

# **SCIENTIFIC REPORT**

## **EUROPEAN SCIENCE FOUNDATION EXPLORATORY WORKSHOP**

**ON**

### **MICROWAVE CHEMISTRY AND SPECIFIC MICROWAVE EFFECTS**

**Graz - Austria  
September 17-20, 2004**

#### **Convener**

**Prof. C. Oliver Kappe**

**Institute of Chemistry, Karl-Franzens-University Graz  
Heinrichstrasse 28, A-8010 Graz - Austria  
P: +43-316-3805352 F: +43-316-3809840  
oliver.kappe@uni-graz.at, www.maos.net**

#### **Workshop Location**

**Hotel Mercure, Graz (Accor Hotels)  
Waltendorfer Gürtel 8-10, A-8010 GRAZ - Austria  
P: +43-316-826300 F: +43-316-826300630  
E-mail : [H2212@accor-hotels.com](mailto:H2212@accor-hotels.com)  
<http://www.accorhotels.com/accorhotels/>**

# 1. Executive Summary

Although the use of microwave technology in chemical sciences is rapidly increasing the theoretical background for the enhancement of processes is still incompletely defined. This situation has resulted in many debated controversial suggestions and contradictory results in the organic chemistry literature especially and to rather heated debates at recent conferences. Two of such items are the existence or not of the so-called "specific microwave effects" and "non-thermal microwave effects".

The background for the "specific microwave effects" is that the results for certain chemical reactions performed using microwave or conventional heating differ in terms of product distributions and yields when the reactions are carried out at what is considered to be the same temperature.

The cause of these "non-thermal microwave effects" has been suggested to be due to specific wave-material interactions which would cause a decrease in activation energy, an increased pre-exponential factor in the Arrhenius equation or selectively better interactions between microwaves and transition states that occur late along the reaction coordinate. According to Hammond's postulate, some of these transition states would be more polar, and thus capable of interacting more strongly with the microwaves.

Other researchers have strongly denied the existence of non-thermal effects as the rapid heating and the high temperatures that are attained using microwave heating can explain all rate-enhancements. Other contributing factors suggested are the formation of microscopic or macroscopic hotspots or selective heating of a specific polar component in the reaction mixture.

It has been suggested that "specific microwave effects" should be defined as chemical transformations that can not be achieved or duplicated by conventional heating, but are essentially thermal effects, and "non-thermal microwave effects" as acceleration effects that can not be rationalized by thermal or specific microwave effects.

Another recent controversy is the notion that simultaneous cooling of the reaction mixture while heating by microwaves leads to an enhancement of the overall process. One attempt to explain this effect that has been put forward is that the cooling removes the thermodynamic heat so that more power can enter into the reactants.

Unfortunately, most scientists applying microwave technology in their specific research area today have little knowledge of the complex theory of microwave dielectric heating and theoretical or physical chemistry.

In order to address all these - so far scientifically controversial - suggestions and to provide a scientific rationalization for the observed effects a workshop entitled "Microwave Chemistry and Specific Microwave Effects" was arranged by the European Science Foundation (ESF) in Graz, Austria, convened by C. Oliver Kappe from the University of Graz.

The 21 attendees were all international microwave chemistry users in different fields, such as physical/theoretical chemist, organic, inorganic and analytical chemists, bio- and polymer chemists and experts of microwave dielectric heating and microwave cavity/instrument design. This interdisciplinary assembly engaged itself very actively during the conference and all the various presentations were intensively discussed during the two day meeting.

During the conference it was stated that more studies are needed in which the reaction conditions are carefully controlled before the question regarding the presence of specific activation by microwaves can be answered. Standard experiment conditions and reactions should be used and an improvement of the description of reaction parameters is crucial! Furthermore, more inter- and trans-disciplinary knowledge is necessary.

## **2. Assessment of the Results, Contribution to the Future Direction of the Field**

While the discussion on “microwave effects” among the participants *was* considered to be very fruitful, no rationalization of the effects could be provided. In the short time frame of the workshop, it was also not possible to agree on a “definition of terms”. There was a strong interest from most participants to have a similar meeting again in the future and to form a “working group” on this issue.

In particular, it was recommended to form a link with IUPAC on the issue of a definition of terms related to microwave chemistry (a type dictionary), in order to avoid the ongoing confusion in the literature. Several of the participants have ongoing collaborations already, and some new collaboration within Europe will result from the recently approved COST action D32 (Chemistry in High-Energy Microenvironments) where microwaves play a major role. Some of the participants in the area of organic chemistry will also be involved in a Marie-Curie Research Training Network (RTN) application where microwaves will play a major role.

It has been decided to try to arrange another meeting in September 2005, in conjunction with the AMPERE microwave conference in Modena, Italy, September 11-15, 2005.

### 3. Scientific Content

Several presenters stressed the fact that it is of fundamental importance to have good temperature monitoring and control if the question of thermal and non-thermal effects is to be delineated in a satisfactory scientific manner. It was also emphasized that microwave heating is a collective, bulk effect and that many of the phenomena associated with microwave heating are directly related to the much higher temperature that can be achieved with microwave heating as compared to conventional heating. This is particularly pronounced in microwave heating of solids where the heating rate is even higher due to *thermal runaway effects*. Such reactions may display some special effects, which reflect the higher temperature and thus no change in the activation parameters needs to be proposed.

In sintering processes where claims for a microwave-specific effect are common, the primary criticism has also been focused on the accuracy of the temperature measurement. It was concluded that a 'microwave effect' of some form appears to exist in some of these processes but no clear picture of these effects has emerged so far.

Many microwave-assisted polymerization processes have been shown to result in similar product properties as under conventional conditions. It was stated during the conference that a real cross-disciplinary approach has to be considered to fully understand all the limitation and advantages of microwave processing of polymerization reactions. It was also concluded that generation of hot spots can rationalize all "special effects" in these reactions and that any such effects can be explained by difficulties in measuring the temperature.

In microwave-assisted photochemical reactions it was suggested that the microwave field could influence the spin dynamics of radicals, which could be considered as an archetype of a non-thermal microwave effect. Alternative explanations were put forward, once again indicating that more research is needed.

Careful temperature measurements in polymerase chain reactions (PCR) supported the assumption that pure thermal processes were involved. Of particular interest was that using microwave heating it was possible to perform PCR reactions in 15 mL scale, which is impossible under conventional conditions.

