manufacturing processes [28–31]. Synthetic chemists

P Prevent waste
R Renewable materials
O Omit derivatization steps
D Degradable chemical products
U Use safe synthetic methods
C Catalytic reagents
T Temperature, pressure ambient
I In-process monitoring
V Very few auxiliary substances
E E-factor, maximize feed in product
L Low toxicity of chemical products
Y Yes, it is safe!

Scheme 1 Condensed principles of Green Chemistry.

have traditionally not been adventurous in their choice of the reactor type. The familiar round-bottomed flask with (mechanical, magnetic) stirrer remains almost always the automatic choice for most, even when the planned chemistry is innovative, e.g., the use of a non-volatile solvent (ionic liquids) or an immobilized homogeneous or heterogeneous catalyst as an alternative to a soluble reagent. However, an enhanced number of research articles describing Green Chemistry (Green Engineering) reactions are based on alternative (flow) reactors [32, 33], partly in combination with microwave heating.

Energy questions have been often neglected in the calculations of resource utilization for a chemical process. Batch processes based on scale-up reaction setups can run for many hours or even days to maximize yield, and often suffer from poor mixing and heat transfer characteristics. As the cost of energy increases and greater efforts are made to control emissions associated with generating energy, energy assumption will increasingly become one of the most important parts of Green Chemistry metrics calculations.

Microwaves are characterized by electromagnetic waves, low energy photons (which are unable to break chemical bonds), dipole rotation and ionic conduction, volumetric heating throughout an absorbing material. Microwaves can be reflected, transmitted or absorbed. Microwave-assisted chemistry is based on the use of intensively directed irradiation and its balanced application can lead to some advantages [8]:

- to short heating times
- to higher yields/selectivities
- to a wide temperature and pressure range
- to accumulation of inserted energy in the system
- to inversion of heating flux in the reactor

I Inherently non-hazardous and safe
M Minimize material diversity
P Prevention instead of treatment
R Renewable material and energy inputs
O Output-led design
V Very simple
E Efficient use of mass, energy, space and time
M Meet the need
E Easy to separate by design
N Networks for exchange of local mass and energy
T Test the life cycle of the design
S Sustainability throughout product life cycle.

Scheme 2 Condensed principles of Green Engineering.

- to high(er) energy efficiency
- to sophisticated measurement and safety technology, and
- to modular systems which allow changing from the mg up to the kg scale.

3. Microwave-assisted reactions: process development

Considering the relevant market [e.g., Biotage, CEM, Anton Paar, MLS (Milestone)], microwave systems which are currently commercially available, were almost initially developed for chemical digestions. The consequence is, therefore, the limitation of the reactor size for chemical syntheses. With effective volumes of 25–50 ml, seldom up to 250 ml, reactions on the 10–50 mmol scale can be performed. The development of microwave systems for applications in organic chemistry led to different directions [24, 34].

One direction is the development of small devices that are tailored to a special application. The small-scale devices allow for the reaction on a mmol scale, in a short time (several min) with comparatively high power input. They possess a small microwave cavity (<1 L), and have a reactor tool installed directly in the waveguide, in which often only small and closed vessels can be used. These systems are advantageous for organic chemists for yes-or-no-answers with respect to the experimental results. If the research scope is extended to questions about the reproducibility [35], the reaction kinetics, or the increase of the synthesis to afford 0.1 mol product (factor 100), these devices will fail or are recently available (cf. Anton Paar, Graz, Austria). One product line was developed by Biotage (Sweden), with their automated products on the Emrys line. To mention is furthermore the enterprise CEM (USA) with the Discover line. CEM also produce a wide range of multimode devices, which are mainly used for sample preparation (decomposition, ashing) and also for carrying out organic syntheses (MARS line).

Manufacturers and chemical engineers have started a concept of the transition of conventionally heated reactions in the microwave field, which tries to find solutions through "scale-down" and "numbering-up" approaches [8, 34] as well as through "scale-up" concepts [36–46]. The aim of these activities is to obtain a holistic view and to question all reaction parameters employed in order to discover new innovative ways of carrying out known reactions.

