Microwave-assisted synthesis is set to change organic chemistry; the technology is generally applicable to syntheses in medicinal and combinatorial chemistry, and compared to conventional methods offers enhanced speed, reproducibility and scalability. This technique solves many of the challenges currently facing pharmaceutical chemists and today’s easy to use instrumentation, integrated robotics and verified synthesis methods are designed to provide a complete lab solution. To explore the significance and pharmaceutical application of microwave assist organic synthesis in drug discovery process and To study some multicomponent synthesis under microwave. To study the advantages of microwave assist organic synthesis as comparing with other traditional heating.

**Keyword:** Microwave System

**INTRODUCTION:** Microwave irradiation has been successfully applied in organic chemistry. Spectacular accelerations, higher yields under milder reaction conditions and higher product purities have all been reported. The effect of microwave irradiation in organic synthesis is a combination of thermal effects, arising from the heating rate, superheating or “hot spots” and the selective absorption of radiation by polar substances.

Such phenomena are not usually accessible by classical heating and the existence of non-thermal effects of highly polarizing radiation—the “specific microwave effect”—is still a controversial topic. Indeed, a number of authors have described success in reactions that do not occur by conventional heating and even modifications of selectivity (chemoselectivity, regioselectivity and stereoselectivity). Microwave heating is very attractive for chemical applications and has become a widely accepted non-conventional energy source for performing organic synthesis. This statement is supported by the increasing number of related publications in recent years—particularly in 2003 with the general availability of new and reliable microwave instrumentation.

Corresponding Author’s Contact information:

Debjit Bhowmik
Karpagam University, Coimbatore, India
E-mail: bhowmikdebjit6@gmail.com
MICROWAVE-ASSISTED SYNTHESIS

A large number of examples of reactions have been described in organic synthesis. Several reviews have been published on the application of microwaves to solvent-free reactions, cycloaddition reactions, the synthesis of radioisotopes, fullerene chemistry, polymers, heterocyclic chemistry, carbohydrates, homogeneous and heterogeneous catalysis, medicinal and combinatorial chemistry and green chemistry. Microwave-assisted organic synthesis is characterized by the spectacular accelerations produced in many reactions as a consequence of the heating rate, which cannot be reproduced by classical heating. Higher yields, milder reaction conditions and shorter reaction times can be used and many processes can be improved. Indeed, even reactions that do not occur by conventional heating can be performed using microwaves.

This effect is particularly important in

(i) The preparation of isotopically labelled drugs that have a short half-life ($^{11}$C, $t_{1/2} = 20$ min; $^{125}$I, $t_{1/2} = 3.6$ min and $^{18}$F, $t_{1/2} = 100$ min).  

(ii) High throughput chemistry (combinatorial chemistry and parallel synthesis)  

(iii) Catalysis where the short reaction times preserve the catalyst from decomposition and increase the catalyst efficiency.

Microwave assisted organic synthesis (MAOS) has emerged as a new “lead” in organic synthesis. The technique offers simple, clean, fast, efficient, and economic for the synthesis of a large number of organic molecules. In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis. Important advantage of this technology include highly accelerated rate of the reaction, Reduction in reaction time with an improvement in the yield and quality of the product. Now day’s technique is considered as an important approach toward green chemistry, because this technique is more environmentally friendly. This technology is still under used in the laboratory and has the potential to have a large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development. Conventional method of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents or reagents lead to environmental pollution. This growth of green chemistry holds significant potential for a reduction of the by product, a reduction in waste production and a lowering of the energy costs. Due to its ability to couple directly with the reaction molecule and by passing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses.

In many of the published examples, microwave heating has been shown to dramatically

- Reduce reaction times,
- Increase product yields and
- Enhance product purities by reducing unwanted side reactions compared to conventional heating methods.

The advantages of this enabling technology have, more recently, also been exploited in the context of multistep total synthesis and medicinal chemistry drug discovery and have additionally penetrated related fields such as polymer synthesis material sciences nanotechnology and biochemical processes. The use of microwave irradiation in chemistry has thus become such a popular technique in the scientific community 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. The statement that, in principle, any chemical reaction that requires heat can be performed under microwave conditions has today been generally accepted as a fact by the scientific community.
The short reaction times provided by microwave synthesis make it ideal for rapid reaction scouting and optimization of reaction conditions, 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”? Not surprisingly, therefore, many scientists, both in academia and in industry, have turned to microwave synthesis as a frontline methodology for their projects.

