Microwaves in Organic and Medicinal Chemistry
Methods and Principles in Medicinal Chemistry

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Preface

Until recently, the application of microwaves in organic synthesis was a curiosity. Starting in 1986, but increasing in use only from the mid-nineties onwards, microwave heating has now become a wide-spread technique in organic chemistry. On the one hand, this development was enabled and assisted by the availability of commercial microwave equipment, which produces much more homogeneous heating conditions than the formerly used domestic microwave ovens. On the other hand, organic chemists realized that microwave heating not only significantly speeds up chemical reactions from hours or days to minutes but also enables “new” chemistry.

Medicinal chemistry has the need for large sets of new compounds, with druglike character and structural diversity. Originally, combinatorial chemistry was expected to generate a vast amount of new drug candidates, due to the sheer numbers of analogs that can be produced in parallel. Unfortunately, these early expectations were not met. Large series of chemically related analogs were produced, in libraries of up to millions of compounds, but most of these compounds were completely inactive. Design was dominated by synthetic accessibility, not by medicinal chemistry knowhow. Thus, in recent years combinatorial chemistry developed from mixtures of impure compounds to libraries of purified, single compounds, from mere chemicals to druglike structures, and from large libraries to much smaller libraries with different scaffolds. Microwave applications aid to produce such libraries within extremely short time – this application possibly being the most important use of this fascinating new approach.

Since long C. Oliver Kappe, Karl Franzens University, Graz, Austria, is an internationally leading expert in microwave chemistry. In 2000, he created the “microwaves in organic chemistry” (MAOS) Website as information source for organic and medicinal chemists (www.maos.net), informing there about recent literature and providing links to the Websites of instrument vendors and other MAOS-related organizations. Correspondingly, the Editors of the series “Methods and Principles of Medicinal Chemistry” asked Oliver Kappe and his former coworker Alexander Stadler, now at Anton Paar GmbH, Graz, to contribute to our series “Methods and Principles in Medicinal Chemistry” a book on practical applications of microwave chemistry.

“Microwaves in Organic and Medicinal Chemistry” is the very first monograph on this topic, which deals not only with mere synthetic applications of microwave
chemistry but primarily with typical applications in medicinal chemistry. After a brief introduction into microwave synthesis and its history, theory and differences to classical heating are discussed, followed by a chapter on different commercial equipment for microwave heating. Microwave processing techniques, the use of microwave reactors and general comments on reaction optimization are discussed in the next two chapters. Two literature surveys, Part A, General organic synthesis, and Part B, Combinatorial and high-throughput synthesis methods, constitute the major part of the book. Organic reactions, from Heck to Pauson-Khand reactions and from Diels-Alder reactions to Michael additions, are discussed in a systematic manner. Afterwards syntheses of N-, O-, and S-containing five- and six-membered heterocyclic ring systems are presented, followed by sections on, e.g., peptide synthesis, multicomponent reactions, and the use of polymer-supported reagents, catalysts, and scavengers. The final chapter presents an outlook and conclusions.

This book is a treasure trove for every organic and medicinal chemist. From personal experience we confirm: once being familiar with microwave heating one would not like to miss it any longer! Oliver Kappe and Alexander Stadler aid with their monograph to the further broad distribution of microwave-supported organic synthesis. We are very grateful for their excellent contribution, as well as we thank the publisher Wiley-VCH, especially Dr. Frank Weinreich, for ongoing support of the series “Methods and Principles in Medicinal Chemistry”.

May 2005

Raimund Mannhold, Düsseldorf
Hugo Kubinyi, Weisenheim am Sand
Gerd Folkes, Zurich
Personal Foreword

We are currently witnessing an explosive growth in the general field of “microwave chemistry”. The increase of interest in this technology stems from the realization that microwave-assisted synthesis, apart from many other enabling technologies, actually provides significant practical and economic advantages. Although microwave chemistry is currently used in both academic and industrial contexts, the impact on the pharmaceutical industry especially, has led to the development of microwave-assisted organic synthesis (MAOS) from a laboratory curiosity in the 1980s and 1990s to a fully accepted technology today. The field has grown such that nearly every pharmaceutical company and more and more academic laboratories now actively utilize this technology for their research.

One of the main barriers facing a synthetic chemist contemplating the use of microwave synthesis today is – apart from access to suitable equipment – obtaining education and information on the fundamental principles and possible applications of this new technology. Thus, the aim of this book is to give the reader a well-structured, up-to-date, and exhaustive overview of known synthetic procedures involving the use of microwave technology, and to illuminate the “black box” stigma that microwave chemistry still has.

Our main motivation for writing “Microwaves in Organic and Medicinal Chemistry” derived from our experience in teaching microwave chemistry in the form of short courses and workshops to researchers from the pharmaceutical industry. In fact, the structure of this book closely follows a course developed for the American Chemical Society and can be seen as a compendium for this course. It is hoped that some of the chapters of this book are sufficiently convincing as to encourage scientists not only to use microwave synthesis in their research, but also to offer training for their students or co-workers.

We would like to thank Hugo Kubinyi for his encouragement and motivation to write this book. Thanks are also due to Mats Larhed, Nicholas E. Leadbeater, Erik Van der Eycken and scientists from Anton Paar GmbH, Biotage AB, CEM Corp., and Milestone s.r.l., who have been kind enough to read various sections of the manuscript and to provide valuable suggestions. Foremost we would like to thank Doris Dallinger, Bimbisar Desai, Toma Glasnov, Jenny Kremsner and the other members of the Kappe research group for spending their time searching the “microwave literature”, and for tolerating this distraction. We are particularly indebted to
Doris Dallinger for carefully proofreading the complete manuscript, and to Jenny Whedbee for providing the cover art. We are very grateful to Frank Weinreich and his colleagues at Wiley-VCH for their assistance during the preparation of the manuscript and for the preparation of the finished book.

This book is dedicated to Rajender S. Varma, a pioneer in the field of microwave synthesis, who inspired us to enter this exciting research area in the 1990s.

Graz, Austria, April 2005

C. Oliver Kappe
Alexander Stadler
1

Introduction: Microwave Synthesis in Perspective

1.1 Microwave Synthesis and Medicinal Chemistry

Improving research and development (R&D) productivity is one of the biggest tasks facing the pharmaceutical industry. In the next 10 years, the pharmaceutical industry will see many patents of drugs expire. In order to remain competitive, pharmaceutical companies need to pursue strategies that will offset the sales decline and see robust growth and shareholder value. The impact of genomics and proteomics is creating an explosion in the number of drug targets. Today’s drug therapies are based solely on approximately 500 biological targets, while in 10 years from now the number of targets could well reach 10,000. In order to identify more potential drug candidates for all of these targets, pharmaceutical companies have made major investments in high-throughput technologies for genomic and proteomic research, combinatorial chemistry, and biological screening. However, lead compound optimization and medicinal chemistry remain the bottlenecks in the drug discovery process. Developing chemical compounds with the desired biological properties is time-consuming and expensive. Consequently, increasing interest is being directed toward technologies that allow more rapid synthesis and screening of chemical substances to identify compounds with functional qualities.

Medicinal chemistry has benefited tremendously from the technological advances in the field of combinatorial chemistry and high-throughput synthesis. This discipline has been the innovative machine for the development of methods and technologies which accelerate the design, synthesis, purification, and analysis of compound libraries. These new tools have had a significant impact on both lead identification and lead optimization in the pharmaceutical industry. Large compound libraries can now be designed and synthesized to provide valuable leads for new therapeutic targets. Once a chemist has developed a suitable high-speed synthesis of a lead, it is now possible to synthesize and purify hundreds of molecules in parallel to discover new leads and/or to derive structure–activity relationships (SAR) in unprecedented timeframes.

The bottleneck of conventional parallel/combinatorial synthesis is typically optimization of reaction conditions to afford the desired products in suitable yields and purities. Since many reaction sequences require at least one or more heating steps for extended time periods, these optimizations are often difficult and time-consum-
Ing. Microwave-assisted heating under controlled conditions has been shown to be an invaluable technology for medicinal chemistry and drug discovery applications since it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds. Many reaction parameters can be evaluated in a few hours to optimize the desired chemistry. Compound libraries can then be rapidly synthesized in either a parallel or (automated) sequential format using this new, enabling technology. In addition, microwave synthesis allows for the discovery of novel reaction pathways, which serve to expand “chemical space” in general, and “biologically relevant, medicinal chemistry space” in particular.

Specifically, microwave synthesis has the potential to impact upon medicinal chemistry efforts in at least three major phases of the drug discovery process: lead generation, hit-to-lead efforts, and lead optimization. Medicinal chemistry addresses what are fundamentally biological and clinical problems. Focusing first on the preparation of suitable molecular tools for mechanistic validation, efforts ultimately turn to the optimization of biochemical, pharmacokinetic, pharmacological, clinical, and competitive properties of drug candidates. A common theme throughout this drug discovery and development process is speed. Speed equals competitive advantage, more efficient use of expensive and limited resources, faster exploration of structure–activity relationships (SAR), enhanced delineation of intellectual property, more timely delivery of critically needed medicines, and can ultimately determine positioning in the marketplace. To the pharmaceutical industry and the medicinal chemist, time truly does equal money, and microwave chemistry has become a central tool in this fast-paced, time-sensitive field.

Chemistry, like all sciences, consists of never-ending iterations of hypotheses and experiments, with results guiding the progress and development of projects. The short reaction times provided by microwave synthesis make it ideal for rapid reaction scouting and optimization, allowing very rapid progress through the “hypotheses-experiment-results” iterations, resulting in more decision points per unit time. In order to fully benefit from microwave synthesis, one has to “be prepared to fail in order to succeed”. While failure could cost a few minutes, success would gain many hours or even days. The speed at which multiple variations of reaction conditions can be performed allows a morning discussion of “What should we try?” to become an after lunch discussion of “What were the results?” (the “let’s talk after lunch” mantra) [1]. Not surprisingly, therefore, most pharmaceutical, agrochemical, and biotechnology companies are already heavily using microwave synthesis as frontline methodology in their chemistry programs, both for library synthesis and for lead optimization, as they realize the ability of this enabling technology to speed chemical reactions and therefore the drug discovery process.

1.2 Microwave-Assisted Organic Synthesis (MAOS) – A Brief History

While fire is now rarely used in synthetic chemistry, it was not until Robert Bunsen invented the burner in 1855 that the energy from this heat source could be applied
to a reaction vessel in a focused manner. The Bunsen burner was later superseded by the isomantle, the oil bath or the hot plate as a means of applying heat to a chemical reaction. In the past few years, heating and driving chemical reactions by microwave energy has been an increasingly popular theme in the scientific community [1, 2].

Microwave energy, originally applied for heating foodstuffs by Percy Spencer in the 1940s, has found a variety of technical applications in the chemical and related industries since the 1950s, in particular in the food-processing, drying, and polymer industries. Other applications range from analytical chemistry (microwave digestion, ashing, extraction) [3] to biochemistry (protein hydrolysis, sterilization) [3], pathology (histoprocessing, tissue fixation) [4], and medical treatments (diathermy) [5]. Somewhat surprisingly, microwave heating has only been implemented in organic synthesis since the mid-1980s. The first reports on the use of microwave heating to accelerate organic chemical transformations (MAOS) were published by the groups of Richard Gedye (Scheme 1.1) [6] and Raymond J. Giguere/George Majetich [7] in 1986. In those early days, experiments were typically carried out in sealed Teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements. The results were often violent explosions due to the rapid uncontrolled heating of organic solvents under closed-vessel conditions. In the 1990s, several groups started to experiment with solvent-free microwave chemistry (so-called dry-media reactions), which eliminated the danger of explosions [8]. Here, the reagents were pre-adsorbed onto either an essentially microwave-transparent (i.e., silica, alumina or clay) or strongly absorbing (i.e., graphite) inorganic support, that additionally may have been doped with a catalyst or reagent. Particularly in the early days of MAOS, the solvent-free approach was very popular since it allowed the safe use of domestic microwave ovens and standard open-vessel technology. While a large number of interesting transformations using “dry-media” reactions have been published in the literature [8], technical difficulties relating to non-uniform heating, mixing, and the precise determination of the reaction temperature remained unresolved, in particular when scale-up issues needed to be addressed.

Alternatively, microwave-assisted synthesis has been carried out using standard organic solvents under open-vessel conditions. If solvents are heated by microwave irradiation at atmospheric pressure in an open vessel, the boiling point of the solvent typically limits the reaction temperature that can be achieved. In order to none-

Scheme 1.1 Hydrolysis of benzamide. The first published example (1986) of microwave-assisted organic synthesis.
1 Introduction: Microwave Synthesis in Perspective

Nevertheless achieve high reaction rates, high-boiling microwave-absorbing solvents have been frequently used in open-vessel microwave synthesis [9]. However, the use of these solvents presented serious challenges in relation to product isolation and recycling of the solvent. Because of the recent availability of modern microwave reactors with on-line monitoring of both temperature and pressure, MAOS in dedicated sealed vessels using standard solvents – a technique pioneered by Christopher R. Strauss in the mid-1990s [10] – has been celebrating a comeback in recent years. This is clearly evident surveying the recently published (since 2001) literature in the area of controlled microwave-assisted organic synthesis (MAOS). It appears that the combination of rapid heating by microwaves with sealed-vessel (autoclave) technology will most likely be the method of choice for performing MAOS on a laboratory scale in the future. Importantly, recent innovations in microwave reactor technology now allow controlled parallel and automated sequential processing under sealed-vessel conditions, and the use of continuous- or stop-flow reactors for scale-up purposes.

Since the early days of microwave synthesis, the observed rate accelerations and sometimes altered product distributions compared to oil-bath experiments have led to speculation on the existence of so-called “specific” or “non-thermal” microwave effects [11]. Historically, such effects were claimed when the outcome of a synthesis performed under microwave conditions was different from that of the conventionally heated counterpart at the same apparent temperature. Reviewing the present literature [12], it appears that today most scientists agree that in the majority of cases the reason for the observed rate enhancements is a purely thermal/kinetic effect, i.e., a consequence of the high reaction temperatures that can rapidly be attained when irradiating polar materials in a microwave field, although effects that are caused by the unique nature of the microwave dielectric heating mechanism (“specific microwave effects”) clearly also need to be considered. While for the medicinal chemist in industry this discussion may seem largely irrelevant, the debate on “microwave effects” is undoubtedly going to continue for many years in the academic world. Regardless of the nature of the observed rate enhancements (for further details on microwave effects, see Section 2.5), microwave synthesis has now truly matured and has moved from a laboratory curiosity in the late 1980s to an established technique in organic synthesis, heavily used in both academia and industry.

The initially slow uptake of the technology in the late 1980s and 1990s has been attributed to its lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating. The risks associated with the flammability of organic solvents in a microwave field and the lack of available dedicated microwave reactors allowing for adequate temperature and pressure control were major concerns. Important instrument innovations (see Chapter 3) now allow for careful control of time, temperature, and pressure profiles, paving the way for reproducible protocol development, scale-up, and transfer from laboratory to laboratory and from scientist to scientist. Today, microwave chemistry is as reliable as the vast arsenal of synthetic methods that preceded it. Since 2001, therefore, the number of publications related to MAOS has increased dramatically (Fig. 1.1), to such a level that it might be assumed that, in a few years, most chemists
will probably use microwave energy to heat chemical reactions on a laboratory scale [1, 2]. Not only is direct microwave heating able to reduce chemical reaction times significantly, but it is also known to reduce side reactions, increase yields, and improve reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a technology for rapid reaction optimization, for the efficient synthesis of new chemical entities, or for discovering and probing new chemical reactivity.

1.3 Scope and Organization of the Book

Today, a large body of work on microwave-assisted synthesis exists in the published and patent literature. Many review articles [8–20], several books [21–23], and information on the world-wide-web [24] already provide extensive coverage of the subject. The goal of the present book is to present carefully scrutinized, useful, and practical information for both beginners and advanced practitioners of microwave-assisted organic synthesis. Special emphasis is placed on concepts and chemical transformations that are of importance to medicinal chemists, and that have been reported in the most recent literature (2002–2004). The extensive literature survey is limited to reactions that have been performed using controlled microwave heating conditions, i.e., where dedicated microwave reactors for synthetic applications with adequate
temperature and pressure measurements have been employed. After a discussion of microwave dielectric heating theory and microwave effects (Chapter 2), a review of the existing equipment for performing MAOS is presented (Chapter 3). This is followed by a chapter outlining the different processing techniques in a microwave-heated experiment (Chapter 4) and a chapter on “how to get started” with microwave synthesis, including safety aspects (Chapter 5). Finally, a literature survey with more than 600 references is presented in Chapters 6, 7, and 8.

References


[24] For online resources on microwave-assisted organic synthesis (MAOS), see: www.maos.net.
The physical principles behind and the factors determining the successful application of microwaves in organic synthesis are not widely familiar to chemists, possibly because electric field theory is generally taught in engineering or physics rather than in chemistry. Nevertheless, it is essential for the synthetic chemist involved in microwave-assisted organic synthesis to have at least a basic knowledge of the underlying principles of microwave–matter interactions and on microwave effects. The basic understanding of macroscopic microwave interactions with matter was formulated by von Hippel in the mid-1950s [1]. In this chapter, a brief summary on the current understanding of microwaves and their interactions with matter is given. For more in depth discussion of this quite complex field, the reader is referred to recent review articles [2–5].

2 Microwave Theory

Microwave irradiation is electromagnetic irradiation in the frequency range of 0.3 to 300 GHz, corresponding to wavelengths of 1 cm to 1 m. The microwave region of the electromagnetic spectrum (Fig. 2.1) therefore lies between infrared and radio frequencies. Wavelengths between 1 cm and 25 cm are extensively used for RADAR transmissions and the remaining wavelength range is used for telecommunications. All domestic “kitchen” microwave ovens and all dedicated microwave reactors for chemical synthesis that are commercially available today operate at a frequency of 2.45 GHz (corresponding to a wavelength of 12.25 cm) in order to avoid interference with telecommunication and cellular phone frequencies. There are other frequency allocations for microwave heating applications (ISM frequencies, see Table 2.1) [6], but these are not generally employed in dedicated reactors for synthetic chemistry. Indeed, published examples of organic syntheses carried out with microwave heating at frequencies other than 2.45 GHz are extremely rare [7].
From comparison of the data presented in Table 2.2 [8], it is obvious that the energy of the microwave photon at a frequency of 2.45 GHz (0.0016 eV) is too low to cleave molecular bonds and is also lower than Brownian motion. It is therefore clear that microwaves cannot “induce” chemical reactions by direct absorption of electromagnetic energy, as opposed to ultraviolet and visible radiation (photochemistry).

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Table 2.2 Comparison of radiation types and bond energies (data from [6, 8]).

<table>
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<th>Radiation type</th>
<th>Frequency (MHz)</th>
<th>Quantum energy (eV)</th>
<th>Bond type</th>
<th>Bond energy (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma rays</td>
<td>$3.0 \times 10^{14}$</td>
<td>$1.24 \times 10^6$</td>
<td>CC single bond</td>
<td>3.61</td>
</tr>
<tr>
<td>X-rays</td>
<td>$3.0 \times 10^{13}$</td>
<td>$1.24 \times 10^5$</td>
<td>CC double bond</td>
<td>6.35</td>
</tr>
<tr>
<td>Ultraviolet</td>
<td>$1.0 \times 10^9$</td>
<td>4.1</td>
<td>CO single bond</td>
<td>3.74</td>
</tr>
<tr>
<td>Visible light</td>
<td>$6.0 \times 10^8$</td>
<td>2.5</td>
<td>CO double bond</td>
<td>7.71</td>
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<tr>
<td>Infrared light</td>
<td>$3.0 \times 10^6$</td>
<td>0.012</td>
<td>CH bond</td>
<td>4.28</td>
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<tr>
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<td>2450</td>
<td>0.0016</td>
<td>OH bond</td>
<td>4.80</td>
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<tr>
<td>Radiofrequencies</td>
<td>1</td>
<td>$4.0 \times 10^{-9}$</td>
<td>Hydrogen bond</td>
<td>0.04–0.44</td>
</tr>
</tbody>
</table>
2.2 Microwave Dielectric Heating

Microwave-enhanced chemistry is based on the efficient heating of materials by "microwave dielectric heating" effects [4, 5]. Microwave dielectric heating is dependent on the ability of a specific material (for example, a solvent or reagent) to absorb microwave energy and convert it into heat. Microwaves are electromagnetic waves which consist of an electric and a magnetic field component (Fig. 2.2). For most practical purposes related to microwave synthesis it is the electric component of the electromagnetic field that is of importance for wave–material interactions, although in some instances magnetic field interactions (for example with transition metal oxides) can also be of relevance [9].

![Electric and magnetic field components in microwaves.](image)

The electric component of an electromagnetic field causes heating by two main mechanisms: dipolar polarization and ionic conduction. The interaction of the electric field component with the matrix is called the dipolar polarization mechanism (Fig. 2.3.a) [4, 5]. For a substance to be able to generate heat when irradiated with microwaves it must possess a dipole moment. When exposed to microwave frequencies, the dipoles of the sample align in the applied electric field. As the applied field oscillates, the dipole field attempts to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss. The amount of heat generated by this process is directly related to the ability of the matrix to align itself with the frequency of the applied field. If the dipole does not have enough time to realign (high-frequency irradiation) or reorients too quickly (low-frequency irradiation) with the applied field, no heating occurs. The allocated frequency of 2.45 GHz used in all commercial systems lies between these two extremes and gives the molecular dipole time to align in the field, but not to follow the alternating field precisely. Therefore, as the dipole reorients to align itself with the electric field, the field is already changing and generates a phase difference between the orientation of the field and that of the dipole. This phase difference causes energy to be lost from the dipole by molecular friction and collisions, giving rise to dielectric heating. In summary, field energy is transferred to the medi-
um and electrical energy is converted into kinetic or thermal energy, and ultimately into heat. It should be emphasized that the interaction between microwave radiation and the polar solvent which occurs when the frequency of the radiation approximately matches the frequency of the rotational relaxation process is not a quantum mechanical resonance phenomenon. Transitions between quantized rotational bands are not involved and the energy transfer is not a property of a specific molecule, but the result of a collective phenomenon involving the bulk [4, 5]. The heat is generated by frictional forces occurring between the polar molecules, the rotational velocity of which has been increased by the coupling with the microwave irradiation. It should also be noted that gases cannot be heated under microwave irradiation, since the distance between the rotating molecules is too great. Similarly, ice is also (nearly) microwave transparent, since the water dipoles are constrained in a crystal lattice and cannot move as freely as in the liquid state.

The second major heating mechanism is the ionic conduction mechanism (Fig. 2.3.b) [4, 5]. During ionic conduction, as the dissolved charged particles in a sample (usually ions) oscillate back and forth under the influence of the microwave field, they collide with their neighboring molecules or atoms. These collisions cause agitation or motion, creating heat. Thus, if two samples containing equal amounts of distilled water and tap water, respectively, are heated by microwave irradiation at a fixed radiation power, more rapid heating will occur for the tap water sample due to its ionic content. Such ionic conduction effects are particularly important when considering the heating behavior of ionic liquids in a microwave field (see Section 4.3.3.2). The conductivity principle is a much stronger effect than the dipolar rotation mechanism with regard to the heat-generating capacity.

![Fig. 2.3](image)

(a) Dipolar polarization mechanism. (b) Dipolar molecules try to align with an oscillating electric field. Ionic conduction mechanism. Ions in solution will move in the electric field.

### 2.3 Dielectric Properties

The heating characteristics of a particular material (for example, a solvent) under microwave irradiation conditions are dependent on the dielectric properties of the material. The ability of a specific substance to convert electromagnetic energy into heat at a given frequency and temperature is determined by the so-called loss tangent, \( \tan \delta \). The loss factor is expressed as the quotient \( \tan \delta = \varepsilon''/\varepsilon' \), where \( \varepsilon'' \) is the dielectric loss, indicative of the efficiency with which electromagnetic radiation is
2.3 Dielectric Properties

converted into heat, and $\varepsilon'$ is the dielectric constant describing the polarizability of the molecules in the electric field. A reaction medium with a high $\tan \delta$ is required for efficient absorption and, consequently, for rapid heating. Materials with a high dielectric constant such as water ($\varepsilon'$ at 25°C = 80.4) may not necessarily also have a high $\tan \delta$ value. In fact, ethanol has a significantly lower dielectric constant ($\varepsilon'$ at 25°C = 24.3), but heats much more rapidly than water in a microwave field due to its higher loss tangent ($\tan \delta$: ethanol = 0.941, water = 0.123). The loss tangents for some common organic solvents are summarized in Table 2.3 [10]. In general, solvents can be classified as high ($\tan \delta > 0.5$), medium ($0.1 \leq \tan \delta \leq 0.5$), or low microwave-absorbing ($\tan \delta < 0.1$). Other common solvents without a permanent dipole moment, such as carbon tetrachloride, benzene, and dioxane, are more or less microwave-transparent. It has to be emphasized that a low $\tan \delta$ value does not preclude a particular solvent from being used in a microwave-heated reaction. Since either the substrates or some of the reagents/catalysts are likely to be polar, the overall dielectric properties of the reaction medium will in most cases allow sufficient heating by microwaves. Furthermore, polar additives such as alcohols or ionic liquids can be added to otherwise low-absorbing reaction mixtures in order to increase the absorbance level of the medium (see Section 4.3.3.2).

The loss tangent values are both frequency- and temperature-dependent. Fig. 2.4 shows the dielectric properties of distilled water as a function of frequency at 25°C [1, 4, 5]. It is apparent that the dielectric loss $\varepsilon''$ has an appreciable value over a wide frequency range. The dielectric loss $\varepsilon''$ goes through a maximum as the dielectric constant $\varepsilon'$ falls. The heating, as measured by $\varepsilon''$, reaches its maximum at around 18 GHz, while all domestic microwave ovens and dedicated reactors for chemical synthesis operate at a much lower frequency, 2.45 GHz. The practical reason for the lower frequency is the necessity to heat food efficiently throughout its interior. If the frequency is optimal for a maximum heating rate, the microwaves are absorbed in the outer regions of the food, and penetrate only a short distance [4].

According to definition, the penetration depth is the point where 37% (1/e) of the initially irradiated microwave power is still present [6]. The penetration depth is in-

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$\tan \delta$</th>
<th>Solvent</th>
<th>$\tan \delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene glycol</td>
<td>1.350</td>
<td>N,N-dimethylformamide</td>
<td>0.161</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.941</td>
<td>1,2-dichloroethane</td>
<td>0.127</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>0.825</td>
<td>Water</td>
<td>0.123</td>
</tr>
<tr>
<td>2-propanol</td>
<td>0.799</td>
<td>Chlorobenzene</td>
<td>0.101</td>
</tr>
<tr>
<td>Formic acid</td>
<td>0.722</td>
<td>Chloroform</td>
<td>0.091</td>
</tr>
<tr>
<td>Methanol</td>
<td>0.659</td>
<td>Acetonitrile</td>
<td>0.062</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>0.589</td>
<td>Ethyl acetate</td>
<td>0.059</td>
</tr>
<tr>
<td>1-butanol</td>
<td>0.571</td>
<td>Acetone</td>
<td>0.054</td>
</tr>
<tr>
<td>2-butanol</td>
<td>0.447</td>
<td>Tetrahydrofuran</td>
<td>0.047</td>
</tr>
<tr>
<td>1,2-dichlorobenzene</td>
<td>0.280</td>
<td>Dichloromethane</td>
<td>0.042</td>
</tr>
<tr>
<td>1-methyl-2-pyrrolidone</td>
<td>0.275</td>
<td>Toluene</td>
<td>0.040</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>0.174</td>
<td>Hexane</td>
<td>0.020</td>
</tr>
</tbody>
</table>
versely proportional to $\tan \delta$ and therefore critically depends on factors such as temperature and irradiation frequency. For a solvent such as water, the penetration depth at room temperature is only of the order of a few centimeters. The dielectric loss and loss tangent of water and most other organic solvents decrease with increasing temperature (Fig. 2.5), hence the absorption of microwave radiation in water
decreases at higher temperatures. In turn, the penetration depth of microwaves increases. Issues relating to the penetration depth are critically important when considering the scale-up of MAOS (see Section 4.5).

The interaction of microwave irradiation with matter is characterized by three different processes: absorption, transmission and reflection. Highly dielectric materials such as polar organic solvents strongly absorb microwaves and consequently rapid heating of the medium ensues. Non-polar materials exhibit only small interactions with penetrating microwaves and can thus be used as construction materials for reactors. If microwave radiation is reflected by the material surface, there is little or no coupling of energy in the system. The temperature of the material increases only marginally. This holds true in particular for metals with high conductivity.

2.4 Microwave Versus Conventional Thermal Heating

Traditionally, organic synthesis is carried out by conductive heating with an external heat source (for example, an oil bath or heating mantle). This is a comparatively slow and inefficient method for transferring energy into the system since it depends on convection currents and on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture. In addition, a temperature gradient can develop within the sample and local overheating can lead to product, substrate or reagent decomposition.

![Fig. 2.6 Inverted temperature gradients in microwave versus oil-bath heating [12]. Temperature profiles (finite element modeling) after 1 min as affected by microwave irradiation (left) compared to treatment in an oil bath (right). Microwave irradiation raises the temperature of the whole volume simultaneously (bulk heating), whereas in the oil-heated tube the reaction mixture in contact with the vessel wall is heated first. Temperature scales in Kelvin. Reproduced with permission from [12].](image-url)
In contrast, microwave irradiation produces efficient internal heating (in core volumetric heating) by direct coupling of microwave energy with the molecules (solvents, reagents, catalysts) that are present in the reaction mixture. Since the reaction vessels employed are typically made out of (nearly) microwave-transparent materials such as borosilicate glass, quartz or Teflon, the radiation passes through the walls of the vessel and an inverted temperature gradient as compared to conventional thermal heating results (Fig. 2.6). If the microwave cavity is well designed, the temperature increase will be uniform throughout the sample. The very efficient internal heat transfer results in minimized wall effects (no hot vessel surface), which may lead to the observation of so-called specific microwave effects (see Section 2.5.2), for example in the context of diminished catalyst deactivation. It should be emphasized that microwave dielectric heating and thermal heating by convection are totally different processes, and that any comparison between the two is inherently difficult.

2.5 Microwave Effects

Despite the relatively large body of published work on microwave-assisted chemistry (see Chapters 6 and 7), and the basic understanding of high-frequency electromagnetic irradiation and microwave–matter interactions, the exact reasons why and how microwaves enhance chemical processes are still not fully understood. Several groups have speculated on the existence of so-called “microwave effects” [13]. Such “microwave effects” could be the consequence of specific wave–material interactions, leading to a decrease in activation energy or an increase in the pre-exponential factor in the Arrhenius law due to orientation effects of polar species in an electromagnetic field [13]. Other researchers strictly denounce the existence of non-thermal effects and rationalize all rate enhancements in terms of the rapid heating and the high temperatures that are attained in a microwave-heated chemical reaction [14], the formation of microscopic or macroscopic hotspots, or the selective heating of a specific component in the reaction mixture [15]. The controversy about microwave effects has led to heated debates at microwave chemistry conferences and in the chemical literature [13–17]. Although the present chapter cannot provide a definitive answer on the issue of microwave effects, the basic concepts will be illustrated in the following sections.

It should be obvious from a scientific standpoint that the question of microwave effects needs to be addressed in a serious manner, given the rapid increase in the use of microwave technology in chemical sciences, in particular organic synthesis. There is an urgent need to remove the “black box” stigma of microwave chemistry and to provide a scientific rationalization for the observed effects. This is even more important if one considers safety aspects once this technology moves from small-scale laboratory work to pilot- or production-scale instrumentation.

Since the early days of microwave synthesis, the observed rate accelerations and sometimes altered product distributions compared to oil-bath experiments have led to speculation on the existence of so-called “specific” or “non-thermal” microwave effects. Historically, such effects were claimed when the outcome of a synthesis per-