A common requirement associated with the introduction of new technologies, is the possibility to scale-up the respective process, firstly to a mini-plant scale and then to the production scale [47].

4. Microwave-assisted reactions: MW-setups (MLS GmbH)

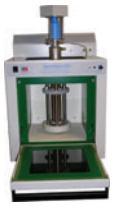
MLS GmbH, located in Leutkirch/Allgäu, Germany, is one of the most innovative microwave setup (batch and flow systems) developers and manufacturers. In the early years of growth and development of microwave chemistry, MLS

GmbH was innovatively involved in, mainly, multimode microwave ovens (Figure 1). From about 1995, MLS GmbH. and the research group "Alternative Energy" of the University in Leipzig, later of the University in Jena (since 1997), started a bilateral co-operation. Their mutual activities are documented by numerous papers and patents in the relevant literature. Aims of the co-operation were and are:

- to scale-up microwave devices (cf. Pilot 4000/4001),
- to develop flow systems driven by microwave irradiation (contFlow),
- to develop reactor systems for the HTS technique (combiCHEM),
- to develop a MW apparatus for teaching (START Praktika),
- to develop setups for microwave-driven micro-structured reactors (cf. microFLOW Ethos)
- and further challenges.

More information on these developments and published results is available [9, 20, 21].

Milestone s.r.l. is the international distributor of MLS setups. For Germany and Austria, MLS GmbH. is the distributor of its own microwave devices. It should be mentioned that Milestone often offers MLS microwave synthesis setups under slightly changed brand names:



contFLOW Since 1994

Max. power: 1500 W	**Max. temperature:** 250°C
Max. pressure: 30 bis 50 bar	

- Leak sensor
- Induktive sensor
- Temperature sensor T1
- Temperature sensor T2
- Pressure sensor

Ethos 1600 Since 1994

Max. power: 1500 W	**Max. temperature:** 300°C
	Max. pressure: dependent from reaction

- Temperature sensor T1
- Temperature sensor T2
- Gas sensor
- Pressure sensor

This system was named from 1994-1996 LAVIS-ETHOS.

Ethos PLUS Since 2004

Max. power: 1500W	**Max. temperature:** 300°C
	Max. pressure: dependent from reaction

- Temperature sensor T1
- Temperature sensor T2
- Gas sensor
- Pressure sensor

Ethos SYNTH 1994–1998

Max. power: 1500W	**Max. temperature:** 250°C
	Max. pressure: 3 bis 30 bar dependent from reaction

- Leak sensor
- Induktive sensor
- Temperature sensor T1
- Temperature sensor T2
- Pressure sensor

Pilot 4000 bzw. 4001 Since 1999

Max. power: 3000 W	**Max. temperature:** 250 °C
	Max. pressure: 30 bar

- 4 IR sensors, 4 cone-temperature controls
- With Pilot 5000 an additional reactor

Figure 1 Microwave ovens and their most important properties (MLS GmbH/Milestone s.r.l.).
The maximum pressure and maximum temperature are a function of the relative rotor or reactor system and container, respectively.

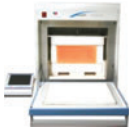
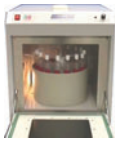
	-
	**pyroPLUS** **Since 1991** **Max. power:** 1200 W | **Max. temperature:** 1100°C - Temperature sensor T1 (temperature within oven) additional system: **PCM** (pyrolysis gas-condensation-module)
	**rotaPREP** **Since 2002** **Max. power:** 1200 W | **Max. temperature:** 300°C **Vacuum** - Temperature sensor T1 - axial support - Temperature sensor T2 - Gas sensor - Vacuum control
	**START Praktika** **Since 2001** **Max. power:** 1000 W | **Max. temperature:** 200°C **Max. pressue:** 10 bar - Low cost variante (without teflon surface in the cavity) - Temperature sensor T1 - Temperature sensor T2
	**synthWAVE** **Since 2009** **Max. power:** 1500 W | **Max. temperature:** 300°C **Max. pressure:** 190 bar - Temperature sensor thermotube - Pressure sensor - Position sensors - Magnetic stirring
	**microFLOW Ethos** **Since 2008** **Micro-Flow reactor from SiC with temperature control** **Max. temperature:** 210°C **Max. pressure:** 50 bar (possible up to 100 bar) - Temperature sensor - Pressure sensor - Leak sensor - SiC-reactor

Figure 1 (Continued)

- for academic solutions: StartSYNTH and RotoSYNTH
- from microliter to milliliter scale: MultiSYNTH and MicroSYNTH
- from milliliter to liter scale: MicroSYNTH and Rotosynth
- from liter to production scale: MicroSYNTH, BatchSYNTH, and FlowSYNTH.