Arguably, the breakthrough in the field of MAOS on its way from laboratory curiosity to standard practice started in the pharmaceutical industry around the year 2000. Medicinal chemists were among the first to fully realize the true power of this enabling technology. Microwave synthesis has since been shown to be an invaluable tool 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 therefore 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 microwave technology. In addition, microwave synthesis often allows the discovery of novel reaction pathways, which serve to expand “chemical space” in general, and “biologically-relevant medicinal chemistry space”, in particular.

In the early days of microwave synthesis, experiments were typically carried out in sealed Teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements. Kitchen microwave ovens are not designed for the rigors of laboratory usage: acids and solvents corrode the interiors quickly and there are no safety controls. 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. Here, the reagents were pre-adsorbed onto either a more or less microwave transparent inorganic support (i.e., silica, alumina or clay) or a strongly absorbing one (i.e., graphite), that additionally may have been doped with a catalyst or reagent. Particularly in the beginning 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, technical difficulties relating to non-uniform heating, mixing, and the precise determination of the reaction temperature remained unsolved, in particular when scale-up issues needed to be addressed.

Alternatively microwave-assisted synthesis was, in the past, often 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 nonetheless achieve high reaction rates, high-boiling microwave absorbing solvents were frequently used in open-vessel microwave synthesis. However, the use of these solvents presented serious challenges during product isolation and recycling of solvent. In addition, 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. The initial slow uptake of microwave technology in the late 1980s and 1990s has often been attributed to its lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating.
In particular, the use of kitchen microwave ovens in combination with non-reliable temperature monitoring devices led to considerable confusion in the microwave chemistry community in the late 1990s and has given MAOS a bad reputation and the stigma of a “black box” science. The majority of organic chemists at that time were not taking microwave chemistry seriously and the discussion and irritation around the topic of “microwave effects” has probably contributed to this situation. Historically, since the early days of microwave synthesis, the observed rate accelerations and sometimes altered product distributions compared to oil-bath experiments led to speculation on the existence of so-called “specific” or “non-thermal” microwave effects. Such effects were claimed when the outcome of a synthesis performed under microwave conditions was different from the conventionally heated counterpart at the same apparent temperature. Reviewing the present literature 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, that is, a consequence of the high reaction temperatures that can rapidly be attained when irradiating polar materials in a microwave field, although clearly effects that are caused by the uniqueness of the microwave dielectric heating mechanism (“specific microwave effects”) must also be considered. While for the chemist in industry this discussion may seem futile, the debate on “microwave effects” is undoubtedly going to continue for many years in the academic world. Because of the recent availability of modern dedicated microwave reactors with online accurate monitoring of both temperature and pressure, some of the initial confusion on microwave effects has subsided. This can also be attributed, to some extent, to the fact that microwave synthesis today is mostly carried out in solution phase using organic solvents, where the temperature of the reaction mixture can generally be adequately monitored.

Controlled MAOS in sealed vessels using standard solvents—a technique pioneered by Strauss in the mid 1990s—has thus celebrated a steady comeback since the year 2000 and today clearly is the method of choice for performing microwave-assisted reactions. This is evident from surveying the recently published literature in the area of microwave-assisted organic synthesis.

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. Among the about 850 original publications that appeared in 2007 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 micro-wave instruments...
has been employed. A recent survey has, however, found that as many as 30% of all published MAOS papers still employ kitchen microwave ovens \(^{51}\), a practice 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 publication guidelines \(^{52}\).

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 to organic synthesis. All these 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 had 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 now also being carried out by microwave heating. One of the major drawbacks of this relatively new technology remains the 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 standard equipment in every chemical laboratory.

In conventional thermal demagnetisation heat is applied to a sample which creates lattice vibrations (phonons). These phonons are in a higher energy state than the surrounding magnetic system so they exchange energy with the magnetic system, and spin waves (magnons) are created (Walton \(et al\.), 1992; 1993). The generation of spin waves within the magnetic grains enables the individual domain magnetisations to reverse and thus demagnetise in zero field (Walton,1986) or to realign with an ambient fixed field to produce a TRM.