The explanation suggested for the fact that microwave-assisted 1,3-dipolar cycloadditions of C<sub>70</sub> fullerenes gave different isomer distributions as compared to conventional conditions was that the transition state for this isomer is the softest saddle point and the most polarizable transition structure. Thus, it should interact less efficiently with the microwaves, favoring the formation of the remaining adducts. It was suggested that the hardest TS should be favored under microwave irradiation.

When graphite is used as "sensitizer" in organic reactions the faster reactions found as compared to conventional heating were reported to be due to the fast heat transfer and possibility of hot spots formations on the graphite surface.

One example of a product that was formed at room temperature or under classical heating but could *not* be found under microwave irradiation was presented. This was called an “inverse specific microwave effect”, a suggestion that resulted in much discussion.

The results from thousands of transition metal-catalyzed homogeneous transformations as Heck couplings, cross-couplings, asymmetric allylic substitutions and different types of carbonylation processes using microwave or classic heating clearly showed the absence of any “non-thermal microwave effect”. No difference in reaction mechanisms have been observed between microwave or conventional conditions

In all microwave-assisted heterogeneous reactions using solid catalysts or supports presented, thermal effects could explain all results and thus all non-thermal effects could be excluded.

For some reactions, the simultaneous cooling and microwave irradiation has been claimed to increase the power input that in turn would result in greater conversion to product and higher yields, given the same timeframe. Work has also been done showing that microwave irradiation at sub-ambient temperatures serves to increase the rate of reaction. Even at temperatures below that of the conventional reaction, microwaves were claimed to accelerate the reaction rate. These suggestions were met with many questions and it was clear that more investigations were needed. Using simultaneous cooling and heating the origins of non-thermal microwave effects in a range of organic transformations had been investigated. When these reactions had been compensated for differences between microwave runs with and without cooling on, the same results were obtained for all reactions tested with one exception.

## ABSTRACTS

### CHEMICAL REACTIONS UNDER MICROWAVE CONDITIONS - BASIC THEORY

D. Michael P. Mingos

*Chemistry Department and St Edmund Hall, University of Oxford, Oxford OX1 4AR, United Kingdom*

Following a brief historical introduction into the development of microwave sources and their utilization for dielectric heating the application of this technique to chemical problems is discussed. The dielectric properties of organic solvents and compounds has now been fully documented and is generally available for computer modeling purposes. Heating organic solvents in a microwave cavity raises specific safety and operational issues which have now been largely solved. Indeed there exists a range of commercially available equipment which may be used for exploratory and pilot studies. The importance of temperature monitoring and control cannot be emphasized too strongly if the question of thermal and non-thermal effects are to be delineated in a satisfactory scientific manner. The microwave dielectric heating technique provides a temperature profile which is very different from that commonly available for conventional resistive heating and is more akin to flash thermolysis. Specific applications of the technique to synthetic and catalytic problems in organometallic and co-ordination chemistry have been studied in my group and will be discussed.

### **A quantum mechanical approach to studying microwave molecule interactions and some consequences for cavity design.**

Nils Elander

*Alba Nova University Center, Department of Physics, Univ. of Stockholm, Sweden*

We have studied if and how it is possible to use quantum mechanical terms to describe the interaction between reacting molecules and the electromagnetic field in a microwave-assisted reaction. A model of an S(N)2 reaction was studied by Density Functional Theory and Hartree Fock methods. By adding solvent molecules in the form of water, it was computationally shown that several of the models of solvated reaction complexes have vibrational modes whose frequencies are close to the normally used microwave frequency of 2.45 GHz. We thus find it likely that there may exist vibrational motion in the form of hindered rotation which overlaps with this normal microwave heating frequency in turn suggesting that microwave photons may excite these vibrational modes.

These some what speculative results are meant to encourage the search for microwave enhancements in chemical reactions. Considering the transfer of energy from the microwave field to a sample, our results are the same as in the more classical formulation originally given by Debye. Only the electric part of the microwave interacts with matter. In order to test this we have designed a cavity in which the magnetic field component in the sample is minimized.

## Microwave-Enhanced Sintering – Reality or Delusion?

A.G. Whittaker

*School of Chemistry, University of Edinburgh. West Mains Road, Edinburgh, Scotland.*

Sintering is the single most important method of sample preparation in solid state chemistry, but the process is energy intensive, requiring high thermal energies in order to overcome the high energy barriers which prevent rapid motion of the ions during the course of the reaction. Enhanced sintering by microwaves has been extensively reported in the literature, and claims for a microwave-specific effect that results in a 2-300K processing temperature reduction are common. However, the primary criticism of any solid state study under microwave irradiation focuses on the accuracy of the temperature measurement. Improved methods for monitoring temperatures in the solid phase, however do not necessarily dispel the intrinsic problems with comparative studies. It is very difficult, if not impossible, to demonstrate that the sample temperature which is measured is representative of the sample as a whole. Even with the best direct measurement techniques, it is not possible to absolutely preclude localized generation of hot spots as the source of any rate enhancements.

On the other hand, if a microwave-enhanced sintering is a real effect, then understanding the mechanism is important if the effect is to be best exploited. The claims for microwave-enhanced ion transport are difficult to verify. In this paper, a brief history of the claims for enhancement is given, along with methods for evaluating the strength of microwave effects within a single, uniformly heated, sample. This paper describes the development of an experimental arrangement that almost entirely circumvents the need to measure the sample temperature. Comparison is no longer made between two different samples, where one is conventionally heated and one heated using microwaves. Instead, the comparison is made between diffusion parallel *with* the electric field vector and diffusion perpendicular *to* the microwave electric field vector. Whilst the results do not necessarily point to a precise mechanism for the rate enhancement, they do appear to confirm that a ‘microwave effect’ of some form exists. At a minimum, the enhancement appears to result from highly selective energy transfer to the intergrain boundaries that matter most in the sintering process.

# Microwave Processing of Ceramics and Inorganic Materials

Monika Willert-Porada

University Bayreuth, Chair of Materials Processing, Bayreuth, Germany

Microwave processing of inorganic materials started 15 years ago, with reports on dramatic acceleration of reaction rates and strong microwave absorption observed for different inorganic solids [1-3]. At the same time, particularly for microwave sintering of ceramics, a significant lowering of the activation energy accompanied with sintering, and therefore tightly connected to mass and charge transfer in inorganic substances, was reported [4], raising questions about the nature of such effects.