Two reactor setups are shown in Figure 1. The combiCHEM system is suitable for small-scale combinatorial applications with usage of a barrel-type rotor. The early developed system "microCLAVE" was very powerful. More information on experimental details and scientific results are given in [24, 48]. The multiSYNTH system, recently developed, is a hybrid instrument [24]. The latter combines both microwave modes; the monomode and the multimode. It offers magnetic stirring capabilities and an exclusive vessel shaking system.

The co-operation between MLS and another research group from the Institute of Pharmacy and Food Chemistry at the University of Würzburg (Germany) should be mentioned too. Selected papers report on possibilities for controlling reactions under microwave-driven setups and real-time conditions by IR- or UV-spectroscopy [49–51].

5. Microwave-assisted reactions: selected results (ITUC, FSU Jena)

The availability of almost all MLS setups at the earliest moment, and permanent contact between both partners, made it possible to test the systems and to evaluate these with respect to qualification and validation. More (teaching) information on microwave chemistry can be found at www.oc-praktikum.

Figure 2 Microwave apparatus multiSYNTH (MLS GmbH, Leutkirch, Germany) with integrated QRS device (left) and the single reactor (right).

de. This homepage (sustainability in the organic chemistry lab course) is currently available in eight languages (Arabic, German, Greek, English, Indonesian, Italian, Russian and Turkish) [52].

Furthermore, the microwave devices were used for academic studies, as well as for projects with national and international industrial partners. The following papers represent the plethora of activities related to microwave-assisted applications in Jena [48, 53–63].

The hydrogenation and the C-C-coupling of model substances using the microwave system multiSYNTH and the QRS reactor (Figures 2 and 3), are representative examples for the bilateral co-operation between Leutkirch and Jena. The so-called Quartz Reactor System (QRS) head consists of stainless steel and the reaction vessel is made of inert and pressure-stable quartz glass. Regulating valves on the reactor head affords the direct discharge of reaction gases (e.g., hydrogen, oxygen) and/or inert gases (e.g., nitrogen, argon) into the reaction mixture. Over a polytetrafluoroethylene (PTFE)-capillary, samples of the reaction mixture can be taken easily. The reaction vessel is cooled by pressurized air and additionally, the reactor head can be tempered with water or other cooling/heating media. The microwave equipment allows permanent control and monitoring of temperature and pressure inside the reactor vessel. The pressure working area (≤12 bar) is protected by a pressure control valve (15 bar). The maximum working temperature is 200°C, controlled with an ATC-CE Sensor. A magnetic stirrer is used for homogenization of the reaction mixture.

Both the liquid-phase hydrogenation with gaseous dihydrogen and the C-C-coupling reactions were successfully accomplished in this reactor system. The reduction shows on acceptable conversion of benzalacetophenone at different temperatures and pressures and also with different catalysts on the basis of porous glass. The Suzuki-, Heck- and Sonogashira reactions were also carried out successfully with different aryl halogenides. The QRS device is an easily manageable reactor system, which allows use of microwave equipment, directly in the laboratory. The possibility of gas-inlet directly into the reaction mixture affords a few applications with simple and safe handling.