In microwave demagnetisation / remagnetisation, the first steps are bypassed; magnons are directly excited with the use of high frequency microwaves thus eliminating the need to heat the bulk sample. Some heating of the bulk sample does occur due to the generation of phonons in the relaxation process but to a much lesser extent than in conventional heating.

Microwaves are electromagnetic waves that have a frequency range from around 0.3 GHz (there is no actual specified lower frequency limit) to 300 GHz with corresponding wavelengths ranging from 1m to 1mm. Microwaves are coherent and polarised in contrast to visible waves (apart from lasers). They obey the laws of optics and can be transmitted, absorbed or reflected depending on the type of material, as illustrated below -
Everyone is familiar with the domestic microwave oven; indeed the majority of households contain one. The microwave heating process is however, fundamentally different from the heating process used in conventional ovens. With microwaves, heat is generated internally within the material as opposed to originating from external heating sources. As a result, the thermal gradients and flow of heat is the reverse of those in materials heated by conventional means. A conventionally cooked Baked Alaska has the ice cream on the inside whereas a microwave cooked one has the ice cream on the outside! It is possible to heat both large and small shapes very rapidly and uniformly and as the absorption of microwave energy varies with composition and structure it is also possible to have selective heating.

Selective heating is desirable for palaeomagnetic purposes as the magnetic constituents can be specifically targeted. In fact it is possible to go one better by using ferromagnetic resonance (FMR) to demagnetise directly the magnetic particles with the microwave energy, before the energy is transferred to the lattice as heat. This leads to reduced heating of the bulk matrix of the sample and hence less alteration during experiments. As far as the magnetic particles are concerned, however, microwave heating is exactly the same as with conventional heat. In the demagnetisation process, the spin system of the magnetic grains is excited (Walton, 1986, Section 1.1.3) both with microwaves and conventional heat. It is solely the method of getting the energy to the spin system that differs between the two processes. In the Liverpool microwave technique the mechanism of FMR is used.

There are different mechanisms by which microwaves (and lower frequency electromagnetic waves) can couple to a material and a whole host of ways that the microwave energy is subsequently lost to the system. The main loss mechanisms are electric, conduction (eddy current), hysteresis and resonance [domain wall and electron spin (FMR)]. It is often difficult to ascertain which loss mechanism, or combination of mechanisms is occurring for a particular sample in given conditions. The different mechanisms do however have different dependencies on certain properties such as sample type and microstructure, frequency and temperature. A brief description of these different loss mechanisms will be given below for background purposes before a detailed description of ferromagnetic resonance (FMR) phenomena including high power effects is given. Finally the role of microwave heat in industry will be touched upon with particular reference to magnetite.

Traditionally, organic reactions are heated using an external heat source (such as an oil bath), and therefore heat is transferred by conductance. This is a comparatively slow and inefficient method for transferring energy into the system because it depends 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. By contrast, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the polar molecules (for example, solvents, reagents and catalysts) that are present in the reaction mixture.
BENEFITS OF MICROWAVE ASSIST ORGANIC SYNTHESIS

Literature review state that microwave assist organic synthesis have the following benefits:

- Very rapid reactions.
- Higher degree of purity achieved due to short residence time at high temperatures.
- No local overheating, minor decomposition & minor occurrence of secondary reactions.
- Yield often better.
- Short reaction time.

DISADVANTAGES OF MICROWAVE SYNTHESIS

- Higher reaction temperatures can be obtained by combining rapid microwave heating with sealed-vessel (autoclave) technology.
- In many instances significantly reduced reaction times, higher yields and cleaner reaction profiles will be experienced, allowing for more rapid reaction optimization and library synthesis.
- Solvents with lower boiling points can be used under pressure (closed vessel conditions) and be heated at temperatures considerably higher than their boiling point.
- Microwave heating allows direct ‘in core’ heating of the reaction mixture, which results in a faster and more even heating of the reaction mixture.
- Specific microwave effects that cannot be reproduced by conventional heating can be exploited — for example, the selective heating of strongly microwave-absorbing catalysts.
- Easy on line control of temperature and pressure profiles is possible, which leads to more reproducible reaction conditions.
- Microwave heating is more energy efficient than classical oil bath heating because of direct molecular heating and inverted temperature gradients.
- Can easily be adapted to automated sequential or parallel synthesis.