According to M. Mingos “Chemists frequently confuse microwave rotational spectroscopy and microwave dielectric heating”, [5], nevertheless, among chemists, physicists and material scientists for some time expectations were high towards a distinct “microwave effect”, namely a direct influence of microwave heating on the path of reactions or the speed of diffusion. Frequently such effects are summarized as “non thermal” effects.

Some model experiments were performed, e.g., on charge extraction upon microwave pulsed heating in doped single crystal halides [6], spinodal decomposition in solid solutions of a poorly microwave absorbing material [7] and porosity development in nanosized [8], in conventional [9-11], and in high- $\epsilon$ -ceramics [12-14]. Influence of microwave heating on solution-precipitation, grain growth and phase transition upon microwave heating was systematically investigated for oxide doped  $\text{Si}_3\text{N}_4$ -ceramics and for different grades of  $\text{Al}_2\text{O}_3$  as well as  $\text{ZrO}_2$ -ceramics [15-20]. A heuristic model of a “sintering master curve” was developed based on the comparison of microwave, plasma and conventional sintering [21]. However, a clear theoretical description has been developed for the charge transfer only, based on the ponderomotive force [22, 23]. A first critical review of model experiments performed with the aim to unequivocally prove “microwave accelerated diffusion”, based on results of sintering experiments, raised more questions than it could provide answers [24].

Based on this brief review of the literature on microwave sintering of ceramics, the paper will concentrate on *different concepts* of analysis on microwave-material interaction with respect to charge and mass transfer phenomena, such as

1. Energy balance based concepts related to absorption of microwave radiation by the material (thermodynamic approach, heat and mass transfer, thermal runaway, thermal gradients)
2. Charge generation or extraction and transport based on the presence of an alternating electromagnetic field (plasma contribution, ponderomotive force)
3. Chemical potential gradients based on the presence of an alternating electromagnetic field in an inhomogeneous material (electrochemical & space charge approach)
4. Mechanical gradients based on the presence of an alternating electromagnetic field in an inhomogeneous material (photon pressure, secondary effects)
5. Electro- and magneto-migration (self assembly, “local dielectric constant”)

Each concept will be discussed with respect to the phase boundaries and the “active volume” relevant for the mass and charge transfer process. The maximum local electrical field strength will serve as critical quantity, separating thermal and non thermal contributions, reached due to electric breakdown conditions.



# MICROWAVE ASSISTED SYNTHESIS, CROSSLINKING, AND PROCESSING OF POLYMERIC MATERIALS

Dariusz Bogdal

Department Chemistry and Technology, Politechnika Krakowska ul. Warszawska 24,  
31-155 Krakow, Poland

Microwave technology (i.e., the application of electromagnetic radiation ranges from 0.3 MHz to 300 GHz), has been developed primarily for communication and some areas of processing such as cooking food, thawing, and curing wood and rubber. As a heat source, microwaves allow a sample to be irradiated instantly with an associated rapid heating rate. Moreover, microwaves offer a number of advantages over conventional heating such as non-contact heating (reduction of overheating of material surfaces), energy transfer instead of heat transfer (penetrative radiation), material selective and volumetric heating, fast start-up and stopping and reverse thermal effect, i.e. heat starts from the interior of material body.

In the last decade, microwaves have attracted the attention of chemists who have begun to apply this unconventional technique as a routine in their practice. The reduced time of processing under microwave conditions found for a great number of chemical reactions was the main reason that microwave techniques become so attractive for chemists. The result and advantages of microwave processing of material can be increase of productivity, improved product characteristics, uniform processing, less manufacturing space required, and controllability of the process. Microwave processing seems to be easily scaled up from a small batch process to a continuous process employing a conveyor. Besides ceramic, polymer processing forms probably the largest single discipline in microwave technology, and the methods and procedures used therein are certainly seen among the most developed. The purpose of this report is to provide some details concerning the application of microwave irradiation to polymer chemistry and technology. A survey of the past achievements in polymer synthesis can be found together with discussion of the free-radical polymerization, polyaddition as well as polycondensation reactions, crosslinking and processing of polymeric materials with the stress on chemistry of those processes. A short description of the nature of microwaves as well as their interactions with different matter, in particular with organic substances, will be given [1].

1. D.Bogdał, P.Penczek, J.Pielichowski, A.Prociak, *Microwave Assisted Synthesis, Crosslinking, and Processing of Polymeric Materials*, Adv. Polym. Sci. 163, 193-263 (2003).

## Application of microwaves in sample preparation for element analysis

Günther Knapp

Institute for Analytical Chemistry and Radiochemistry, Graz University of Technology

Sample preparation methods for element analysis can be significantly improved by means of microwaves e.g.:

1. Drying
2. Evaporation
3. Wet digestion in open and closed vessels
4. Wet digestion with flow systems
5. Dry ashing
- 6. Oxygen plasma ashing**
- 7. UV-digestion**
- 8. Combustion**

Microwaves mostly act as primary energy sources, that means sample or reagents are directly heated by microwaves (1.-5.). But microwaves can also be applied as secondary energy sources (6.-8.). That means microwaves do not transfer their energy directly to sample or reagents, but they create excited species (6.) or high energy radiation (7.). In another case microwaves can be used for ignition of samples in a pure oxygen environment (8.).

This contribution will show opportunities and advantages of microwave assisted sample preparation methods with microwaves as secondary energy source.

Oxygen plasma can be easily produced in low pressure quartz vessels which are located in focused microwaves. Important is the geometry, that the sample is not placed within the microwave field to prevent an excessive heating of the sample material.

For an optimum microwave assisted UV-digestion high temperature of the digestion solution and intensive UV-radiation are important. Special UV-discharge lamps are have been developed for that purpose.

Oxygen combustion of organic materials in closed quartz vessels and subsequent microwave assisted dissolution of the remaining ash can be very powerful particularly for the determination of nonmetals.

The main advantage of these methods is the low amount of acids used to dissolve the remaining trace elements of organic sample materials. Contamination and matrix interferences with the subsequent measurement techniques are comparably low.