6. Microwave-assisted reactions: batch vs. flow in industry and in the laboratory

Considering the industrial side, it is commonly accepted that the continuous processes are the "work horses" in the production of commodities, such as petro- and industrial bulk chemicals. These industries have developed and optimized highly efficient processes using continuous equipment to fulfill

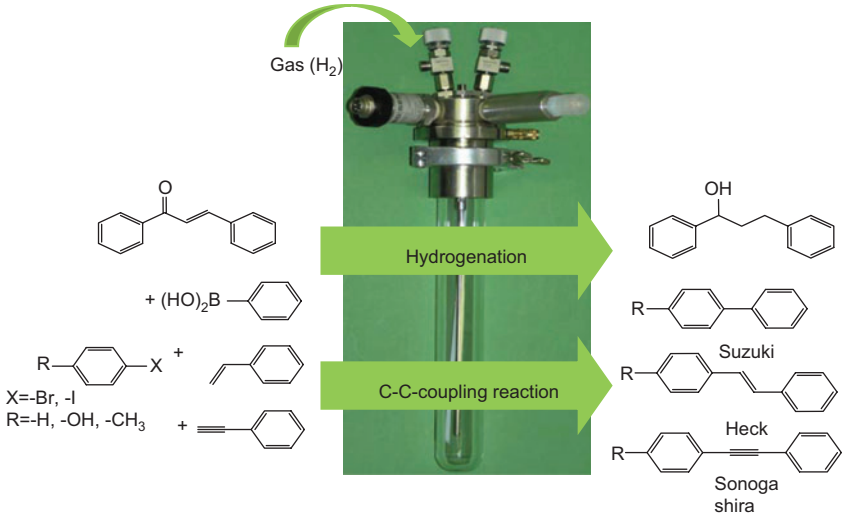


Figure 3 Applications of the QRS reactor [Ch. Schmöger et al., "Pd on porsous glass: a versatile and easily recyclable catalyst for Suzuki and Heck reactions" and "A practical approach for ambient-pressure hydrogenations using Pd on porous glass", *ChemSusChem* 1, 339–347 (2008) and 2, 77–82 (2009)].

the steady and high demand for their products. Production facilities are often dedicated mono-plants, optimized for high throughput based on full (or to a large extent) automation and high plant utilization. In contrast to this, fine chemicals companies are frequently batch processes because of their customized and complex products, smaller and fluctuating volumes and specialized applications.

Some years ago, one could note trends towards continuous processing in fine chemical and even pharmaceutical industries and academia. The continuous approach becomes more and more attractive as a concept to overcome the lag of research and development productivity and to address pressure in the pharmaceuticals industry. Therefore, some pharmaceutical companies and university groups have recently and intensively established their own flow chemistry groups, to obtain more knowledge and to investigate potentially cost-effective production of intermediates.

Flow reactors, of course also applying microwave energy, are preferably used for reactions with fast kinetics and hazardous reactions in order to keep the critical volumes small. Fast reactions are often highly exothermic, due to the use of highly reactive and/or toxic reagents or the formation of unstable compounds. Reactions with selectivity issues are examples for flow chemistry, due to the accurate control of the more narrow temperature profile in a flow system. Microstructured reaction devices, with their heat and mass transfer characteristics, appear to be the technology for rapid developments in this very active research field. Today, micro-reaction technology is well established in research and development. After some problematic cases, the dimensions of the microreactor were increased often to the millimeter scale, to avoid clogging and other disadvantages. In principle, many reactions can be run continuously. The main question is whether there is any scientific and/or economic benefit.

Some noted research groups, e.g., Hessel, Kappe, Leadbeater, Organ, are working successfully in this field, either as "normal" flow microwave chemistry or in combination with microwave irradiated with micro-reactors. Common interest is high and is documented by many relevant papers and by the existence of international meetings, for example the 3rd Symposium on Continuous Flow Reactor Technology for Industrial Applications at Lake Como (Italy) in October 2011.

7. Microwave-assisted reactions: energy efficiency

In general, a discussion on energy efficiency should always relate to comparable reaction parameters [13, 14]. The question as to whether microwave energy can be used for activation of chemical reactions more efficiently, cannot be answered spontaneously. In most of the published papers, investigations were only carried out with very small amounts of reaction mixtures, which were irradiated with comparatively high power (up to 1000 W). Fortunately, a factor which describes the efficiency of the microwave input is more and more included in recent relevant papers and is discussed [64–66]. Such a discussion is required independently from the selected (mmol to mol to kmol) scale, the studied reaction, or reaction type.