ADVANTAGES AND DISADVANTAGES OF MICROWAVE SYSTEM:

( Dr. HOLLY SHULMSN., Ceralink Inc, June 4, 2009)
MICRO WAVE SET-UP

[DIAGRAMS AND TEXT PRESENTED IN THE DOCUMENT]
MICROWAVE APPARATUS:

Most pioneering experiments in chemical synthesis using microwaves were carried out in domestic microwave ovens. However, developments in microwave equipment technology have enabled researchers to use dedicated apparatus for organic reactions. The following are the two categories of apparatus.

(i) Single-mode apparatus

(ii) Multi-mode apparatus

(i) SINGLE-MODE APPARATUS:

The differentiating feature of a single-mode apparatus is its ability to create a standing wave pattern, which is generated by the interference of fields. This interface generates an array of nodes where microwave energy intensity is zero, and an array of antinodes where the magnitude of microwave energy is at its highest.

The factor that governs the design of a single-mode apparatus is the distance of the sample from the magnetron. This distance should be appropriate to ensure that the sample is placed at the antinodes of the standing electromagnetic wave pattern.

(ii) MULTI-MODE APPARATUS:

An essential feature of a multi-mode apparatus is the deliberate avoidance of generating a standing wave pattern inside it. The goal is to generate as much chaos as possible inside the apparatus. The greater the chaos, the higher is the dispersion of radiation, which increases the area that can cause effective heating inside the apparatus. As a result, a multi-mode microwave heating apparatus can accommodate a number of samples simultaneously for heating, unlike single-mode apparatus where only one sample can be irradiated at a time. A major limitation of multi-mode apparatus is that even with radiation distributed around them, heating samples cannot be controlled efficiently.
THEORY:

MAOS is mainly based on the efficient heating of materials by “microwave dielectric heating” effects. Microwave dielectric heating is dependent on the ability of a specific material to absorb microwave energy and convert it to heat. Microwave irradiation triggers heating by two main mechanisms: dipolar polarization and ionic conduction. Whereas the dipoles in the reaction mixture (for example, the polar solvent molecules) are involved in the dipolar polarization effect, the charged particles in a sample (usually ions) are affected by ionic conduction. When irradiated at microwave frequencies, the dipoles or ions of the sample align in the applied electric field. As the applied field oscillates, the dipole or ion 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 capacity of the matrix to align itself with the frequency of the applied field. If the dipole does not have enough time to realign, or reorients too quickly 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. Under such conditions, rapid heating of chemical reaction mixtures to high temperatures will be observed, particularly if a sealed vessel system is used (FIG. 1Aa).

In MAOS, reactions frequently occur much faster than under conventional oil-bath conditions. On reviewing the present literature, it seems that in most of these cases the rate enhancements observed in MAOS are the result of a purely thermal/kinetic effect (applying the Arrhenius law). This means they are a consequence of the higher reaction temperatures that can rapidly be attained when irradiating polar materials in a microwave field (FIG. 1Aa). In addition, so-called ‘microwave effects’ are also thought to contribute to the frequent discrepancies in reaction rate between conventional and microwave heating.

**Figure 1:** Differences between conventional and microwave heating, and examples of microwave reactor technology. A. Difference in temperature profiles for a 5-ml sample of ethanol (boiling point 78 °C) heated under single-mode, sealed-vessel microwave irradiation (maximum set temperature 160 °C) and open-vessel oil-bath conditions (oil-bath temperature 100 °C) for 3 minutes. Dielectric heating with microwave energy is significantly more rapid than heating in an oil-bath by convection currents. Both experiments were carried out in the same reaction vessel with stirring using an internal fibre-optic temperature-monitoring device. Using sealed-vessel microwave irradiation, a significantly higher temperature can rapidly be reached,
compared with the oil-bath experiment, which was carried out under standard open-vessel reflux conditions. After the set temperature of 160 °C is reached in the microwave experiment (~100 s), an algorithm controlled by feedback with the temperature-monitoring device adjusts the microwave power to maintain the set temperature. Active gas-jet cooling (180–400 s) then rapidly cools the reaction mixture after microwave irradiation. Ab. Inverted temperature gradients in microwave versus oil bath heating. Temperature profiles (modelling) 1 minute after heating by microwave irradiation (left) compared with 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 scale in Kelvin. B: Microwave reactor technology for high throughput synthesis and scale up. Ba: Automated single-mode microwave synthesizer (Initiator 60; Biotage AB). A robotic gripper device moves the sealed reaction vessels (0.2–20 ml) in and out of the microwave cavity. Up to 60 reactions can be processed in an automated sequential fashion. Bb: Continuous-flow single-mode microwave reactor (Voyager; CEM Corp.). Scale-up is achieved by pumping reaction mixtures in and out of an 80-ml sealed reaction vessel following a stop-flow processing regime. Bc: Set-up for parallel microwave synthesis (Combi CHEM system; Milestone Inc.). The barrel-type overhead rotor system (left) can hold up to two 96-deep-well microtitre plates (right) for parallel synthesis on a 0.5–4-ml scale. The set-up is irradiated in a multimode microwave reactor (not shown). Bd: Multimode microwave scale-up system for parallel batch processing (Synthes 3000; Anton Paar GmbH). Microwave synthesis is performed in multivessel rotors (8 or 16 vessels) with reaction volumes of up to one litre.