## PHOTOCHEMISTRY IN THE MICROWAVE FIELD

Petr Klán

*Department of Organic Chemistry, Faculty of Science, Masaryk University, Kotlarska 2, 611 37 Brno, Czech Republic; e-mail: [klan@sci.muni.cz](mailto:klan@sci.muni.cz)*

Photochemistry in the microwave field<sup>1</sup> presents a combined chemical activation by two distinctive kinds of electromagnetic radiation. Energy of MW radiation ( $E = 0.4\text{--}40 \text{ J mol}^{-1}$  at  $\nu = 1\text{--}100 \text{ GHz}$ ) is considerably lower than that of UV/VIS radiation ( $E = 600\text{--}170 \text{ kJ mol}^{-1}$  at  $\lambda = 200\text{--}700 \text{ nm}$ ), thus insufficient to disrupt bonds of common organic molecules. The objective of photochemistry in the microwave field is frequently, but not irreplaceably, connected to the electrodeless discharge lamp (EDL), which generates UV radiation when placed into the MW field. Our group reported on applications in a photochemical reactor that takes advantage of an EDL inside a reaction mixture<sup>2-4</sup>. Such an arrangement was proposed for the first time by Den Besten and Tracy<sup>5</sup>, and later applied by Cirkva and Hajek<sup>6</sup> in experiments using a modified microwave oven. The right choice of a filling, envelope material, and temperature can dramatically modify the emission spectrum, being thus advantageous in planning specific photochemical experiments.<sup>7</sup>

In addition, the microwave field can also influence the spins spin dynamics of radicals. Radical pairs and biradicals are enormously common intermediates in many organic photochemical (or some thermal) reactions. Radical pairs in solution coherently fluctuate between singlet and triplet electronic states and the recombination reactions are often controlled by electron-nuclear hyperfine interactions (HFI) on a nanosecond time scale, which can be influenced by an external magnetic or microwave field.<sup>8,9</sup> This may be considered as an archetype of a non-thermal MW effect.

- (1) Klan, P.; Cirkva, V. Microwave Photochemistry. In *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-WCH: Weinheim, 2002; pp 463.
- (2) Klan, P.; Literak, J.; Hajek, M. *J. Photochem. Photobiol. A-Chem.* 1999, 128, 145.
- (3) Literak, J.; Klan, P. *J. Photochem. Photobiol. A-Chem.* 2000, 137, 29.
- (4) Klan, P.; Hajek, M.; Cirkva, V. *J. Photochem. Photobiol. A-Chem.* 2001, 140, 185.
- (5) Den Besten, I. E.; Tracy, J. W. *J. Chem. Educ.* 1973, 50, 303.
- (6) Cirkva, V.; Hajek, M. *J. Photochem. Photobiol. A-Chem.* 1999, 123, 21.
- (7) Muller, P.; Klan, P.; Cirkva, V. *J. Photochem. Photobiol. A-Chem.* 2003, 158, 1.
- (8) Woodward, J. R. *Prog. React. Kinet. Mech.* 2002, 27, 165.
- (9) Woodward, J. R.; Sakaguchi, Y. *J. Phys. Chem. A* 2001, 105, 4010.

## Microwave-assisted high speed and large-scale PCR

Peter Nilsson

*Department of Medicinal Chemistry, Organic Pharmaceutical Chemistry; BMC, Uppsala University, box 574, SE- 751 23 Uppsala, SWEDEN*

Historically, microwave irradiation has been utilized in biological research mainly for denaturation purposes.<sup>1</sup> Recently, reports on enzyme catalysis under microwave irradiation have indicated its usefulness also in biosyntheses.<sup>2</sup> Notably, it has been suggested in the literature that microwaves can affect protein configurations independently of the bulk temperature.<sup>3</sup> PCR amplification has emerged as a very important tool in biological research. The utility of the PCR is, however, hampered by the fact that it is a slow technique. Faster heating cycles are therefore needed, both to enhance the activity of the enzyme, and to enable shortening of the reaction times. DNA polymerase (e.g. Taq), the enzyme used in PCR, replicates DNA with surprisingly high fidelity despite the small energy differences in hydrogen bonding between correct and incorrect base pairs. A study of the influence from microwave irradiation on nucleic acid stability as well as enzyme stability under microwave-promoted high temperature conditions was carried out. Polymerase chain reactions with directed microwave irradiation as the source of heat is demonstrated for the first time.<sup>4</sup> Thus, it was established that pulsed microwave heating does not terminate the enzymatic function of the polymerase. The results indicate the possibility to shorten the total reaction time. In addition, the technique also gives the possibility to perform PCR reactions in milliliter scale.<sup>5</sup>

(1) a) deMeulemeester, M.; Vink, A.; Jakobs, M.; Hermsen, M.; Steenman, M.; Slater, R.; Dietrich, A.; Mannens, M. *Genetic Analysis-Biomolecular Engineering* **1996**, *13*, 129-133. b) Devece, C.; Rodriguez-Lopez, J. N.; Fenoll, L. G.; Tudela, J.; Catala, J. M.; de los Reyes, E.; Garcia-Canovas, F. *J Agric Food Chem* **1999**, *47*, 4506-4511.

(2) a) CarrilloMunoz, J. R.; Bouvet, D.; GuibeJampel, E.; Loupy, A.; Petit, A. *J Org Chem* **1996**, *61*, 7746-7749. b) GeloPujic, M.; GuibeJampel, E.; Loupy, A.; Galema, S. A.; Mathe, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2777-2780. c) GeloPujic, M.; GuibeJampel, E.; Loupy, A. *Tetrahedron* **1997**, *53*, 17247-17252.

(3) a) de Pomerai, D. I.; Smith, B.; Dawe, A.; North, K.; Smith, T.; Archer, D. B.; Duce, I. R.; Jones, D.; Candido, P. M. *Febs Letters* **2003**, *543*, 93-97. b) Roy, I.; Gupta, M. N. *Tetrahedron* **2003**, *59*, 5431-5436.

(4) Fermér, C.; Nilsson P.; Larhed, M. *Eur. J. Pharm. Sci.* **2003**, *18*, 129-132.

(5) Orrling, K.; Nilsson, P.; Gullberg, M.; Larhed, M. *Chem. Commun.* **2004**, 790-791.

## Microwaves in Chemistry of Fullerenes and Carbon Nanotubes

F. Langa

Fullerenes are suitable building blocks for the construction of systems displaying photoinduced energy and electron transfer as models for artificial photosynthetic centers. In the other hand, the chemical modification of carbon nanotubes is an emerging area in material science. In this lecture, I will present the recent results of our group in functionalization of fullerenes (C<sub>60</sub> and C<sub>70</sub>) and Carbon nanotubes

## Microwave assisted heterocyclic chemistry : from the experimental design to results. Application to the synthesis of various molecules with therapeutic activity.