The field homogeneity of the microwave applicator is an essential criterion within the reactor design. The results observed in domestic microwave ovens demonstrate clearly inhomogeneity of the irradiation fields. Most important problems in scale-up from microwave cavities are the:

- energy efficiency
- uniformity of heating in the irradiated zone, and
- safe monitoring and control of reaction.

The control of energy input plays an essential role in reaching the predefined reaction conditions for the overall treatment of reaction mixtures in organic chemistry. In kitchen microwave devices, reaction time and the irradiated power could be varied preferably as reaction parameters. Measurement of the temperature was undetermined. A practical, but insufficient method to control the temperature, was the on- and off-switching of the microwave field, within a defined time interval. However, in modern commercial laboratory microwave setups, computer controls, which allow setting the upper temperature or pressure as limiting parameters, are state-of-the-art. This feature is very important with regard to safety aspects of handling chemicals and crucial for the reproducibility and scale-up of reactions under good management conditions. After reaching the selected parameters, the energy input is reduced to a level necessary to maintain the present values. This power control contributes essentially to increasing the efficiency of the power input by microwaves. The microwave energy proceeds almost free of loss through a microwave-transparent reactor wall into the reaction mixture, and is then converted into thermal energy, in heat, which is accumulated in the reaction mixture and stays there because the reactor materials are also heat insulators.

This illustrates the benefit of power input by microwaves. High power can be applied to reaction mixtures which are able to absorb microwaves in a controlled and fast manner. Other reaction parameters, such as the use of real setups and reactions, also play an important role. These features require synthetic chemists to be educated in the field of chemical engineering.

Working with microwave irradiation exhibits advantages for refluxing, distilling conditions and photoreactions under microwave radiation. Sensitive substances should not be overheated. The disadvantage of power supplies in comparison to older systems is higher technical complexity. The use of supplies will result in advantages in the long run, including with respect to energy efficiency.

The term "penetration depth" should also be mentioned. Microwaves penetrate from all sides into the sample and lead to a mostly homogeneous energy input, which is additionally improved by stirring the samples. Considering the penetration depth of water under microwave irradiation at 25°C or 95°C, so one must register that the penetration depth is elongated from 1.4 to 5.7 cm. The reactor dimensions are more or less limited. More precise prediction for organic solvents is hardly possible at the moment due to a lack of relevant data. However, since water has a comparatively high dielectric coefficient, higher

penetration depths can be expected at ambient temperatures, for a lot of substances used in organic chemistry.

8. Microwave-assisted reactions: qualification of devices and validation of reactions and processes

The qualification of technical devices and the validation of reactions and processes are, as always, basic factors for the introduction of new techniques, technologies and methods in the laboratory as well as in industry [14]. In the pharmaceutical industry, product development and production is unimaginable without qualification and validation. The definition and reproducibility of system parameters and reaction conditions are pivotal elements in addition to the ability to keep exact records of reactions and processes. Quality management is often, unfortunately, neglected for basic chemistry research and process development in academia. Often it is also completely omitted from the chemical education. Consideration of both the above mentioned criteria is the best guarantor for discussions on the existence of microwave effects or phenomena.

9. Conclusion and outlook

Recent literature on microwave-assisted chemistry has described different effects on chemical reactions and processes based on microwave irradiation. Important factors, required for qualification and validation, as reproducibility, transparency of reactions and processes, are still too seldom reported.

The availability of technical microwave systems represents an important first step toward the use of microwave energy for technical syntheses. The actual scale-up of organic synthetic reactions in microwave setups is, however, still too underdeveloped. Comparisons between microwave systems with different technical parameters should provide a measure for the qualification of the employed systems. This is essential for the validation of reactions and processes carried out in commercial larger scale devices [18, 19].

Recent trends in chemistry, especially in synthesis challenges, are concerned with efficient reactions. The most important focus is on selective reactions and avoidance of the application of environmentally unfriendly solvents or reagents, with the benign aim to reduce waste. A comparably important aspect is the energy transport into the reaction system.

It is hoped that the use of microwave tools will be applied more and more in innovative enterprises and the chemical industry in the next decade(s), as they are already in both analytical and chemical laboratories.

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