Microwave RADAR equipment operates at the lower wavelengths (0.01 - 0.25 m) of this band, and much of the band is used for telecommunications. In order to avoid interference with these uses, the wavelengths at which industrial and domestic microwave apparatus may operate is regulated at both national and international levels. In the majority of countries, 2.450 (+/- 0.050) GHz is the major operating frequency for this purpose, although other frequency allocations exist (Table 1).

**HEATING OCCURS BY TWO (2) MAJOR MECHANISMS:**
- Dipolar polarization, and
- Conduction.

**DIPOLAR POLARIZATION MECHANISMS:**

For a substance to generate heat when irradiated with microwaves it must possess a dipole moment. It is the electric field component of
the microwave irradiation, rather than magnetic field component, that is responsible for the effect, when a dipole tries to re-orientate itself with respect to an alternating electric field, it loses energy in the form of heat, by molecular friction. The heat generation is dependent on the nature of the dipole and the frequency of the applied radiation. If the frequency of the radiation is too high the dipole does not have time to align itself with the field before the field changes direction again.

Table 1: Permitted Frequencies for Industrial, Medical and Scientific uses

<table>
<thead>
<tr>
<th>Frequency (GHz)</th>
<th>Tolerance (%)</th>
<th>Area permitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.434</td>
<td>0.2%</td>
<td>Austria, Netherlands, Portugal, Germany, Switzerland</td>
</tr>
<tr>
<td>0.896</td>
<td>10 MHz</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>0.915</td>
<td>13 MHz</td>
<td>North and South America</td>
</tr>
<tr>
<td>2.450</td>
<td>50 MHz</td>
<td>Worldwide, except where 2.375 is used</td>
</tr>
<tr>
<td>3.390</td>
<td>0.6%</td>
<td>Netherlands</td>
</tr>
<tr>
<td>5.800</td>
<td>5 MHz</td>
<td>Worldwide</td>
</tr>
<tr>
<td>6.780</td>
<td>0.6%</td>
<td>Netherlands</td>
</tr>
<tr>
<td>24.150</td>
<td>25 MHz</td>
<td>Worldwide</td>
</tr>
<tr>
<td>40.600</td>
<td>25 MHz</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>

In these circumstances, no motion and consequently no heating occurs. Similarly, no heating occurs if the dipole aligns itself perfectly with the alternating electric field and, therefore, follows the field fluctuations. However, if the applied field is in the intermediate frequency region (e.g. microwave radiation), a phenomenon occurs that lies between these two extremes. In this situation the dipole has time to respond and align itself with the field, but the fluctuations of the field are so rapid that the dipole does not follow it perfectly, this results in the generation of heat.

**CONDUCTION MECHANISM:**

A solution containing ions or even a single isolated ion with a hydrogen bonded cluster, in the sample the ion will move through the solution under the influence of an electric field, resulting in expenditure of energy due to an increased collision rate, converting the kinetic energy to heat.

Where the irradiated sample is an electrical conductor, the charge carriers (electrons, ions, etc.) are moved through the material under the influence of the electric field, $E$, resulting in a polarisation, $P$. These induced currents will cause heating in the sample due to any electrical resistance. For a very good conductor, complete polarisation may be achieved in approximately $10^{-18}$ seconds, indicating that under the influence of a 2.45GHz microwave, the conducting electrons move precisely in phase with the field.

