Methods and Principles in Medicinal Chemistry

C. Oliver Kappe, Alexander Stadler,
and Doris Dallinger

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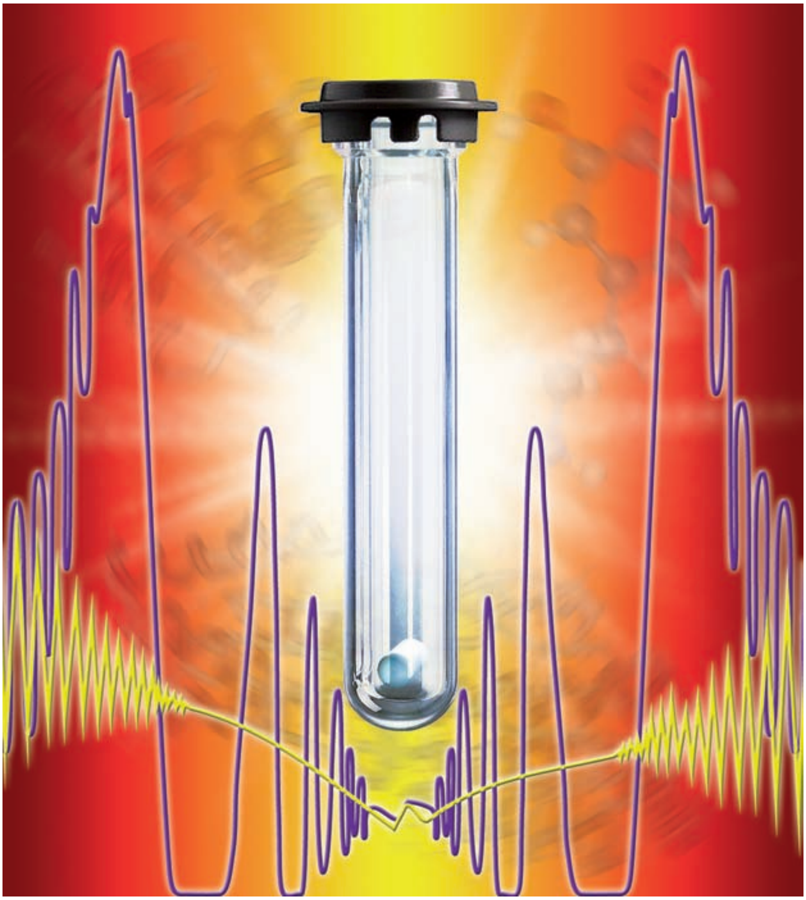
Microwaves in Organic and Medicinal Chemistry

Second, Completely Revised and
Enlarged Edition



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C. Oliver Kappe, Alexander Stadler, and Doris Dallinger

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Preface

The application of microwaves marks a real revolution in synthetic organic chemistry. Although it was more or less a curiosity, only a few decades ago, the rapid development within this field made it necessary to come up with a second, completely revised edition of the standard monograph, *Microwaves in Organic and Medicinal Chemistry*, by Oliver Kappe and Alexander Stadler, published in this book series in 2005. Indeed, the current edition is not just an updated version, but a completely new monograph as one can see from the increase in size, from originally 409 pages to almost 700 pages! An enormous amount of recent literature has been considered and included, making these two volumes now the new "gold standard" of microwave chemistry.

Especially in medicinal chemistry, yield and elegance of the synthesis of a new compound are no issue – only a minor amount of pure material is needed to screen for biological properties. Only later and only for a negligibly small number of potential candidates, better synthetic strategies have to be developed. Thus, microwave-supported synthesis is the first choice to quickly (and simply) create a multitude of test compounds.

We, the editors of the book series Methods and Principles in Medicinal Chemistry, are very grateful to Oliver Kappe, Alexander Stadler, and Doris Dallinger for having undertaken this enormous effort. We are also grateful to Frank Weinreich for his ongoing engagement in our book series and to Heike Noethe, both at Wiley-VCH Verlag GmbH, for her editorial support.

January 2012
Düsseldorf *Raimund Mannhold*
Weisenheim am Sand *Hugo Kubinyi*
Zurich *Gerd Folkers*

Personal Foreword to the First Edition

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 developed 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 to use 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 coworkers.