Thierry Besson

Laboratoire de Biotechnologies et Chimie Bio-organique, FRE CNRS 2766, UFR Sciences Fondamentales et Sciences pour l'Ingénieur, Université de la Rochelle, Bâtiment Marie-Curie, 17042 La Rochelle Cedex 1, France

Microwave-assisted reactions are now well established and the various possibilities offered by this technology are particularly attractive for multi-step synthesis and drug discovery processes where high yielding protocols and avoidance or facility of purification are highly desirable [1]. Microwaves have also shown an advantage where processes involve sensitive reagents or when products may decompose under prolonged reaction conditions.

The main activity for our group consists to perform the synthesis of heterocyclic structures with potential pharmaceutical value. Our molecular targets are inspired by natural marine or terrestrial alkaloids for which interesting biological activity was detected. Then, we recently described the synthesis of new thiazole derivatives [2] derived from natural alkaloids extracted from marine organisms (*e.g.* dercitine and kuanoniamines) [3] or plants (*e.g.* ellipticine) [4]. In these studies, our strategy consisted to combine the thiazole ring with various heterocyclic structures in the hope to detect interesting cytotoxicity profiles.

The necessity to have high energy for such transformations led us to use microwaves and to study the opportunity to use homogeneous or solvent-free conditions in order to achieve better yields and cleaner reactions than for the purely thermal processes. Two approaches are usually investigated: the first one involves the use of polar solvents which by themselves are good candidates for microwave heating. The second solvent-free approach includes the use of support (*e.g.* graphite) which may allow a rapid and safe heating of the reactants.

The examples described [5] are clearly demonstrating that, with well-established experimental conditions, microwave irradiation can be used as a very useful alternative to classical methods. Scale-up and technical transposition to various multi-step synthesis are also studied in our group and will be discussed. Because it is now possible to combine drug discovery strategy with microwave heating for a rapid access to new drugs, the interest to combine microwave heating and pressurized reactions will also be described.

1. (a) *Microwave enhanced chemistry*, Kingston, H. M.; Haswell, S. J., Eds.; American Chemical Society: Washington DC, 1997; (b) *Microwaves in organic synthesis*, Loupy, A., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2002; (c) Hayes, B. L. *Microwave synthesis : chemistry at the speed of light*, CEM Publishing, Matthews (USA), 2002; (d) *Microwave-Assisted Organic Synthesis*; Lidström, P.; Tierney, J., P., Eds.; Blackwell Publishing: Oxford, 2004.
2. (a) Chabane, H.; Lamazzi, C.; Thiéry, V.; Pierré, A.; Léonce, S.; Pfeiffer, B.; Renard, P.; Guillaumet, G.; Besson, T., *J. Enz. Inh. Med. Chem.* 2003, 18, 167-174. (b) Lamazzi, C.; Chabane, H.; Thiéry, V.; Pierré, A.; Léonce, S.; Pfeiffer, B.; Renard, P.; Guillaumet, G.; Besson, T., *J. Enz. Inh. Med. Chem.* 2002, 17, 397-401; (c) Bénétteau, V.; Besson, T.; Guillard, J.; Leonce, S.; Pfeiffer, B., *Eur. J. Med. Chem.* 1999, 34, 1053-1060.
3. (a) Molinski T.F., *Chem. Rev.* 1993, 93, 1825-1838.
4. Sengupta, S. K., *Topoisomerase II inhibitors*, in *Cancer Chemotherapeutic Agents*, W. O. Foye (Ed.), ACS Professional Reference Books, Washington DC, 1995, pp. 246-260.
5. (a) Frère, S.; Thiéry, V.; Bailly, C.; Besson, T. *Tetrahedron*, 2003, 59, 773-779. (b) Alexandre, F.R.; Berecibar, A.; Besson, T. *Tetrahedron Lett.* 2002, 43, 3911-3913. (c) Domon, L.; Le Coeur, C.; Grelard, A.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* 2001, 42, 6671-6674. (d) Alexandre, F.R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron Lett.* 2003, 44, 4455-4458.

**Microwave and classical activation of solvent-free synthesis of alkenes, cyclohexenes and cyclohexanols : good models for specific microwave effects discussions.**

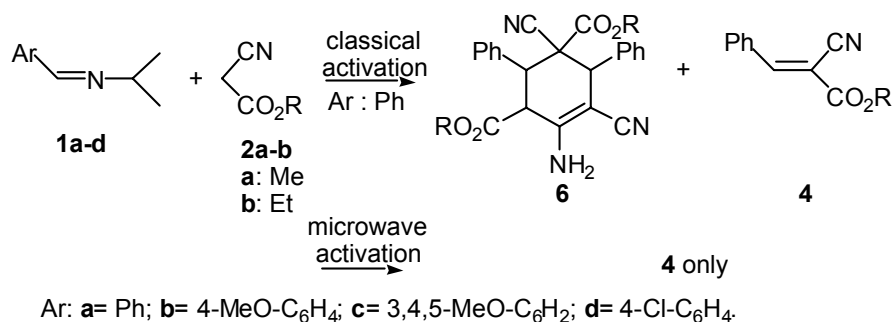
Jack Hamelin and Françoise Texier-Boullet

*Synthèse et Electrosynthèse Organiques 3, UMR 6510, Université de Rennes I, Campus de Beaulieu , 35042 Rennes, France, [Jack.Hamelin@univ-rennes1.fr](mailto:Jack.Hamelin@univ-rennes1.fr); [Francoise.Texier@univ-rennes1.fr](mailto:Francoise.Texier@univ-rennes1.fr)*

Part A : Jack Hamelin

According to scheme 1, the reaction of neat N-isopropyl benzylidene amine **1a** with cyanoacetates **2a** or **2b** at room temperature (8 days) or under classical activation (5 days) leading to new functionalized cyclohexenes **6aa** or **6ab**-by MIMIRC reaction and subsequent dealkoxycarbonylation of cyclohexenes **5aa** or **5ab**- is unexpected (**6ab** and **5ab** structures were established by X-ray analysis).

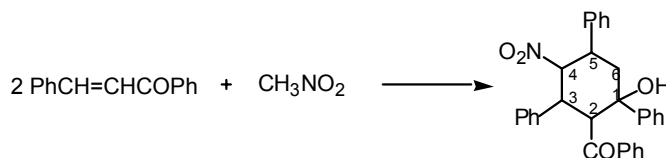
Cyclohexenes could not be obtained under microwave irradiation and to our knowledge this is the first experimental example of a reaction working under classical heating which is not working under microwaves which we could call an «*inverse specific microwave effect*».



Scheme 1

The first step of the reaction –*i.e* the alkene **4** formation (from an aminoester **3**)-exhibits an obvious specific microwave effect (3 mn at 80°C under microwaves or 15 h in an oil-bath at the same temperature). The subsequent steps leading to cyclohexenes are not operating under microwave irradiation at 2.45 GHz and are available only under classical activation.

The second model to be discussed is the synthesis of nitrocyclohexanols<sup>1</sup> (scheme 2).



Scheme 2

Under microwaves, the mixture of chalcone and nitromethane over  $\text{KF}/\text{Al}_2\text{O}_3$  leads to nitrocyclohexanol which could not be formed under classical heating in strictly the same conditions : obviously this is an evidence for a specific microwave effect. The mechanisms, the stereochemistries and the reactions conditions will be carefully discussed and then the influence of microwaves will be discussed in Part B.

#### Part B : Françoise Texier-Boullet

In order to understand the phenomena previously described (Part A) *i.e* strong favorable effect for alkene synthesis (the transition state and the intermediate aminoester 3 being more polar than the reactants) « *inverse effect* » for cyclohexene synthesis (the transition states and the intermediates being symmetrical and non polar) and again strong effect for nitrocyclohexanols synthesis, we measured the dielectric parameters  $\epsilon'$  and  $\epsilon''$  for the starting materials, the final products and the reaction mixture during the reaction under classical heating by warm air stream and under microwave irradiation at 2.45GHz. These measurements were performed in the framework of a European project thanks to the collaboration of Dr Michel Delmotte at M.E.S Technologies in Paris.

With these results in hand, we will discuss the synthetic results and suggest a proposal to rationalize the microwaves effects observed .

<sup>1</sup> Correc, O. ; Guillou, K. ; Hamelin, J. ; Paquin, L. ; Texier-Boullet, F. ; Toupet, L. *Tetrahedron Lett.* 2004, 45, 391.

## Homogeneous Catalysis under High-Density Microwave Irradiation

Mats Larhed

*Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, BMC, Uppsala University, Box 574, SE-751 23, Uppsala, Sweden, mats@orgfarm.uu.se*

This specific presentation summarizes mainly our own experiences, observations and thoughts from developing a number of rapid, robust and selective microwave-heated and transition metal-catalyzed homogeneous transformations. Applications include Heck couplings, cross-couplings, asymmetric allylic substitutions and different types of carbonylation processes using different types of single-mode reactors.

When attempting to compare preparative results from microwave and classic heating, we have in a number of homogeneous metal-catalyzed reactions detected differences in both yield and selectivity (chemo-, regio- and stereo-). The observations can be summarized as follows:

1) With higher reaction temperatures and shorter reaction times (down to 6 s), the advantages with microwave heating are clear e.g. yield and selectivity is superior to results with classic heating,

2) With temperature-controlled microwave heating and long reaction times (more than 15 min), we do not note any difference between microwave and classic heating,

3) We have never observed improved selectivity with increased reaction temperature.

Microwaves generate heat by internal friction as a bulk effect, i.e. the heat is created in the interior of the sample. The reaction vessels employed are made of a material transparent (or largely transparent) to microwaves at the operating frequency, commonly borosilicate glass, quartz or Teflon. We believe the efficient internal high-density heat transfer, as compared to the wall heat transfer occurring with the conventional heating systems, oil bath etc, minimizes the wall effects (no thermal boundary layer) and thus suppresses the tendency for breakdown of the catalytic system. The improved outcome under accelerated high-temperature microwave-conditions is therefore a direct consequence of a smoother heating, which avoids catalytic decomposition before complete conversion, and not a result of a “non-thermal microwave effect”



## Microwave Effects in Heterogeneous Catalysis

Milan Hájek

Institute of Chemical Process Fundamentals,  
Academy of Sciences of the Czech Republic, Prague, Czech Republic

Microwave activation of catalytic reactions has been the subject of many studies, however, the mechanism of these reactions is not yet fully understood. The question is how to interpret differences in rates or in selectivities in conventionally and microwave heated reactions under the same conditions. There are the following microwave effects which does not exist in conventionally heated reactions and which can explain these differences.

### **Superheating**

occur in liquid reaction mixture where reactants are heated above their boiling point. In solids like in solid catalysts or supports superheating can be much higher than in liquid phase due to lower heat transfer. Such a localized superheating produces hot spots (*vide infra*), which is advantageously used by synthetic chemists, especially for reactions performed on inorganic supports under solvent free (dry media) conditions.

### Selective heating

means that in a sample containing more than one component, only that component which couple with microwaves is selectively heated. Selective heating is very important in catalytic reactions where catalyst is selectively heated in nonpolar media.

### Hot spots

are created by a nonlinear dependence of thermal and electromagnetic properties of the catalyst being heated. There are two kinds of hot spots – *macroscopic* and *microscopic*.

- *Macroscopic* hot spots are large scale nonisothermality, which can be detected and measured.

- *Microscopic* hot spots possess molecular dimensions and in catalysts can be created, for example by selective heating of active sites.

### Microwave heating under simultaneous cooling

is most recent discovered microwave effect which can significantly improve yields and selectivity of catalytic reactions[1-5].

It is obvious that nonisothermal conditions induced in catalyst by microwave heating lead to very different results from those obtained under conventional heating conditions. When intensive cooling is used, e.g. with liquid nitrogen, these differences are more profound[1-3,5]. Because the temperature of the reaction mixture is lower than the temperature of the catalyst, the back, side or consecutive reaction can occur to a lesser extent, i.e. selectivity of the reaction can be significantly improved.

In our studies of microwave activation of catalytic reactions all results were explained by above mentioned thermal effects. Non-thermal effects, i.e. specific effects, were excluded.

1. M. Hájek, M.T. Radoiu, *Ceram. Trans.* **2001**, 111, 257-264.
2. J. Kurfürstová, M. Hájek, *8th Int. Conf. Microwave and High Frequency Heating*, Bayreuth, Germany, 3-7 September **2001**, Book of Abstracts pp. 269-270.
3. M. Hájek, *Microwave Catalysis in Organic Synthesis in Microwaves in Organic synthesis*, ed. A. Loupy, Wiley-VCH, Weinheim, **2002**, pp. 368.
4. C.E. Humphrey et al, *Org. Letters*, **2003**, 5, 849-852.
5. J. Kurfürstová, M. Hájek, *Res. Chem. Intermed.*, **2004**, 30, 673-681.

## **Remake to: “Specific activation by microwaves: Myth or Reality?”**

Bernd Ondruschka

*Friedrich Schiller University Jena, Lessingstr. 12, D-07743 Jena, www.ituc.uni-jena.de*

In the a.m. paper published in 1992 (cf. J. Org. Chem. 57, 7099-7102) one can read: “In the last few years there have been a growing interest in the use of microwave heating in organic synthesis ... it is unresolved whether the use of microwaves provides specific activation. Accurate comparing the use of microwave to conventional heating are needed. .... More studies are needed in which the reaction conditions are carefully controlled before the title question can be answered.”

About two decades later the team from Jena will offer a state-of-the-art-document on probability of the upper question.

At first we introduce our understanding to the semantic formulation “effect”, “microwave effect”, “(non)thermal effect” or “specific microwave effect”. It is clear as simple all comparisons need a relevant partner, in other words: a balance basis. All results (conversions, yields, selectivities, turnover numbers ...) are compared with these from thermal irradiated runs. With this both the comparability of the experimental parameters and the exact(!) measurement of temperature are necessary. Important is furthermore the distinction between the used phases (gas, liquid, plasma), the properties of educts and used catalysts, last but not least the regime parameters and possible consequences within the heating, material, and impulse balances.

At second we report on own new and newer results:

- Microwave-assisted liquid phase experiments – a list of selected runs is given - show no improvements or alterations (cf. disdescribing relevant reviews).
- Microwave-assisted liquid phase experiments in presence of lipases show also no improvement (cf. different citations).
- Microwave-assisted liquid phase experiments does not allow the enhancement of selectivities by very rapid heating rate.
- Microwave-assisted gas phase experiments in presence of catalysts led to results, which can be interpreted in the mirror of microwave effects.
- Combined microwave-UV experiments with an environmental remediation background let conclude the existence of cross-linked microwave effects.

At third it is informed on our attempts to define conditions for qualification and validation within microwave-initiated experiments. The consideration of these conditions would be the best guarantor for emotionless discussions on the existence of specific microwave effects.

As consequence we conclude the existence of effects under microwave regime is only to answer within a network of familiarity, of acceptance of good management practice, and of availability of innovative setups including top sensors and whose correct use.

## **Advancing Microwave Energy to New Heights with Simultaneous Cooling.**

E. Keller Barnhardt

*CEM Corporation, P.O. Box 200, 3100 Smith Farm Road, Matthews, NC 28106-0200.*

[Keller.Barnhardt@cem.com](mailto:Keller.Barnhardt@cem.com)

Microwave energy has been found to substantially enhance the rate of reactions. Through direct molecular activation and the resulting efficient energy transfers, chemists are able to use this novel technology to complete reactions in minutes instead of hours, or even days. More recent work has shown that, by using airflow to cool the reaction vessel while irradiating with microwave energy, a greater amount of power can be introduced to the reaction at the same temperature point. For some reactions, this increased power input results in greater conversion to product and higher yields, given the same timeframe. Work has also been done showing that microwave irradiation at sub-ambient temperatures serves to increase the rate of reaction; even at temperatures below that of the conventional reaction, microwaves accelerate the rate of transformation. Examples, supported by additional literature results, will be shown, demonstrating the benefits of being able to maintain a high energy input throughout the reaction.

### **Microwave-effects in synthetic chemistry**

NICHOLAS E. LEADBEATER

Department of Chemistry, U-3060, University of Connecticut, 55 North Eagleville Rd.  
Storrs, CT 06269-3060, USA, e-mail: [nicholas.leadbeater@uconn.edu](mailto:nicholas.leadbeater@uconn.edu)

The talk will outline our attempts to probe the evidence for and against a non-thermal microwave effect in relation to synthetic organic chemistry. Using the CEM microwave technologies PowerMax function, we have investigated the origins of non-thermal microwave effects in a range of organic transformations including Heck couplings, Michael additions, alkylations and Diels-Alder cycloadditions. Our results will be presented and the implications discussed.

## 4. Final Programme

### Friday 17 September 2004

Afternoon *Arrival*

### Saturday 18 September 2004

08:00 *Breakfast*

09:00 **Gabriel Crean**  
(Standing Committee for Physical and Engineering sciences)  
Presentation of the European Science Foundation (ESF)

09:15 **Oliver Kappe**  
Opening remarks

#### **Background: Microwave Theory**

09:30 **D. Michael P. Mingos , Nils Elander**  
Cavity Design (Multimode - Monomode), Dielectric Heating, Wave-Material Interactions

11:00 *Coffee break*

#### **Inorganic Chemistry / Material Sciences**

11:15 **Gavin Whittaker, Monika Willert-Porada  
Dariusz Bogdal**  
Inorganic Synthesis, Ceramics, Polymer Chemistry

13:00 *Lunch*

#### **Analytical Chemistry, Photochemistry, Biochemistry**

14:30 **Günther Knapp, Petr Klán / Peter Nilsson,  
Fernando Langa**  
Photochemistry, Biochemistry (PCR, enzymes),  
Analytical Chemistry

(16:00-16:15) *Coffee break*

17:30 Close of the day

18:00 *Dinner*

## Sunday 19 September 2004

### Organic Chemistry 1

09:00

**Jack Hamelin, Françoise Texier-Boullet /  
Thierry Besson Mats Larhed**

Dry Media Reactions, Homogeneous Catalysis,  
Heterocycle Synthesis

(10:30-10:45)

*Coffee break*

12:30

*Lunch*

### Organic Chemistry 2

13:30

**Milan Hajek, Bernd Ondruschka / Keller  
Barnhardt Nicholas E. Leadbeater**

Heterogeneous Catalysis, Gas-Phase Reactions,  
Heating-while-cooling

(15:00-15:30)

*Coffee break*

16:30

Round Table Discussion: Specific Microwave Effects,  
Nomenclature, Final Report

17:30

End of workshop  
*Dinner*

## Monday 20 September 2004

Morning

*Departure*

## 5. Final List of Participants

### Speakers

#### Austria

Prof. C. Oliver Kappe (Convenor)  
Institut für Chemie, Karl-Franzens-Universität  
Graz, Heinrichstrasse 28, A-8010 Graz, Austria  
P: +43-316-3805352; F: +43-316-3809840  
oliver.kappe@uni-graz.at

Prof. Günther Knapp  
Institut für Analytische Chemie, Mikro- und  
Radiochemie, Technische Universität Graz,  
Technikerstrasse 4, A-8010 Graz, Austria  
P: +43-316-8738302; F: +43-316-8738809  
knapp@analytchem.tu-graz.ac.at

#### Czech Republic

Prof. Milan Hájek  
Institute of Chemical Process Fundamentals  
Academy of Sciences of the Czech Republic  
Rozvojova 135, 165 02 Prague 6 - Suchbátka  
Czech Republic  
P: +420 220 390 334, 292  
Hajek@icpf.cas.cz

Prof. Petr Klán  
Department of Organic Chemistry  
Faculty of Science, Masaryk University  
Kotlarska 2, 611 37 Brno, Czech Republic  
P: +420-541129356; F: +420-541129641  
klan@sci.muni.cz

#### France

Prof. Jack Hamelin  
Synthèse et Electrosynthèse Organiques 3,  
C.N.R.S. UMR 6510  
Université de Rennes 1, Campus de Beaulieu, F-  
35042 RENNES Cedex, France  
P: +33 2 23 23 62 78; F: +33 2 23 23 63 74  
jhamelin@univ-rennes1.fr

Prof. Françoise Texier-Boullet  
Synthèse et Electrosynthèse Organiques 3,  
C.N.R.S. UMR 6510  
Université de Rennes 1, Campus de Beaulieu, F-  
35042 RENNES Cedex, France  
P: + 33 2 23 23 57 82, F: +33 2 23 23 63 74

Prof. Thierry Besson  
[Laboratoire de Génie Protéique et Cellulaire](#),  
EA3169 - UFR Sciences et Technologie,  
Université de La Rochelle, Avenue Michel  
Crépeau, 17042 La Rochelle cedex 1, France  
P : +33-546458276; F: +33-546458247  
tbesson@univ-lr.fr

#### Spain

Prof. Fernando Langa  
Fac. Ciencias del Medio Ambiente  
Campus de la Fabrica de Armas  
Univ. Castilla-La Mancha  
45071 TOLEDO, Spain  
P: +34-925-268843; F: +34-925-268840  
flanga@amb-to.uclm.es

#### Germany

Prof. Bernd Ondruschka  
Institut fuer Technische Chemie  
and Umweltchemie, Friedrich-Schiller-  
Universitaet Jena, Lessingstrasse 12  
D-07743 Jena, Germany  
P: +49-3641-948400; F:+49-3641-948402  
bernd.ondruschka@uni-jena.de

Prof. Monika Willert-Porada  
Universität Bayreuth  
Lehrstuhl für Werkstoffverarbeitung  
Bayreuth, Germany  
P: +49-921-557200  
bta701@uni-bayreuth.de

#### Poland

Prof. Dariusz Bogdal  
Department of Chemistry and Technology,  
Politechnika Krakowska ul. Warszawska 24  
31-155 Krakow, Poland  
P: +48-126282572; F: + 48-126282038  
pcbogdal@cyf-kr.edu.pl

#### Sweden

Dr. Mats Larhed  
Department of Medicinal Chemistry, Organic  
Pharmaceutical Chemistry; BMC, Uppsala  
University, Box 574, SE- 751 23  
Uppsala, SWEDEN  
P: +46 18 4714667, F: +46 18 4714474  
mats@orgfarm.uu.se

Dr. Peter Nilsson  
Department of Medicinal Chemistry, Organic  
Pharmaceutical Chemistry; BMC, Uppsala  
University, Box 574, SE- 751 23  
Uppsala, SWEDEN  
F: +46 18 4714474  
peter.nilsson@orgfarm.uu.se

Prof. Nils Elander  
Stockholm University, Department of Physics,  
SE 106 91 Stockholm, Sweden  
P: +46-8-55378656, F: +46-8-55378601  
elande@physto.se

#### **United Kingdom**

Prof. D. Michael P. Mingos  
The Principal's Lodgings  
St. Edmund Hall, Queens Lane  
Oxford, OX1 4AR  
United Kingdom  
P: +44-1865-279000  
michael.mingos@st-edmund-hall.oxford.ac.uk

Dr. Gavin Whittaker  
School of Chemistry, University of Edinburgh  
West Mains Road, Edinburgh, EH9 3JJ  
Scotland, United Kingdom  
P: +44-131 6504736; F: +44-131 6504745  
g.whittaker@ed.ac.uk

#### **Non ESF member countries:**

Dr. Keller Barnhardt  
CEM Corporation  
P.O. Box 200, 3100 Smith Farm Road  
Matthews, NC 28106-0200, USA  
P: +1-704-821-7015; F: +1-704-821-7894  
Email: keller.barnhardt@cem.com

Prof. Nicholas E Leadbeater  
Department of Chemistry  
University of Connecticut  
55 North Eagleville Road  
Storrs, CT 06269-3060, USA  
P: +1-860-486 5076; F: +1-860-4862981  
nicholas.leadbeater@uconn.edu

#### **Discussion Participants:**

Dr. Alexander Stadler  
Anton Paar GmbH  
Anton-Paar-Str. 20  
A-8054 Graz, Austria  
P: +43-316-257-356; F: +43-316-257-9360  
alexander.stadler@anton\_paar.com

Prof. Pino Pilotti  
Biotage AB, Kungsgatan 76  
SE-753 18 Uppsala, Sweden  
P: +46 18 489 9000; F: +46 18 489 9200  
pino.pilotti@personalchemistry.com

Dr. Bimbisar Desai  
Institut für Chemie, Karl-Franzens-Universität  
Graz, Heinrichstrasse 28, A-8010 Graz, Austria  
P: +43-316-3805336; F: +43-316-3809840  
bimbisar.desai@uni-graz.at

## **6. Statistical Information**

### **Age Structure of Participants (Young Scientists)**

11 participants (out of 21) were under the age of 40 with less than 5 years in a permanent position (Kappe, Klan, Besson, Bogdal, Larhed, Nilsson, Whittaker, Barnhardt, Leadbeater, Stadler, Desai)

### **Countries of Origin, see also point 5 above**

ESF: Austria (4), Czech Republic (2), France (3), Spain (1), Germany (2), Poland (1), Sweden (4), United Kingdom (2)

Non-ESF: United States (2)

### **Gender Distribution**

Male: (18), Female: (3)

### **Industrial/Academic Split**

Industry: 3

Academia: 18