If the sample is too conducting, such as a metal, most of the microwave energy does not penetrate the surface of the material, but is reflected. However, the colossal surface voltages which may still be induced are responsible for the arcing that is observed from metals under microwave radiation.
Thus, if one takes pure water and heats it in a microwave oven, where a variant of the polarisation mechanism dominates, we find that the heating rate is significantly less than when one takes the same volume of water and add salt. In the latter case, both mechanisms occur, and contribute to the heating effect.

**LOSS ANGLE:**

The ability of a material to convert electromagnetic energy into heat energy at a given frequency and temperature is calculated using the following equation: \( \tan \delta = \varepsilon'' / \varepsilon' \), where \( \varepsilon' \) is the relative permittivity, which is a measure of the ability of a molecule (or assembly of molecules) to be polarized by an electric field and \( \varepsilon'' \) is the dielectric loss, which is indicative of the ability of a medium to convert dielectric energy into heat. \( \tan \delta \) is the dielectric loss tangent and defines the ability of a material to convert electromagnetic energy into heat energy at a given frequency and temperature. The value of \( \tan \delta \) of an assembly of molecules depends on several factors which are as follows:

(i) The frequency of the electromagnetic waves.
(ii) The temperature, and
(iii) The physical state and composition of the mixture.

A high value for \( \tan \delta \) indicates a high susceptibility to micro-wave energy (Table 2). Polar solvents have high \( \tan \delta \) value and are, therefore, preferable for micro-wave promoted reactions.

Table 2: Dielectric constants and loss tangent values for some solvents relevant to organic synthesis

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric constant (( \varepsilon' ))</th>
<th>Loss tangent (( \tan \delta ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>2.3</td>
<td>-</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>2.2</td>
<td>-</td>
</tr>
<tr>
<td>Chloroform</td>
<td>0.48</td>
<td>0.174</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>0.13</td>
<td>0.659</td>
</tr>
<tr>
<td>Tetrachloroethane</td>
<td>0.76</td>
<td>0.047</td>
</tr>
<tr>
<td>Methanol</td>
<td>0.91</td>
<td>0.042</td>
</tr>
<tr>
<td>Methanol</td>
<td>0.042</td>
<td>0.722</td>
</tr>
<tr>
<td>Water</td>
<td>80.4</td>
<td>0.123</td>
</tr>
</tbody>
</table>

The relationship between \( \tan \delta \) and \( \varepsilon' \) and \( \varepsilon'' \) is purely mathematical and can be described using simple trigonometric rules (Figure 2).

![Fig. 2: Phase diagrams for: (a) an ideal dielectric where energy is transmitted without loss, (b) phase displacement which results when energy is converted to heat, (c) the relationship between \( \varepsilon' \) and \( \varepsilon'' \), \( \tan \delta = \varepsilon'' / \varepsilon' \).](image-url)
SUPERHEATING EFFECT:
Using microwave heating, boiling points of solvents can be raised up to 260°C, above their conventional values, this phenomenon is known as superheating effect. This higher boiling point can be maintained in pure solvents for as long as the microwave radiation is applied. However, substrates or ion that are present in solvent will aid the formation of “boiling nucleuses”. In these situations the temperature will return to that of the normal boiling point of the solvent at a solvent dependent rate.

SOLVENTS:
It is well known fact that non-polar solvents are not heated under microwave-irradiation. Ionic liquids absorb microwave irradiation in a very efficient manner and, additionally, they exhibit a very low vapour pressure, thereby enhancing their suitability even further for microwave heating.

When the dielectric properties of the sample are too poor to allow efficient heating by microwave radiation the addition of small amounts of additives (ex-ionic salts) that have large loss tangent values can significantly overcome these problems and enable adequate heating of the whole mixture. This often provides an efficient way of using non-polar solvents for running synthesis using microwave radiation. Fluid salts, or ionic liquids, consist entirely of ions and therefore absorb microwave radiation in a highly efficient manner. Many ionic liquids are particularly attractive additives because they are relatively inert, stable up to 200°C and have a negligible vapour pressure.