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 srl, who have been kind enough to read various sections of this book and to provide valuable suggestions. First and foremost, we would like to thank Doris Dallinger, Bimbisar Desai, Toma Glasnov, Jenny Kremsner, and 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 text and to Jenny Wheedby for providing the cover art. We are very grateful to Dr. Frank Weinreich and other editors at Wiley-VCH Verlag GmbH for their assistance in bringing out this 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
December 2004

C. Oliver Kappe
Alexander Stadler

Personal Foreword to the Second Edition

In more than 6 years since the manuscript submission for the first edition of *Microwaves in Organic and Medicinal Chemistry*, many things have changed. In contrast to 2004, microwave chemistry now is truly an established technology, especially in the pharmaceutical industry. Most medicinal chemists are now so accustomed to this nonclassical form of heating that taking their microwave reactors away from them would probably cause significant chaos in the laboratory. To a somewhat smaller extent, dedicated microwave instruments are however slowly replacing oil baths and heating mantles in many academic labs. Importantly, the speculation and confusion about "microwave effects" that persisted for many years have now subsided and most scientists today accept the fact that microwave chemistry is a great way to heat reaction mixtures in sealed tubes with very accurate control of the reaction parameters and to do synthesis in general.

Based on these facts, we now present the second, extensively updated, edition of *Microwaves in Organic and Medicinal Chemistry*. This edition covers the literature till early 2011, which has led to a significant increase in the number of references and examples in most chapters. We have tried not to greatly increase the page numbers of the introductory Chapters 1–4, but rather to selectively update the fundamental and more technical information on the concept of microwave chemistry contained therein (removing some outdated content). Having the practicing organic and medicinal chemist in mind, most of the changes and additions have occurred in the chapters (now Chapters 5–8) describing the examples of microwave chemistry. Close to 1000 additional references have been included in these chapters. We hope that this revised version will become an indispensable reference work for all chemists interested in microwave chemistry.

Graz, Austria
July 2011

C. Oliver Kappe
Alexander Stadler
Doris Dallinger

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 a few years, the pharmaceutical industry will see many patents of drugs expire. In order to remain competitive, pharma companies need to pursue strategies that will offset the sales decline and see robust growth and improved shareholder value. The impact of genomics and proteomics is creating an explosion in the number of drug targets. Today's drug therapies are solely based on approximately 500 biological targets; in a few years' time, it is expected that the number of targets will well reach 10 000. In order to identify more potential drug candidates for all these targets, pharmaceutical companies have made major investments in high-throughput technologies for genomic and proteomic research, automated/parallel chemistry, and biological screening. However, lead compound optimization and medicinal chemistry remain one of 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 an innovative machine for the development of methods and technologies that 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 develops a suitable high-speed synthesis of a lead, it becomes possible to synthesize and purify hundreds of molecules in parallel

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to discover new leads and/or 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 high yields and with suitable purities. Since many reaction sequences require at least one or more heating steps for extended time periods, these optimizations are often difficult and time-consuming. 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 the discovery of novel reaction pathways that serve to expand "chemical space" in general and "biologically relevant, medicinal chemistry space" in particular.

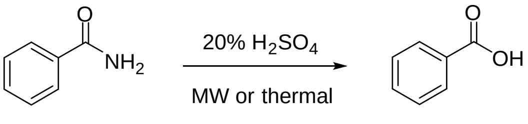
Specifically, microwave synthesis has the potential to impact upon medicinal chemistry efforts in at least three major phases of the drug discovery process: lead generation, hit-to-lead efforts, and lead optimization. Medicinal chemistry addresses what are fundamentally biological and clinical problems. 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 relationship, enhanced delineation of intellectual property, more timely delivery of critically needed medicines, and ultimately determines 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 time unit. 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 foodstuff 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 food processing, drying, and polymer industries. Other applications range from analytical chemistry (microwave digestion, ashing, and extraction) [3] to biochemistry (protein hydrolysis and sterilization) [3], pathology (histoprocessing and tissue fixation) [4], to 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 25 years ago by the groups of Gedye *et al.* (Scheme 1.1) [6] and Giguere *et al.* [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 preadsorbed onto either a more or less 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 nonuniform heating, mixing, and the precise determination of the reaction temperature remained unsolved, in particular when scale-up issues needed to be addressed.



thermal: 1 h, 90 % (reflux)
MW: 10 min, 99 % (sealed vessel)

Scheme 1.1 Hydrolysis of benzamide. The first published example (1986) of microwave-assisted organic synthesis.

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. Nonetheless, in order to achieve high reaction rates, high-boiling microwave-absorbing solvents have been frequently used in an 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 online 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 (Figure 1.1). In addition to the primary and patent literature, many review articles, several books, special issues of journals, feature articles, online databases, information on the World Wide Web, and educational publications provide extensive coverage of the subject (see Section 5.1 for a comprehensive survey). Among the approximately 1000 original publications that appeared in 2010 describing microwave-assisted reactions under controlled conditions, a careful analysis demonstrates that in about 90% of all cases, sealed-vessel processing (autoclave technology) in dedicated single-mode microwave instruments has been employed. A 2007 survey has however found that as many as 30% of all published MAOS papers still employ kitchen microwave ovens [11], a practice

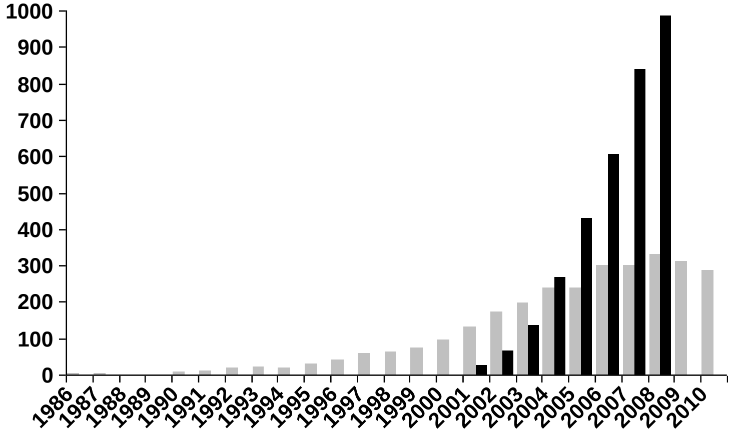


Figure 1.1 Publications on microwave-assisted organic synthesis (1986–2010). Gray graphs: Number of articles involving MAOS for seven selected synthetic organic chemistry journals (*Journal of Organic Chemistry*, *Organic Letters*, *Tetrahedron*, *Tetrahedron Letters*, *Synthetic Communications*, *Synthesis*, and *Synlett*; SciFinder scholar search, keyword: "microwave"). The black graphs represent the number of publications (2001–2008) reporting MAOS experiments in dedicated reactors with adequate process control (about 50 journals, full text search: microwave). Data for 2009 and 2010 are not available, but are estimated to be in the 1000–1200 publications per year range.

banned by most of the respected scientific journals today. For example, the American Chemical Society (ACS) organic chemistry journals will typically not consider manuscripts describing the use of kitchen microwave ovens or the absence of a reaction temperature as specified in the relevant author guidelines [12].

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 “nonthermal” microwave effects [13]. 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 [14, 15], it appears that today most scientists agree that in the majority of cases the observed rate enhancement is a purely thermal/kinetic effect, that is, 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) also need to be considered. While for the medicinal chemist in industry, this discussion may seem futile, the debate on “microwave effects” is undoubtedly going to continue for a few 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 adequate temperature and pressure control were major concerns. Important instrument innovations (see Chapter 3) now allow a careful control of time, temperature, and pressure profiles, paving the way for reproducible protocol development, scale-up, and transfer from laboratory to laboratory and 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 (Figure 1.1) to such a level that it might be assumed that in a few years, many more chemists than today will probably use microwave energy to heat chemical reactions on a laboratory scale [1, 2]. However, it should be emphasized that the potential for growth is still very large as a recent survey has found that less than 10% of all publications in synthetic organic chemistry currently make use of microwave technology [15].

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. In addition, dedicated vessels for solid-phase synthesis, for performing transformations using pre-pressurized conditions and for a variety of other special applications, have been developed. Today, there are four major instrument vendors that produce microwave instrumentation dedicated toward organic synthesis. All those instruments offer temperature and pressure sensors, built-in magnetic stirring, power control, software operation, and sophisticated safety controls. The number of users of dedicated microwave reactors is therefore growing at a rapid rate, and it appears only to be a question of time until most laboratories will be equipped with suitable microwave instrumentation.

In the past, microwave chemistry was often used only when all other options to perform a particular reaction failed or when exceedingly long reaction times or high temperatures were required to complete a reaction. This practice is now slowly changing and due to the growing availability of microwave reactors in many laboratories, routine synthetic transformations are also now being carried out by microwave heating. One of the major drawbacks of this relatively new technology still is equipment cost. While prices for dedicated microwave reactors for organic synthesis have come down considerably since their first introduction in the late 1990s, the current price range for microwave reactors is still many times higher than that of conventional heating equipment. As with any new technology, the current situation is bound to change over the next several years and less expensive equipment should become available. By then, microwave reactors will have truly become the “Bunsen burners of the twenty first century” and will be a standard equipment in every chemical laboratory.

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, several books, and information on the World Wide Web already provide extensive coverage of the subject (see Section 5.1). The goal of the present book is to present carefully scrutinized, useful, and practical information for 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 (2002–2010). The extensive literature survey is limited to reactions that have been performed using controlled microwave heating conditions, that is, 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 will be presented (Chapter 3). This is followed by a chapter outlining the different processing techniques in a microwave-heated experiment (Chapter 4). Finally, a literature survey with more than 1500 references will be presented in Chapters 5–8.

Beginners in the field of microwave-assisted organic synthesis are referred to a recent book containing a chapter with useful practical tips (“How To Get Started”) and an additional section with carefully selected and documented microwave experiments that may be used by scientists in academia to design a course on microwave-assisted organic synthesis [16].

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2
Microwave Theory

The physical principles behind and the factors determining the successful application of microwaves in organic synthesis are not widely familiar to chemists. 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 of the nature of 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 of the current understanding of microwaves and their interactions with matter is given. For more in-depth discussion on this quite complex field, the reader is referred to recent review articles [2–5].

2.1
Microwave Radiation

Microwave irradiation is an electromagnetic irradiation in the frequency range of 0.3–300 GHz, corresponding to wavelengths of 1 mm–1 m. The microwave region of the electromagnetic spectrum (Figure 2.1) therefore lies between infrared (IR) and radio frequencies. The major use of microwaves is either for transmission of information (telecommunication) or for transmission of energy. Wavelengths between 1 mm 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, wireless networks, and cellular phone frequencies. There are other frequency allocations for microwave heating applications (ISM (industrial, scientific, and medical) frequencies (see Table 2.1) [6], but these are generally not employed in dedicated reactors for synthetic chemistry. Indeed, published examples of organic synthesis carried out with microwave heating at frequencies other than 2.45 GHz are extremely rare [7].

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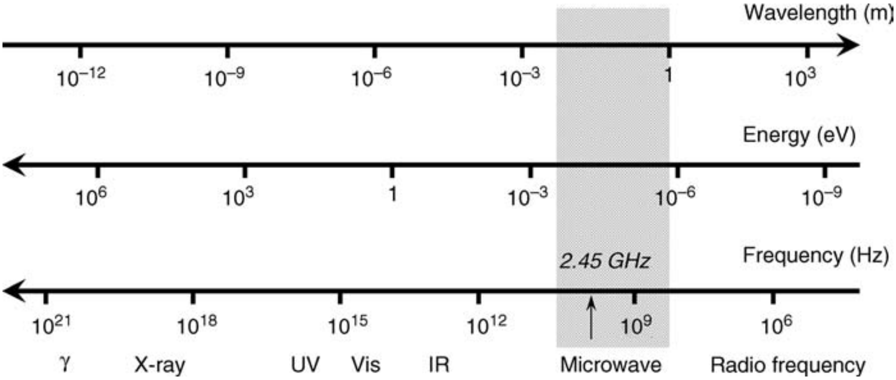

Figure 2.1 The electromagnetic spectrum.

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 (about 10^{-5} 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).

Table 2.1 ISM microwave frequencies.

Frequency (MHz)	Wavelength (cm)
433.92 ± 0.2%	69.14
915 ± 13	32.75
2450 ± 50	12.24
5800 ± 75	5.17
24 125 ± 125	1.36

Data from Ref. [6].

Table 2.2 Comparison of radiation types and bond energies.

Radiation type	Frequency (MHz)	Quantum energy (eV)	Bond type	Bond energy (eV)
Gamma rays	3.0×10^{14}	1.24×10^{6}	C–C	3.61
X-Rays	3.0×10^{13}	1.24×10^{5}	C=C	6.35
Ultraviolet	1.0×10^{9}	4.1	C–O	3.74
Visible light	6.0×10^{8}	2.5	C=O	7.71
Infrared light	3.0×10^{6}	0.012	C–H	4.28
Microwaves	2450	1.01×10^{-5}	O–H	4.80
Radio frequencies	1	4.0×10^{-9}	Hydrogen bond	0.04–0.44

Data from Refs [6, 8].

2.2
Microwave Dielectric Heating

Microwave chemistry is based on the efficient heating of materials by “microwave dielectric heating” effects [4, 5]. Microwave dielectric heating depends on the ability of a specific material (e.g., a solvent or reagent) to absorb microwave energy and convert it into heat. Microwaves are electromagnetic waves that consist of an electric and a magnetic field component (Figure 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 (e.g., with metals or metal oxides) can also be of relevance [9, 10].

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 (Figure 2.3a) [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 with the applied electric field. As the 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 it 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 medium and electrical energy is converted into kinetic or thermal energy and ultimately into heat. It should be emphasized that the interaction between microwave

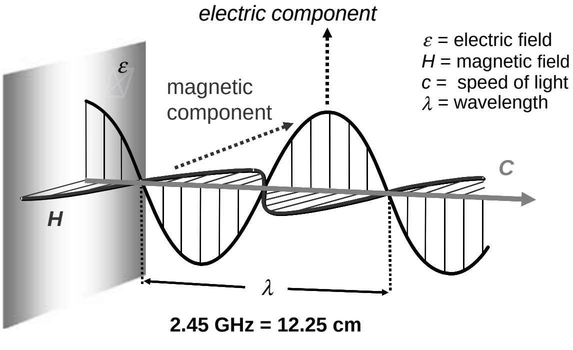

Figure 2.2 Electric and magnetic field components in microwaves.

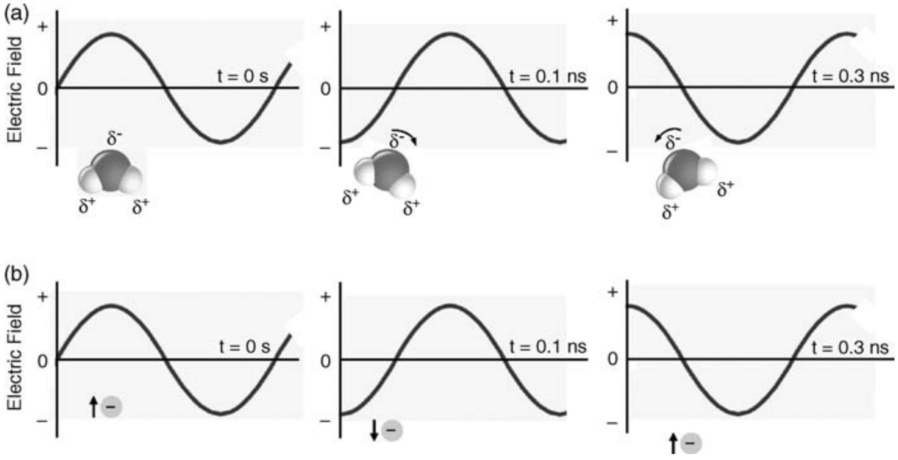

Figure 2.3 (a) Dipolar polarization mechanism. Dipolar molecules try to align with an oscillating electric field. (b) Ionic conduction mechanism. Ions in solution will move in the electric field.

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 whose rotational velocity 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 far. 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 (Figure 2.3b) [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 4.5.2). The conductivity principle is a much stronger effect than the dipolar rotation mechanism with regard to the heat-generating capacity.

A related heating mechanism exists for strongly conducting or semiconducting materials such as metals, where microwave irradiation can induce a flow of electrons on the surface. This flow of electrons can heat the material through resistance (ohmic) heating mechanisms [11]. In the context of organic synthesis, this becomes important for heating strongly microwave-absorbing materials, such as thin metal