THERMAL VS NON-THERMAL EFFECTS:
Microwaves (0.3–300 GHz) lies between infrared and radiofrequency electromagnetic radiations. It is generally believed that the microwave irradiations accelerate chemical reactions by the heating effect. Irradiated with microwaves, a molecule of the medium continually realigns itself with the changing field. This causes electromagnetic energy to get converted into heat energy. The dielectric constant, the ability of a molecule to be polarized by an electric field, dictates the capacity of the medium to get heated with microwave irradiation. Thus, solvents such as water, methanol and dimethyl formamide get heated easily; microwaves have no effect on hexane, toluene and diethyl ether. However, some workers believe that there are non-thermal effects. The two conflicting viewpoints have been nicely summarized in a recent write-up.

Whittaker and Mingos believe that ‘the rate of a reaction in many syntheses is so high that it cannot be accounted for by heating effects alone’. On the other hand, Kappe asserts that ‘there are no general non-thermal effects’, and that the so-called non-thermal effect is due to superheating of solvents above their boiling points. The main difficulty in resolving this controversy is the fact that it has been difficult to experimentally distinguish between thermal and non-thermal effects. During the last decade or so, microwaves with temperature control have become commercially available. This has led to some studies where it is possible to distinguish between thermal and non-thermal effects. Whether such non-thermal effects originate simply in superheating, is not yet clear. However, that is not restricting the everincreasing large number of applications. Microwave irradiation is also being used for accelerating enzymatic reactions.

Nowadays, MAOS is gaining widespread acceptance in drug discovery laboratories. The rapid acceptance of this technology parallels the rising cost of R&D and decrease in the number of FDA approvals, which have led to what is termed as a productivity crisis. Reducing the cost of failure, either by failing candidates sooner or by improving the overall probability of success, is the most powerful solution to improving R&D productivity. Microwave technology, by accelerating chemical reactions from hours or days to minutes, provides quick results. From
time to time microwave heating enables chemistries that were not previously possible by classical methods.

**SYNTHESIS UNDER MICROWAVES APPLICATIONS:**

- Thermal reactions, which need high temperatures for long reaction times. Microwaves will bring acceleration of reactions, lower decomposition of products and consequently enhanced yield.
- Equilibrated reactions, with displacement of equilibrium by vaporization of small polar molecules.
- Application of MWI leads to many advantages, like the use of non-corrosive and inexpensive reagents, in addition to the eco-friendly "green chemistry" economical and environmental impacts.

**CONCLUSION**

One of the biggest tasks facing the pharmaceutical companies is to accelerate drug development by increasing productivity, discovering new leads, and generating novel therapeutic agents against the vast numbers of potential drug targets. The goal of the medicinal chemist is to develop leads efficiently to identify strong candidates early so as to minimize failure rate of compounds in clinical trial and move drugs into the marketing pipeline quickly. Rapid lead generation and optimization has recently been facilitated by the emergence of MAOS and the technique is today one of the major tool for the medicinal chemist. MAOS is undoubtedly going to play a major role in chemistry development; this is substantiated by the fact that in most pharmaceutical and biotechnology companies microwave synthesis is the vanguard methodology today. The recent spurt in research publications, books and patent literature on microwave-assisted reactions testifies to the growing popularity of microwave irradiation as an accepted tool in laboratories. The use of microwave irradiation to enhance the rates of enzymatic reactions is bound to grow as microwave reactors with temperature control become commercially available from more vendors. The results compiled in this review show that microwave irradiation is more than just a method for performing reactions in a shorter time period. It has been demonstrated that numerous processes can not only be improved upon, but can be controlled in the case of competitive reactions, or with respect to chemo-, regio- or stereo-selectivity may be modified or inverted. The most interesting and spectacular results, however, are still to come. In order that they can be realised, the design of new equipment is necessary in which there is proper control of power and reaction temperature and where losses in the waveguide are minimised.

From an organic synthesis point of view, further examples will assist in the understanding of the effects caused by microwave irradiation. Moreover, it is of paramount importance to test...
new reactions that fail to occur, or which take place with some difficulty, by means of classical heating. Finally, it is desirable to introduce the concept of microwave irradiation and its synthetic applications in chemical education so that newly trained chemists become accustomed to this means of performing reactions and the concept of heating that is different from the usual.

REFERENCES:


