

Microwaves in organic synthesis. Thermal and non-thermal microwave effects†

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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. Indeed, a number of authors have described success in reactions that do not occur by conventional heating and even modifications of selectivity (chemo-, regio- and stereoselectivity). 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. An overview of the thermal effects and the current state of non-thermal microwave effects is presented in this *critical review* along with a view on how these phenomena can be effectively used in organic synthesis.

Introduction

Microwave heating is very attractive for chemical applications^{1–5} 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.⁶

A large number of examples of reactions have been described in organic synthesis.^{7–14} Several reviews have been published on the application of microwaves to solvent-free reactions,^{15,16} cycloaddition reactions,¹⁷ the synthesis of radioisotopes,¹⁸ fullerene chemistry,^{19,20} polymers,²¹ heterocyclic

chemistry,^{22–24} carbohydrates,^{25,26} homogeneous²⁷ and heterogeneous catalysis,²⁸ medicinal and combinatorial chemistry^{29–34} and green chemistry.^{35–38}

Microwave-assisted organic synthesis is characterised 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 (¹¹C, $t_{1/2}$ = 20 min; ¹²²I, $t_{1/2}$ = 3.6 min and ¹⁸F, $t_{1/2}$ = 100 min),¹⁸ (ii) high throughput chemistry (combinatorial chemistry and parallel synthesis)^{29–34} and (iii) catalysis where the short reaction times preserve the catalyst from decomposition and increase the catalyst efficiency.³⁹

† Dedicated to Professor José Elguero on the occasion of his 70th birthday.

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Antonio de la Hoz

Antonio de la Hoz obtained his PhD from the Universidad Complutense in Madrid in 1986. After postdoctoral research in 1987 with Professor Begtrup at the Danmarks Tekniske Hoskole he joined the Faculty of Chemistry of the Universidad de Castilla-La Mancha in Ciudad Real in 1988 as an Assistant Professor. In 2000 he became full Professor at this University. His research interests include heterocyclic chemistry, supramolecular chemistry, microwave activa-

tion of organic reactions, solvent-free organic synthesis, and green chemistry.



Ángel Díaz-Ortiz

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compounds by cycloaddition reactions in a microwave environment.

The results obtained cannot be explained by the effect of rapid heating alone, and this has led various authors to postulate the existence of a so-called “microwave effect”. Hence, acceleration or changes in reactivity and selectivity could be explained by a specific radiation effect and not merely by a thermal effect.

The effect of microwave irradiation in chemical reactions is a combination of the thermal effect and non-thermal effects, *i.e.*, overheating, hot spots and selective heating, and non-thermal effects of the highly polarizing field, in addition to effects on the mobility and diffusion that may increase the probabilities of effective contacts.

The aim of this review is to show how thermal effects have been used efficiently to improve processes and to obtain better yields. Furthermore, there is a discussion of observations in terms of the ‘microwave effect’, *i.e.*, non-thermal effects, results, theories and predictive models.

Thermal effects

Thermal effects arise from the different characteristics of microwave dielectric heating and conventional heating (Table 1). Microwave heating uses the ability of some compounds (liquids or solids) to transform electromagnetic energy into heat. Energy transmission is produced by dielectric losses, which is in contrast to conduction and convection processes observed in conventional heating. The magnitude of heating depends on the dielectric properties of the molecules, also in contrast to conventional heating. These characteristics mean that absorption of the radiation and heating may be performed selectively. Microwave irradiation is rapid and volumetric, with the whole material heated simultaneously. In contrast, conventional heating is slow and is introduced into the sample from the surface (Fig. 1).

The thermal effects observed under microwave irradiation conditions are a consequence of the inverted heat transfer, the inhomogeneities of the microwave field within the sample and the selective absorption of the radiation by polar compounds. These effects can be used efficiently to improve processes,

Table 1 Characteristics of microwave and conventional heating

Microwave heating	Conventional heating
Energetic coupling	Conduction/convection
Coupling at the molecular level	Superficial heating
Rapid	Slow
Volumetric	Superficial
Selective	Non selective
Dependent on the properties of the material	Less dependent

modify selectivities or even to perform reactions that do not occur under classical conditions.

Overheating

Overheating of polar liquids is an effect that can be exploited practically. Mingos⁴⁰ detected this effect in polar liquids on using microwaves, where overheating in the range 13–26 °C above the normal boiling point may occur (Fig. 2). This effect can be explained by the “inverted heat transfer” effect (from the irradiated medium towards the exterior) since boiling nuclei are formed at the surface of the liquid. This effect could explain the enhancement in reaction rates observed in organic and organometallic chemistry. This thermal effect, which is not easily reproduced by conventional heating, can be used to improve the yields and the efficiency of certain processes.

Klán⁴¹ successfully evaluated MW superheating effects in polar solvents by studying a temperature-dependent photochemical reaction. Klán described the Norrish type II reaction of valerophenones in microwave photochemistry (Scheme 1). Equimolecular mixtures of both ketones were irradiated at ≥ 280 nm in various solvents; such an experimental arrangement guaranteed identical photochemical conditions for both compounds. The fragmentation–cyclization ratio varied from 5 to 8 and was characteristic for given reaction conditions (Table 2). The photochemical efficiency *R* (Table 2) is temperature-dependent and the magnitude is most likely related to the solvent basicity. The authors consider that superheating by microwave irradiation is most likely responsible for the modification of selectivity observed. Considering the estimated overheating, a linear dependence of *R* with temperature was observed (Fig. 3).

This reaction produced a good linear dependence of the efficiency over a broad temperature range and the system served as a photochemical thermometer at the molecular level.

Klán⁴¹ described the photo-Fries rearrangement of phenylacetate under microwave irradiation and irradiation with an electrodeless discharge lamp (EDL). The reaction provides two principal products: 2- and 4-hydroxyacetophenone (Scheme 2). The product distributions are given in Table 3.

The *ortho*–*para* selectivity was slightly different on comparing conventional heating and microwave irradiation experiments. These differences can be ascribed to superheating effects in the MW field for all solvents and were measured directly with a fibre-optic thermometer or estimated by considering the temperature dependence of the product ratio to be linear.



Andrés Moreno

Andrés Moreno was born in 1962 in Ciudad Real (Spain). He obtained his degree in organic chemistry (1985) from the University Complutense of Madrid and his PhD (1990) from the University of Castilla-La Mancha. He spent a postdoctoral stay in the Dyson Perrins Laboratory, University of Oxford, UK (1991–1992) investigating NMR studies of peptides in solution. He became Assistant Professor of Organic Chemistry in 1995, and his current research interests include NMR studies in solution and the development of environmental synthetic methodologies for organic synthesis.

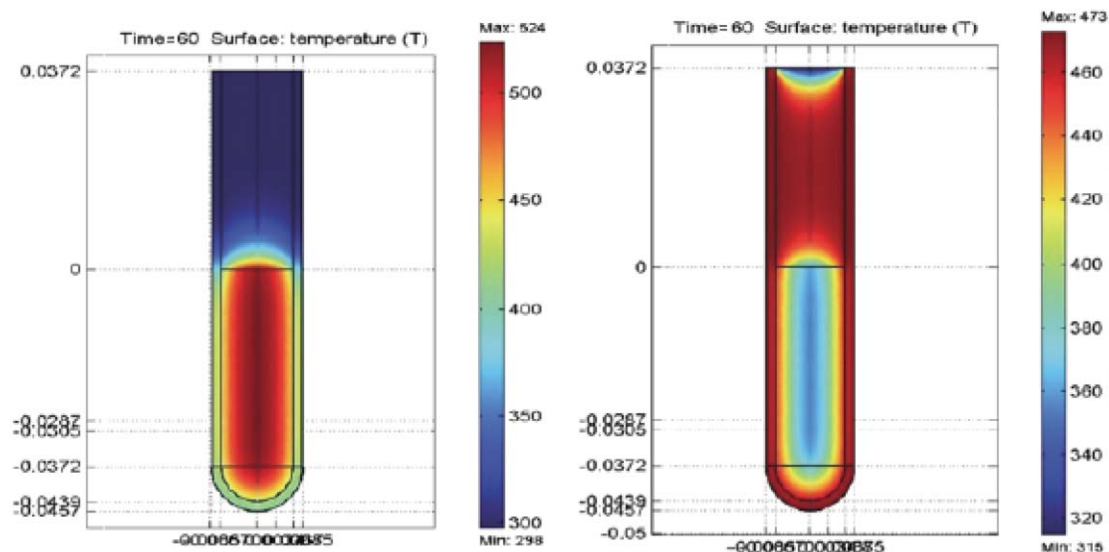


Fig. 1 The temperature profile after 60 sec as affected by microwave irradiation (left) compared to treatment in an oil bath (right). Microwave irradiation raises the temperature of the whole reaction volume simultaneously, whereas in the oil heated tube, the reaction mixture in contact with the vessel wall is heated first. Temperature scale in kelvin. '0' on the vertical scale indicates the position of the meniscus. Reprinted from ref. 108 with kind permission of Springer Science and Business Media.

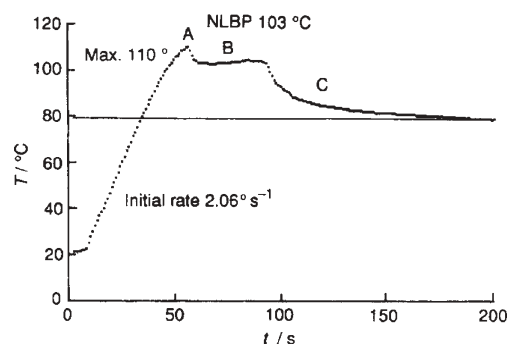
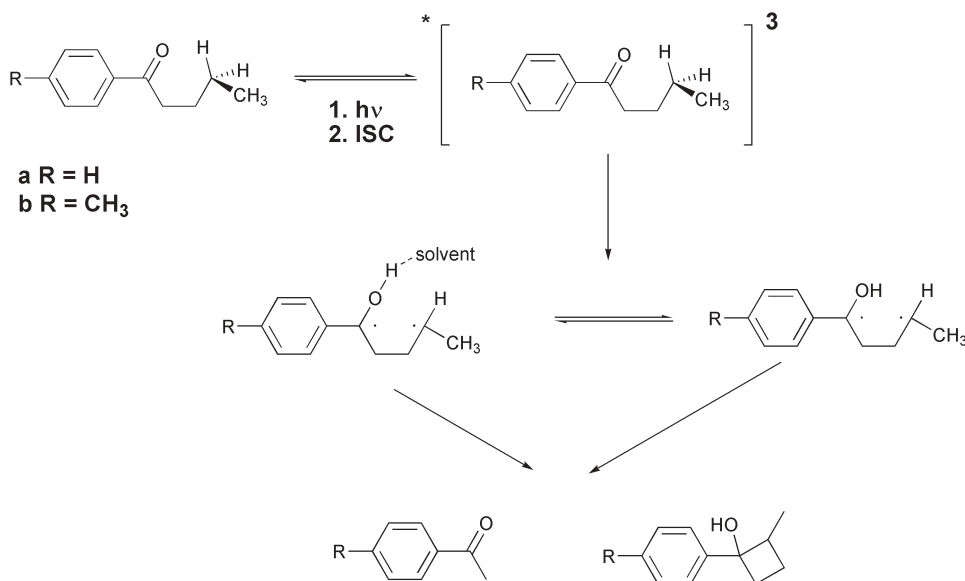


Fig. 2 Heating profile of ethanol under microwave irradiation.⁴⁰ Reproduced by permission of The Royal Society of Chemistry.

Table 2 Product distribution in the Norrish type II reaction of valerophenone

Solvent	Conditions	R^a	$T/^\circ\text{C}$	Overheating/ $^\circ\text{C}$
Methanol	CH	2.25	20	—
	CH	1.52	65	—
	MW	1.34	75	11
Acetonitrile	CH	2.12	20	—
	CH	1.12	81	—
	MW	0.98	90	9

^a Fragmentation–cyclization ratio.



Scheme 1

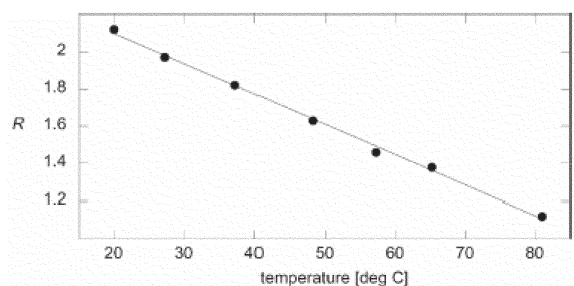


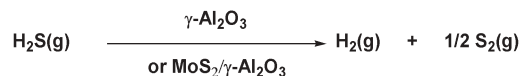
Fig. 3 Linear temperature dependence of a Norrish type II photochemistry system in acetonitrile.

“Hot spots”. Inhomogeneities

Several authors have detected or postulated the presence of “hot spots” in samples irradiated with microwaves. This is a thermal effect that arises as a consequence of the inhomogeneity of the applied field, resulting in the temperature in certain zones within the sample being much greater than the macroscopic temperature. These regions are not representative of the reaction conditions as a whole. This overheating effect has been demonstrated by Mingos in the decomposition of H_2S over $\gamma\text{-Al}_2\text{O}_3$ and $\text{MoS}_2\text{-}\gamma\text{-Al}_2\text{O}_3$ (Scheme 3).⁴² The conversion efficiency under microwave and conventional thermal conditions are compared in Fig. 4. The higher conversion under microwave irradiation was attributed to the presence of hot spots. The authors estimated the temperature in the hot spots to be about 100–200 °C higher than the bulk temperature. This temperature difference was determined by calculations and on the basis of several transformations observed, such as the transition of γ - to α -alumina and the melting of MoS_2 , which occur at temperatures much higher than the measured bulk

Table 3 Product distribution in the photo-Fries rearrangement of phenylacetate

Solvent	Conditions	Fragm./Fries	ortho/para	T/°C	Overheating/°C
CH_3OH	CH	0.21	1.18	20	—
CH_3OH	CH	0.32	0.95	65	—
CH_3OH	MW	0.35	0.98	71	12
CH_3CN	CH	0.25	1.65	20	—
CH_3CN	CH	0.38	1.08	81	—
CH_3CN	MW	0.41	0.96	90	14

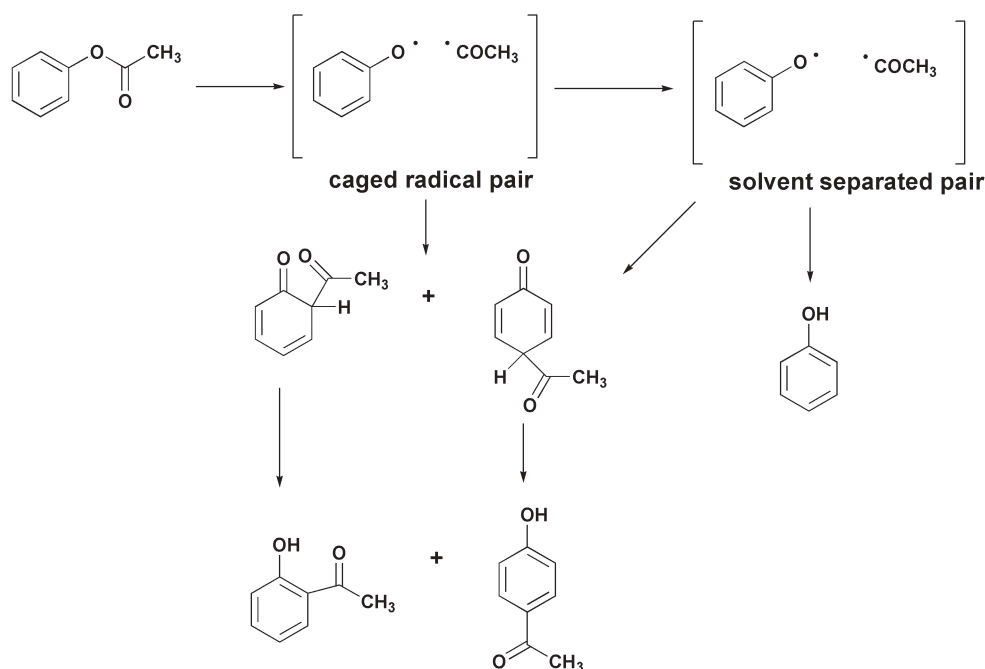


Scheme 3

temperature. The size of the hot spots was estimated to be as large as 100 μm .

Hot spots may be created by the difference in dielectric properties of materials, by the uneven distribution of electromagnetic field strength, or by volumetric dielectric heating under microwave conditions.⁴³

Hihn *et al.*⁴⁴ studied the temperature distribution in the preparation of coumaran-2-one in solvent-free conditions. They divided the volume into three layers of equal thickness. The use of this segmentation allowed them to apply a kinetic law in each cell, where the temperature is considered to be homogeneous. A higher temperature heterogeneity was found at the end of the reaction during microwave heating than on heating with an oil bath. These temperature inhomogeneities during microwave heating are mainly due to the use of a monomode cavity. The results described to date seem to show that the difference between microwaves and standard oil bath heating only concerns the temperature repartition. From the



Scheme 2

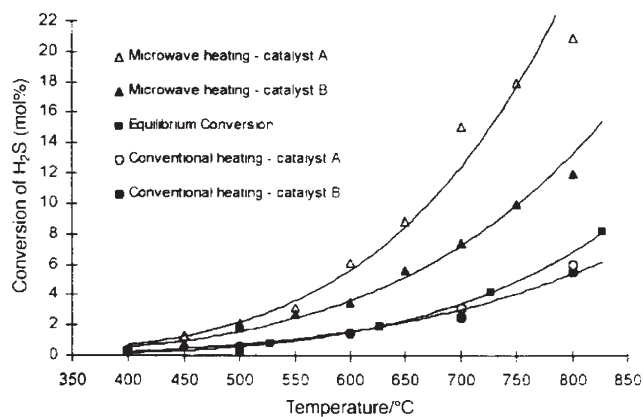


Fig. 4 H_2S conversion vs. temperature with mechanically mixed catalyst A and impregnated catalyst B.⁴² Reproduced by permission of The Royal Society of Chemistry.

point of view of global energy balance, the fact is that microwave heating leads to higher performance because the power consumed is directly useful to the reaction mixture but less so to intermediates such as a caloric fluid.

Selective heating

Solvents

It is clear that microwave irradiation is a selective mode of heating. Characteristically, microwaves generate rapid intense heating of polar substances while apolar substances do not absorb the radiation and are not heated.¹ Selective heating has been exploited in solvents, catalysts and reagents.

Strauss^{8,45} performed a Hoffmann elimination using a two-phase water/chloroform system (Fig. 5). The reaction performed in water at 105 °C led to polymerisation of the final product. However, the reaction proceeds nicely under microwave irradiation in a two phase water/chloroform system. The temperatures of the aqueous and organic phases were 110 and 50 °C, respectively, due to differences in the dielectric properties of the solvents. This difference avoids the decomposition of the final product. Comparable conditions would be difficult to obtain by traditional heating methods.

A similar effect was observed by Hallberg in the preparation of β,β -diarylated aldehydes by hydrolysis of enol ethers in a two phase (toluene/aq. HCl) system.⁴⁶

Marken *et al.*⁴⁷ showed that the effect of 2.45 GHz microwave radiation on electroorganic processes in microwave absorbing (organic) media can be dramatic but is predominantly thermal in nature. They studied the oxidation of 2 mM ferrocene in acetonitrile (0.1 M NBu_4PF_6) with a Pt electrode. Sigmoidal steady-state responses were detected and, as expected, increasing the microwave power led to an increase in the limiting current. This effect has been qualitatively attributed to the formation of a “hot spot” in close proximity to the electrode surface. Focusing of microwaves at the end of the metal electrode is responsible for this highly localized thermal effect. Switching off the microwave power immediately results in a return to the voltammetric characteristics observed at room temperature.

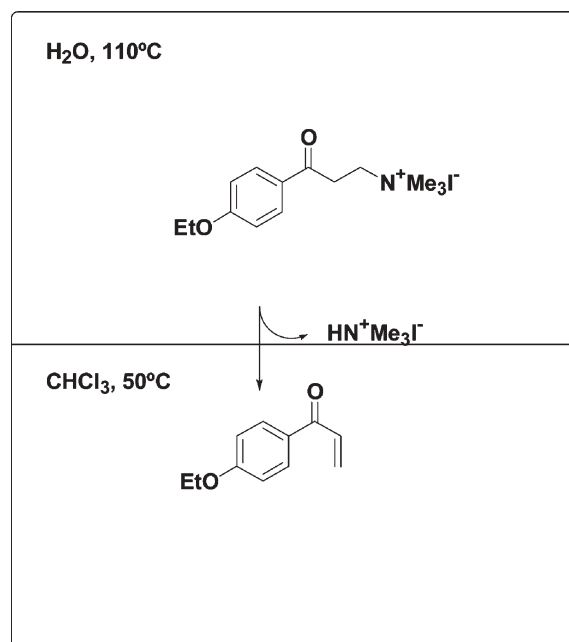


Fig. 5 Selective heating of water/chloroform mixtures. Reprinted with permission from ref. 8. Copyright (1995) CSIRO Publishing.

The temperature can be seen to increase away from the electrode surface with a “hot spot” region at a distance of approximately 40 μm . The “hot spot” temperature (Fig. 6) was 118 °C and is considerably higher than the boiling point of acetonitrile (81.6 °C) and also much higher than the temperature of the electrode (47 °C). Under these conditions the velocity of acetonitrile convection through the “hot spot” region is 0.1 cm s^{-1} and, therefore, the solvent typically passes through the high-temperature region in less than 100 ms.

Hot spots have been also postulated in terms of temperature gradients within a solid. In that way they cannot be directly measured.^{42,48,49}

Catalysts

Selective heating has been exploited efficiently in heterogeneous reactions to heat selectively a polar catalyst. For example, Bogdal^{48,49} describes the oxidation of alcohols using Magtrieve™ (Scheme 4). The irradiation of Magtrieve™ led to rapid heating of the material up to 360 °C within 2 minutes. When toluene was introduced into the reaction vessel, the temperature of Magtrieve™ reached *ca.* 140 °C within

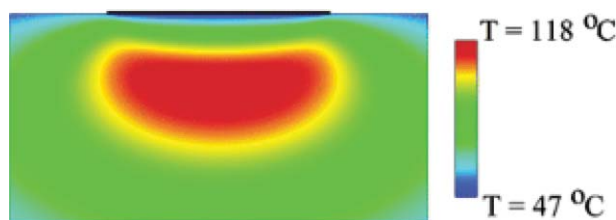
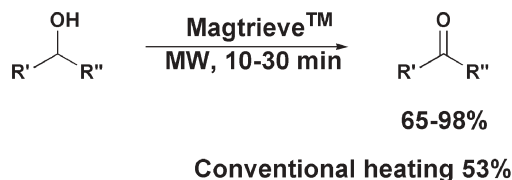
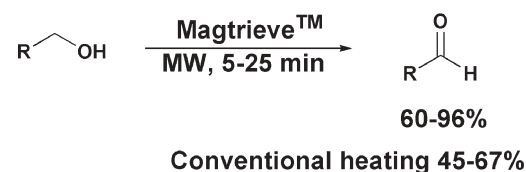


Fig. 6 Thermography of an electroorganic process in acetonitrile under microwave irradiation. Reprinted with permission from ref. 47. Copyright (2002) American Chemical Society.



Scheme 4

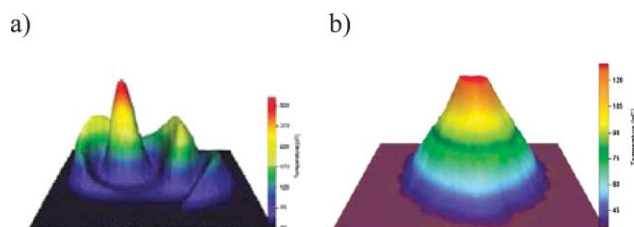


Fig. 7 Temperature profiles after 2 min of the microwave irradiation of Magtrieve™ (a) and its suspension in toluene (b).

2 minutes and was more uniformly distributed (Fig. 7). This experiment showed that the temperature of the catalyst can be higher than the bulk temperature of the solvent, which implies that such a process might be more energy efficient than other conventional processes.

This overheating effect was also determined by Auerbach⁵⁰ through equilibrium molecular dynamics and nonequilibrium molecular dynamics in zeolite–guest systems after experimental work by Conner.⁵¹ The energy distributions in zeolite and zeolite–Na are shown in Fig. 8. At equilibrium all atoms in the system are at the same temperature. In contrast, when Na–Y zeolite is exposed to MW energy, the effective steady-state temperature of Na atoms is considerably higher than that of the rest of the framework, indicating an athermal energy distribution. The steady-state temperature for binary methanol–benzene mixtures in both siliceous zeolites is shown in

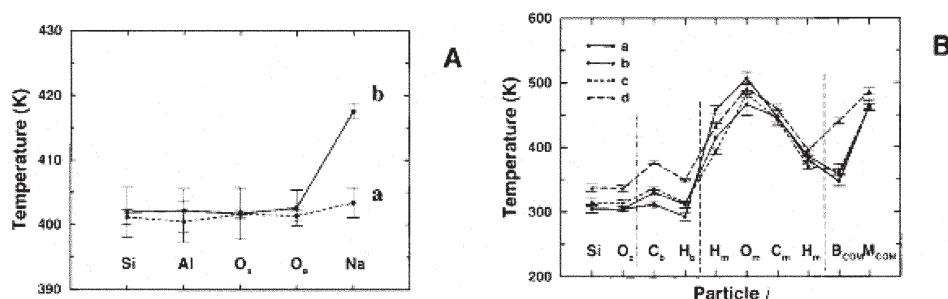


Fig. 8 (A) Energy distributions in NaY at (a) thermal equilibrium and (b) nonequilibrium, with an external field. (B) Steady-state energy distributions for binary mixtures in siliceous-Y (a) 1 : 1, (b) 2 : 2, (c) 4 : 4 and (d) 8 : 8 methanol–benzene per unit. Reprinted with permission from ref. 50. Copyright (2002) American Chemical Society.

Fig. 8(B). Statistically different temperatures for each component were found, where $T_{\text{methanol}} \gg T_{\text{benzene}} > T_{\text{zeolite}}$. This result suggests that methanol dissipates energy to benzene, though much too slowly to approach thermal equilibrium while under steady-state conditions.

However, some controversy also exists concerning the effects of microwave irradiation in heterogeneous catalysis.²⁸ Some authors have proposed the modification of the catalyst's electronic properties upon exposure to microwave irradiation^{52,53} in order to explain the superior catalytic properties of catalysts under these conditions. However, other authors have reported that microwave irradiation has no effect on the reaction kinetics.⁵⁴

Reagents and products

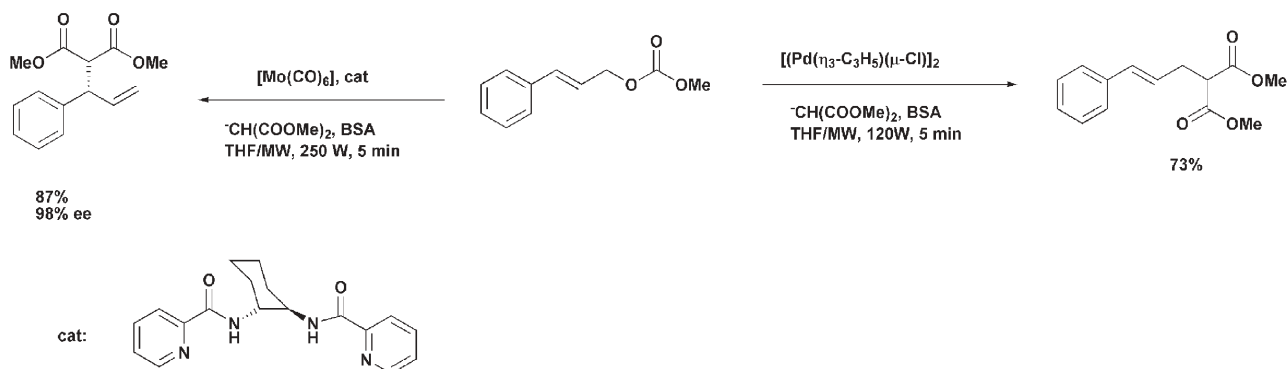
Larhed³⁹ described the molybdenum-catalysed allylic alkylation of (*E*)-3-phenyl-2-propenyl acetate. The reaction occurs with good reproducibility, complete conversion, high yields and excellent ee in only a few minutes (Scheme 5). In the standard solvent (thf), and with an irradiation power of 250 W, a yield of 87% was obtained and high regioselectivity and enantiomeric excess (98%) were achieved. Somewhat lower regioselectivities (17–19 : 1) than in the previously reported two-step method (32–49 : 1) were obtained. Alkylation also worked on polymer-supported reagents and, consequently, can be applied in combinatorial chemistry.

The high temperature obtained (220 °C) is not only due to increased boiling points at elevated pressure, but also to a significant contribution from sustained overheating. The yields from the oil bath experiments are lower than those for the corresponding microwave-heated reactions. In the case of pure, microwave-transparent solvents, the added substances, be they ionic or non-ionic, must therefore contribute to the overall temperature profile when the reaction is carried out. It seems reasonable that when the substrates act as “molecular radiators” in channelling energy from microwave radiation to bulk heat, their reactivity might be enhanced.

The concept and advantages of “molecular radiators” have also been described by other authors.⁵⁵

Susceptors

A susceptor can be used when the reagents and solvents do not absorb microwave radiation. A susceptor is an inert compound



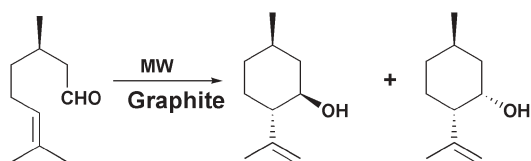
Scheme 5

that efficiently absorbs microwave radiation and transfers the thermal energy to another compound that is a poor absorber of the radiation. This method is associated with an interesting advantage. If the susceptor is a catalyst, the energy can be focused on the surface of the susceptor where the reaction takes place. In this way, thermal decomposition of sensitive compounds can be avoided. In contrast, transmission of the energy occurs through conventional mechanisms.

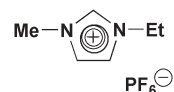
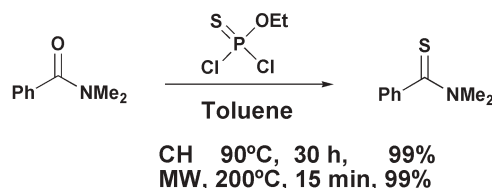
In solvent-free or heterogeneous conditions graphite has been used as a susceptor. For example, Garrigues⁵⁶ described the cyclization of (+)-citronellal to (–)-isopulegol and (+)-neoisopulegol on graphite. The stereoselectivity of the cyclization can be altered under microwave irradiation (Scheme 6). (–)-Isopulegol is always the principal diastereoisomer regardless of the method of heating, but the use of microwaves increases the amount of (+)-neoisopulegol up to 30%.

Ionic liquids have been used both in solution and under homogeneous conditions. For example, Ley⁵⁷ described the preparation of thioamides from amides. Although the reaction under classical conditions occurs in excellent yield, the reaction time can be shortened using microwave irradiation (Scheme 7). The reaction was performed in toluene and, as this is not an optimum solvent for the absorption and dissipation of microwave energy, a small amount of an ionic liquid solvent was added to the reaction mixture to ensure efficient heat distribution.

In this regard, Leadbeater⁵⁸ studied the use of ionic liquids as aids for the microwave heating of a nonpolar solvent (Table 4). It was shown that apolar solvents can, in a very short time, be heated to temperatures way above their boiling points in sealed vessels using a small quantity of an ionic liquid. It was found that 0.2 mmol of ionic liquid was the optimal amount to heat 2 mL of solvent.



Scheme 6



Scheme 7

These solvent mixtures were tested with some model reactions such as Diels–Alder cycloadditions, Michael additions and alkylation reactions.

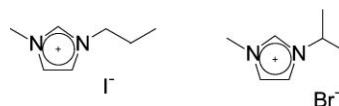
Non-thermal effects

The issue of non-thermal effects (also called not purely thermal and specific microwave effects) is still a controversial matter. Several theories have been postulated and also some predictive models have been published.

Table 4 The microwave heating effects of adding a small quantity of **1** and **2** to hexane, toluene, thf and dioxane

Solvent	IL ^a	<i>T</i> IL/°C	<i>t</i> /sec	<i>T</i> /°C ^b	b.p./°C
Hexane	1	217	10	46	69
	2	228	15	—	—
Toluene	1	195	150	109	111
	2	130	150	—	—
Thf	1	268	70	112	66
	2	242	60	—	—
Dioxane	1	264	90	76	101
	2	248	90	—	—

^a Ionic liquid 1 mmol mL^{–1} of solvent. ^b Temperature reached without ionic liquid.



Loupy has recently published a tentative rationalization of non-thermal effects.⁵⁹ The nature of the microwave effect was studied and classified considering the reaction medium (polar and apolar solvents and solvent-free reactions) and the reaction mechanism, *i.e.*, the polarity of the transition state (isopolar and polar transition states) and the transition state position along the reaction coordinate. Microwave effects should increase in apolar solvents and solvent-free reactions, with polar transition states and late transition states.

Non-thermal effects have been envisaged to have several origins. However, non-thermal effects may arise also from interactions between the microwave field and the material, similar to thermal effects. In this regard, microwave heating strongly interferes with possible non-thermal effects and these cannot be easily separated in mechanistic studies.

Various authors have proposed that changes in thermodynamic parameters under microwave irradiation are the cause of the “microwave effect”. Nevertheless, doubt has subsequently been cast on some of these theories by other authors and, indeed, by the original authors themselves. Jacob *et al.*⁶⁰ published an excellent review on synthetic results to which the microwave effect has been attributed.

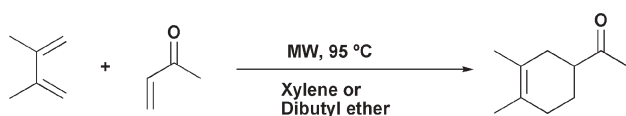
Berlan *et al.*⁶¹ found that in cycloaddition reactions carried out under reflux in xylene or dibutyl ether (Scheme 8) at the same temperature, the reaction rates were always faster under microwave conditions than when using classical heating methods. The observed acceleration is more significant in apolar solvents, which show weak dielectric losses (Fig. 9). Because of this, the authors propose that a modification to ΔG^\ddagger is produced, possibly through a change in the entropy of the system. They also suggest the existence of “hot spots” analogous to those described for ultrasound chemistry.⁶² Subsequently, Strauss *et al.*⁶³ indicated that the kinetics of these and other reactions are similar under microwave irradiation and classical heating, which would mean that there is no specific microwave effect.

Similar results in the cycloaddition of cyclopentadiene with methyl acrylate were described by Gedye (Scheme 9).⁶⁴ Microwave radiation does not alter the *endo:exo* selectivity and the changes that are observed can be explained by the fact that the reactions under microwave conditions occur at higher temperatures than those taking place under reflux. Likewise, Bond⁶⁵ and Strauss^{66,67} showed that the rates of esterification reactions performed in carefully controlled systems are identical in the presence or absence of microwave radiation and that the final yields depend only on the temperature profile—not on the mode of heating.

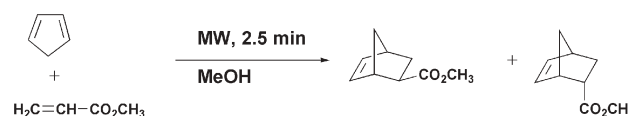
Sun *et al.*⁶⁸ showed that the rate of hydrolysis of ATP is 25 times faster under microwave irradiation than with classical heating at comparable temperatures. The authors attribute this fact to the direct absorption of radiation or to selective excitation of the water of hydration over the bulk solution. They point out that spectroscopic heating (by microwaves) can increase the kinetic energy of the solvent through direct absorption of the irradiated energy. One of the authors later showed⁶⁹ that the rate of hydrolysis solely depends on the temperature and not on the method of heating.

Hájek studied the halogenation of alkenes with tetrahalomethanes in homogeneous conditions and found that the highest rate enhancements were recorded in the presence of polar solvents.⁷⁰ In these homogeneous conditions, rate enhancement seems to be caused mainly by a thermal dielectric heating effect resulting from the effective coupling of microwaves to polar solvents. In heterogeneous reactions the presence of hot spots and selective heating should be responsible for the observed acceleration.⁷⁰ This effect was also observed in the alkylation of secondary amines on zeolites, where temperature gradients of up to 20 °C were observed in the samples.

Some authors^{71,72} have suggested that the direct activation of one or both reagents in the ring closing metathesis process



Scheme 8



Scheme 9

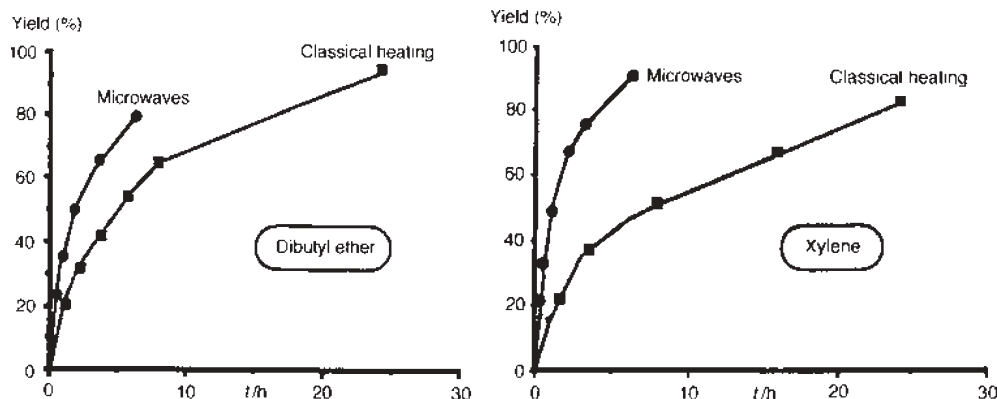
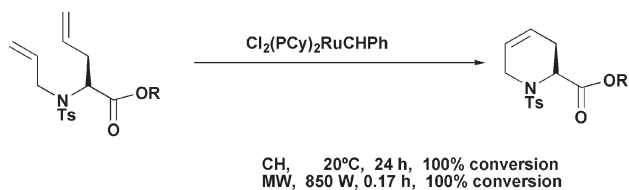


Fig. 9 Conversion vs. time in the cycloaddition of 2,3-dimethylbutadiene with methyl acrylate.



Scheme 10

(i.e., the catalyst and/or the olefin) is responsible for the observed rate enhancements in this reaction (Scheme 10).

Kappe *et al.*⁷³ performed a reinvestigation of microwave-assisted RCM. They showed that absorption of microwave radiation by the Grubbs catalyst was negligible and, in contrast, the diene showed significant microwave absorption and acted as a molecular radiator. However, it was also demonstrated that under thermal conditions the results corresponded to those obtained in the microwave heating experiments. This showed that it is unimportant whether the energy is directly transferred to one of the reactants or to the bulk solvent by thermal microwave heating.

Furthermore, Kappe's results from a study of the Biginelli reaction are clear (Scheme 11);⁷⁴ the kinetic experiments show that there is no appreciable difference in reaction rates and yields between reactions carried out under microwave irradiation and thermal heating at identical temperatures. This result is understandable since a polar solvent (ethanol) was used, meaning that the radiation was absorbed by the solvent and thermal energy transmitted to the reagents by conventional mechanisms (convection and conduction) rather than by dielectric losses.

In this respect, both Berlan⁷⁵ and Strauss⁸ rule out the possibility that microwave radiation can excite rotational transitions. When a compound absorbs microwaves, the dielectric heating causes an increase in the temperature of the system. When the internal energy of the system is raised it is distributed among translational, rotational or vibrational energies regardless of the mode of heating. Consequently, it was concluded that kinetic differences should *not* be expected between reactions heated by microwaves or by classical heating if the temperature is known and the solution is thermally homogeneous.

Similarly, Stuerger indicated that absorption of microwave photons cannot induce any chemical bond breaking (Table 5) and the electric field is too low to lead to induced organization. Moreover, in condensed phases the collision rate induces transfer between rotational and vibrational phases. Hence, it was concluded that an electric field cannot produce any molecular effect.^{76,77} Molecular effects resulting from the

Table 5 Energy of different bonds

	Brownian motion	Hydrogen bond	Covalent bond	Ionic bond	Photon
Energy/eV	~0.025 (200 K)	~0.04–0.44	~5.0	~7.6	0.00001
Energy/kJ mol ⁻¹	1.64	~3.8–4.2	~480	~730	—

microwave field could, however, be observed for a medium that does not heat under microwave irradiation.

However, Miklavc⁷⁸ analysed the rotational dependence of $\text{O} + \text{HCl} (\text{DCl}) \rightarrow \text{OH} (\text{OD}) + \text{Cl}$ reactions performed on a model potential energy surface and concluded that marked accelerations of chemical reactions may occur through the effects of rotational excitation on collision geometry.

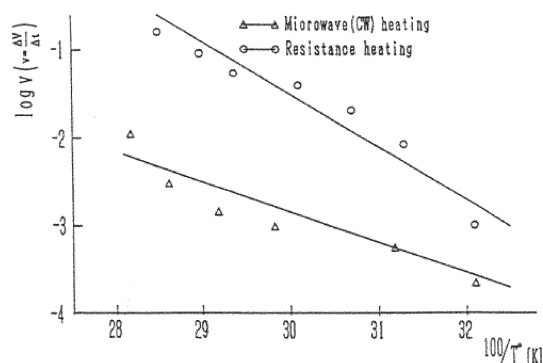
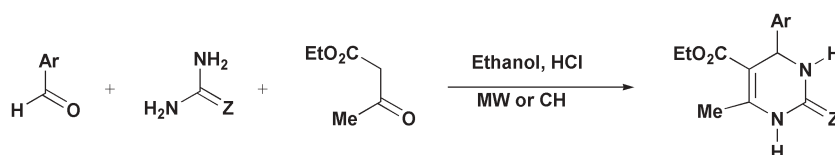
Molecular agitation and mobility are factors that have also been used to explain the effects attributed to microwave radiation.

The thermal decomposition of sodium bicarbonate has recently been studied (Scheme 12).⁷⁹

The authors found that the activation energy of the reaction is reduced by microwave radiation (Fig. 10). Given that temperature control is crucial in these experiments, the authors endeavoured to ensure the reliability of the temperature determination both in the spatial and time domains. Although the mechanism is not well understood, the application of a microwave field to dielectric materials induces rapid rotation of the polarised dipoles in the molecules. This generates heat due to friction while simultaneously increasing the probability of contact between molecules and atoms, thus



Scheme 12

Fig. 10 Arrhenius plot of NaHCO_3 solution.

Scheme 11

enhancing and reducing the reaction rate and activation energy, respectively.

However, after studying the synthesis of titanium carbide, Cross⁸⁰ concluded that molecular mobility can increase in the presence of a microwave field and that in this case it is the Arrhenius pre-exponential factor A that changes and not the energy of activation (eqn. (1)).

$$K = A e^{-\Delta G/RT}, A = \gamma \lambda^2 \Gamma, \gamma = \text{geometric factor that includes the number of nearest-neighbour jump sites, } \lambda = \text{distance between different adjacent lattice planes (jump distance), } \Gamma = \text{jump frequency.} \quad (1)$$

An increase by a factor of 3.3 in the Arrhenius pre-exponential factor could explain the acceleration in reaction rate obtained with microwaves.

The Arrhenius pre-exponential factor depends on the frequency of vibration of the atoms at the reaction interface and it has therefore been proposed that this factor can be affected by a microwave field.

The use of microwaves leads to a temperature reduction of 80–100 °C in the sintering temperature of partially stabilized zirconia,⁸¹ an effect that is non-thermal in nature. Wroe *et al.*⁸¹ showed that a microwave field improves either the volume or grain-boundary mechanism rather than improving diffusion at the surface, that is dominant at low temperatures. Microwaves preferentially increase the flux of vacancies within grain boundaries in the sample.

Other examples have been found of results that cannot be explained solely by a thermal effect. In a study on the mutarotation of α -D-glucose to β -D-glucose (Fig. 11), Pagnota⁸² found that in EtOH–H₂O (1 : 1) the use of microwaves led, apart from a more rapid equilibration compared to conventional heating, to a modification of the equilibrium position to a point where a larger amount of α -D-glucose was obtained than under classical heating (Fig. 11). This extraordinary effect cannot be explained by a classical heating effect and is the clearest example of a possible specific action created by a microwave radiation field.

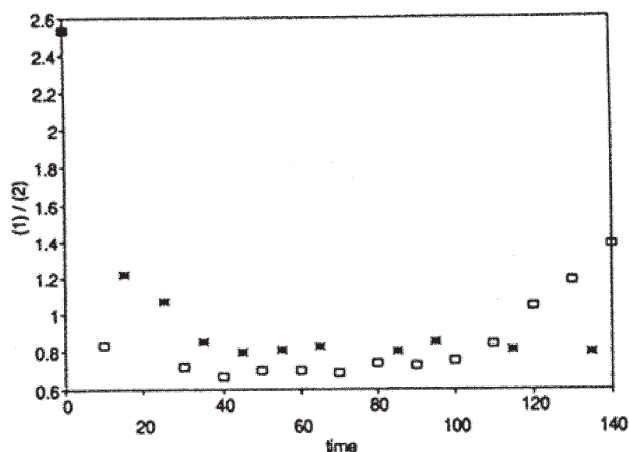
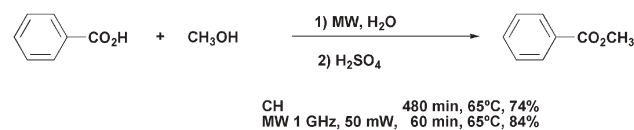


Fig. 11 α -D-glucose : β -D-glucose ratio vs. time. □ Microwave heating. ■ Conventional heating.



Scheme 13

Another interesting study was reported by Zhang⁸³ on the synthesis of aromatic esters by esterification of benzoic acids in refluxing alcohols. The authors used microwave radiation at a frequency of 1 GHz, where there is no microwave heating action but only an athermal microwave effect. Interestingly, under these conditions a reduction in reaction time was still observed (Scheme 13).

Other reports include non-thermal effects in solid phase separation processes,⁸⁴ partitioning of *p*-nitroaniline between pseudo-phases,⁸⁵ structural transformations in amphiphilic bilayers,⁸⁶ and protein-catalysed esterifications and transesterifications.⁸⁷

One possible solution to the interference of thermal effects seems to be the investigation of spin dynamics of photochemically generated biradicals. Photochemical reactions might be accelerated by microwave treatment if they pass through polar transition states and intermediates, *e.g.*, ions or ion-radicals.⁸⁸

In a photochemical reaction only a pair of neutral radicals with singlet multiplicity will recombine. A triplet pair intersystem crosses into the singlet pair or escapes the solvent cage and reacts independently at a later stage (Fig. 12).

The increasing efficiency of triplet-to-singlet interconversion (mixing of states) leads to a more rapid recombination reaction and *vice versa*. It is now well established that a static magnetic field can influence intersystem crossing in biradicals (magnetic field effect, MFE) and this effect has been successfully interpreted in terms of the radical pair mechanism. This concept has enabled the explanation of nuclear and electronic spin polarization during chemical reactions, *e.g.* chemically induced dynamic polarization (CIDNP) or reaction yield-detected magnetic resonance (RYDMAR).

The microwave field, which is in resonance with the energy gaps between the triplet states (T_{+1} or T_{-1}) and T_0 , transfers the excess population from the T_{+1} or T_{-1} states back to a mixed state. Application of a strong magnetic field to the singlet-born radical pair leads to an increase in the probability of recombination, which can, however, also be controlled by microwave irradiation (Fig. 13).

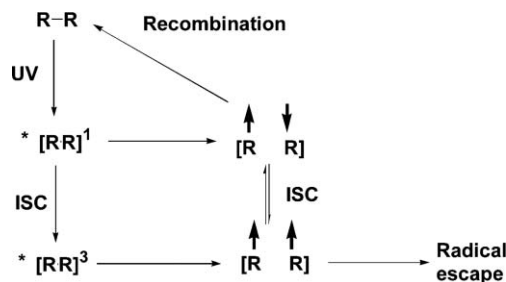


Fig. 12 Schematic illustration of magnetic field and microwave effects in radical-pair chemistry.

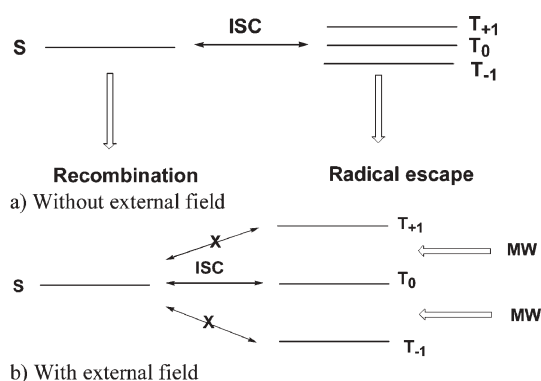


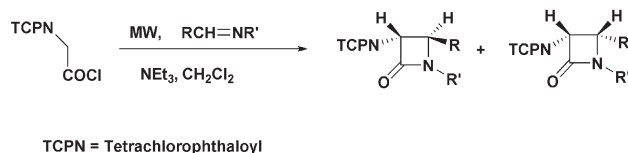
Fig. 13 Schematic illustration of magnetic field and microwave effects in radical-pair chemistry.

These microwave-induced spin dynamics can be considered as an archetype of a non-thermal microwave effect. An interesting example of this behaviour was described by Wasielewski,⁸⁹ who showed that the duration of photosynthetic charge separation can be controlled with microwave irradiation; one microsecond microwave pulses were used that possessed powers up to 20 kW. Similarly, Tanimoto showed that the lifetimes of biradicals can be controlled by the simultaneous application of magnetic fields and microwave radiation; when the microwave energy coincides resonantly with the energies between the triplet sublevels, the ESR transition occurs and the triplet sublevels can mix with a singlet state.⁹⁰

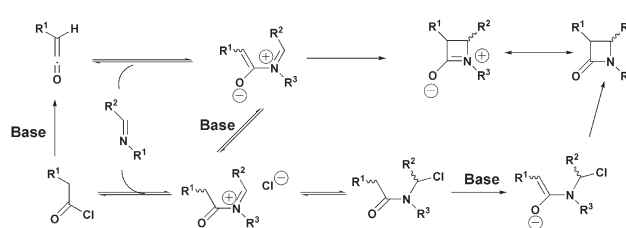
Predictive models

A number of theories have been developed in order to predict the incidence of non-thermal microwave effects in reactivity and selectivity. In this respect, special mention should be made of reactions where the selectivity is modified or inverted.⁹¹

Several reports indicate that the chemo-, regio- and stereo-selectivity can be modified by microwave irradiation.^{91–93} For example, Bose described reactions between acid chlorides and Schiff bases where the stereoselectivity depends on the order of addition of the reagents (Scheme 14).^{94,95} When the condensation was conducted by a “normal addition” sequence (*i.e.* acid chloride last), only the *cis* β-lactam was formed. However, if the “inverse addition” technique (triethylamine last) was used, 30% *cis* and 70% *trans* β-lactams were obtained under the same conditions. When the reaction was conducted in a microwave oven using chlorobenzene, the ratio of *trans* and *cis* β-lactams was 90 : 10 irrespective of the order of addition. Moreover, isomerization to the thermodynamically more stable *trans* β-lactam did not occur.



Scheme 14



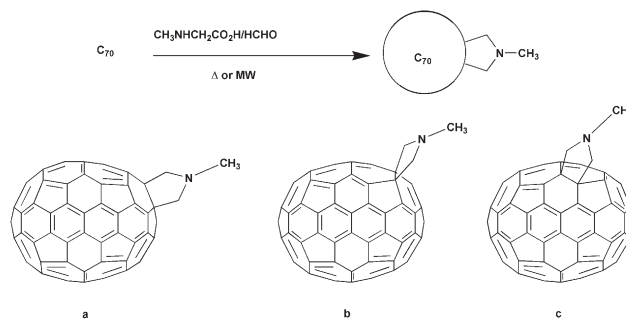
Scheme 15

Cossio explained this effect by considering that under microwave irradiation the route involving direct reaction between the acyl chloride and the imine, *i.e.*, the more polar route, competes efficiently with the ketene–imine reaction pathway (Scheme 15).⁹⁶

Langa described how the cycloaddition of *N*-methylazomethine ylides to C₇₀ gave three regioisomers **a**–**c** by attack at the 1–2, 5–6 and 7–21 bonds (Scheme 16).⁹⁷

Under conventional heating the 7–21 isomer was formed in only a low proportion and the 1–2 isomer was found to predominate. The use of microwave irradiation in conjunction with ODCB, which absorbs microwaves efficiently, gave rise to significant changes. In contrast to classical conditions, isomer **c** was *not* formed under microwave irradiation regardless of the irradiation power and isomer **b** predominated at higher power (Scheme 16 and Fig. 14).

A computational study on the mode of cycloaddition showed that the reaction is stepwise, with the first step consisting of a nucleophilic attack on the azomethine ylide.



Scheme 16

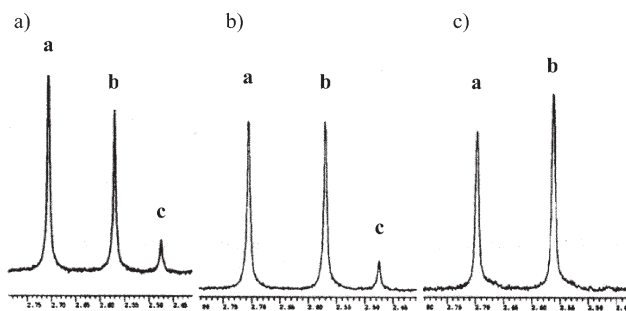


Fig. 14 ¹H NMR region of the methyl group: (a) classical heating in toluene as a solvent, (b) classical heating in ODCB as a solvent, and (c) microwave irradiation in ODCB at 180 W, 30 min. Reprinted with permission from ref. 97. Copyright (2000) American Chemical Society.

The most negative charge of the fullerene moiety in the transition states **a** and **b** is located on the carbon adjacent to the carbon–carbon bond being formed. In transition state **c**, however, the negative charge is delocalized throughout the whole C_{70} subunit. The relative ratio of isomers **a–c** is related to the greatest hardness, and its formation should be favoured under microwave irradiation. It is noteworthy that purely thermal arguments predict the predominance of **c** under microwave irradiation, which is the opposite of the result found experimentally.

This model was used by Díaz-Ortiz⁹⁸ in the preparation of nitroproline esters by the 1,3-dipolar cycloaddition of imines (derived from α -aminoesters) with β -nitrostyrenes in the absence of solvent (Scheme 17). Conventional heating produced isomers **a** and **b**, as expected, by the *endo* and *exo* approaches. However, under microwave irradiation a new compound—*isomer c*—was obtained. It was shown that this isomer arises from a thermal isomerization of the imine by rotation in the carboxylic part of the ylide. Isomer **c** is then produced by an *endo* approach. Formation of the second dipole exclusively under microwave irradiation should be related to its higher polarity, hardness and lower polarizability than the first dipole.

Elander⁹⁹ described a quantum chemical model of an S_N2 reaction ($Cl^- + CH_3Cl \rightarrow$) in a microwave field in order to study the effect of microwave radiation on selectivity. In a similar way to Langa,⁹⁷ a variation of the polarizability was observed. However, the perpendicular component is practically unchanged during the reaction. The polarizability component, which is parallel to the reaction coordinate, increases dramatically when the system proceeds along the reaction path. This parameter increases from $\alpha_{||} = 34$ au in the

starting materials to 92 au for the transition state geometry. A significant increase occurs just after the van der Waals' minimum, where the potential energy starts to grow and the most important chemical transformation develops.

The authors emphasize the importance of taking into consideration solvent effects and, in addition, the following points were established:

(i) From the study of the gas phase reaction complex, they concluded that the effects of induced dipole moment on the microwave energy absorption are negligible when compared to the microwave energy absorption caused by the permanent dipole moment.

(ii) The study of the non-gas phase environment should include solvation shells. The models of the water-solvated reaction complexes were all shown to possess low frequency vibrations or hindered rotations with frequencies overlapping that of the microwave radiation typically used in microwave-enhanced chemistry.

Considering all these points, it was concluded that absorption of microwave photons may play an important role in these types of reactions.

Loupy¹⁰⁰ described the reaction of 1-ethoxycarbonylcyclohexadiene, 3-ethoxycarbonyl- α -pyrone and 2-methoxythiophene in solvent-free conditions and demonstrated the occurrence of a microwave effect (Scheme 18). Diels–Alder cycloaddition reactions occurred and, in the case of 2-methoxythiophene, competition with Michael addition was observed.

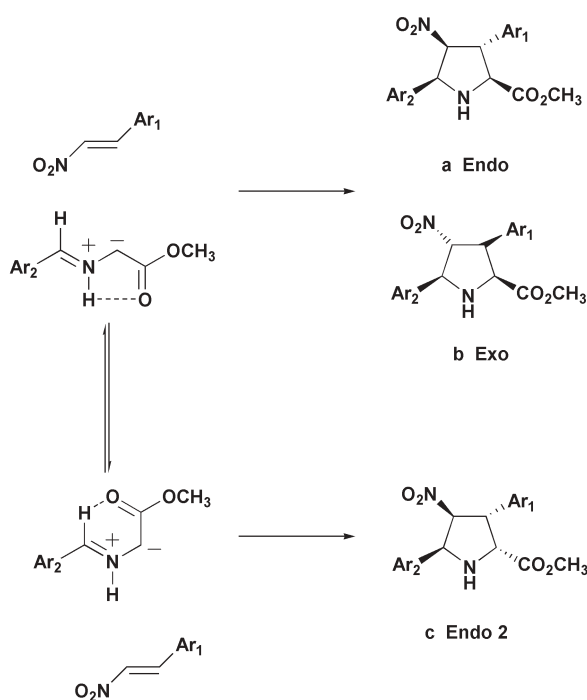
Evidence for a microwave effect was not found in the first reaction. However, in the reaction with α -pyrone a significant increase in yield was observed, although the selectivity was not greatly influenced. The modification of selectivity was only observed on increasing the polarity of the solvent. Finally, microwave effects were found in the reaction with thiophene and these influenced both reactivity and selectivity. The effect on yield was small in the Diels–Alder reaction but was found to be higher in the Michael addition. This process was favoured under microwave irradiation when using acetic acid as the solvent.

The authors claim that higher yields and modifications in selectivity are related to the variation of the dipolar moment from the ground state to the transition state (Table 6).

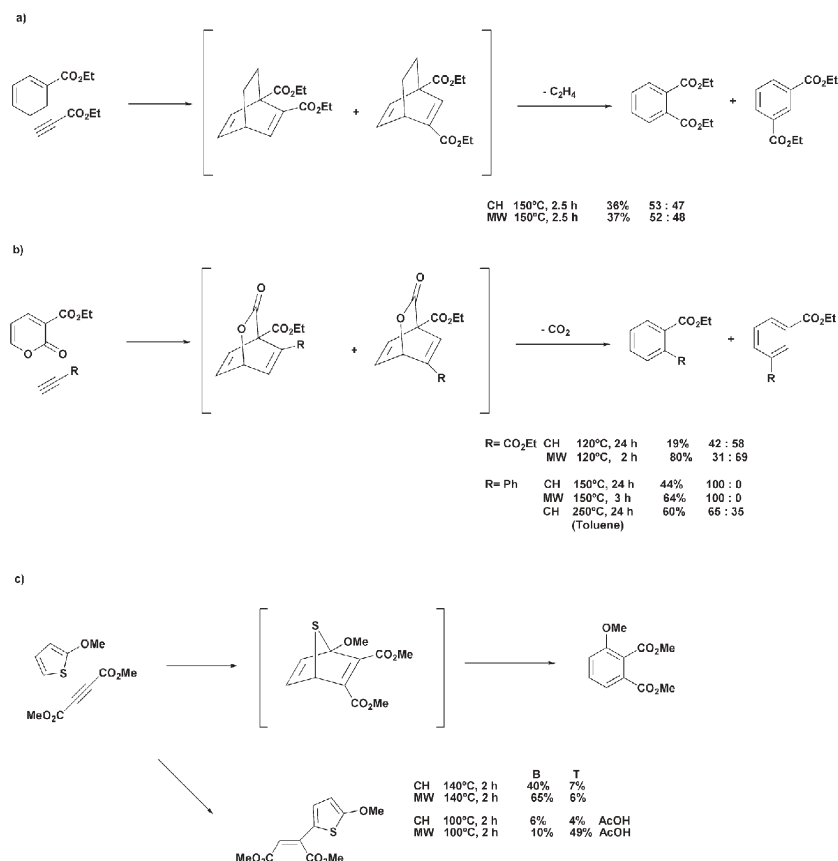
These results are in agreement with the qualitative theory proposed by Loupy,⁵⁹ in which the following points were established:

(i) The acceleration of reactions by microwave exposure results from material-wave interactions leading to thermal effects (which may be easily estimated by temperature measurements) and specific (*i.e.*, not purely thermal) effects. Clearly, a combination of these two contributions could be responsible for the observed effects.

(ii) If the polarity of a system is enhanced from the ground state to the transition state, such a change could result in an acceleration due to an increase in material-wave interactions during the course of the reaction. The most frequently encountered cases concern unimolecular or bimolecular reactions between neutral molecules (as dipoles are developed in the TS) and anionic reactions of tight ion pairs—*i.e.*, involving charge-localized anions (leading to ionic dissociation in the TS). These systems could be more important in cases with a



Scheme 17



Scheme 18

Table 6 Dipole moments of reagents and transition states carried out by HF/6-31G(d) level

	Ground state		Transition state	
Reaction a	EP ^a	Cyclohexane	Is ^c	Ia ^c
μ (Debye)	2.2	2.4	0.4	1.9
Reaction b	EP ^a	Pyron	IIs ^c	Ila ^c
μ (Debye)	2.2	3.3	4.8	5.2
Reaction c	DMAD ^b	Thiophene	IIIs1 ^{c,d}	IIla1 ^{c,d}
μ (Debye)	2.8	1.8	5.83	5.4
			IIIs2 ^{c,d}	IIla2 ^{c,d}
			5.15	8.02

^a EP: ethyl propiolate. ^b DMAD: dimethylacetylenedicarboxylate.^c s, *syn*; a, *anti* approaches. ^d 2 and 1, orientation in the same side or the contrary, respectively, of the methoxy and carbonyl groups.

product-like TS, a situation in agreement with the Hammond postulate.

(iii) By far the most useful scenario is related to solvent-free conditions (green chemistry procedures) as microwave effects are not masked or limited by solvent effects—although non-polar solvents can, of course, always be used. Many types of carefully controlled experiments need to be performed, however, to evaluate the reality and limitations of this approach in order to make valid comparisons.

(iv) The magnitude of a specific microwave effect could be indicative of a polar mechanism or to identify the rate-determining step in a procedure involving several steps.

Conclusion

In conclusion, microwave radiation can be used to improve processes and modify selectivities in relation to conventional heating. A complete survey of the applications and advantages of using microwave irradiation in organic synthesis has been published in a recent book.³ It is possible to take advantage of both thermal and non-thermal effects to obtain the desired results. Overheating of polar solvents and hot spots in solvent-free conditions can be used to accelerate reactions and also to avoid decomposition of thermally unstable compounds. The increased mobility in solids has been used to obtain less harsh reaction conditions under microwave irradiation. Also, the selective heating induced by microwave irradiation can be exploited to heat polar substances in the presence of apolar ones and, in this way, to modify the selectivity of a given reaction or to avoid decomposition of thermally unstable compounds.

Finally, the question arises: is there any effect from the electromagnetic field? Microwave radiation is a very polarizing field and may stabilize polar transition states and intermediates.¹⁰⁰ In this way reactions can be accelerated if such intermediates are involved or, alternatively, in competitive reactions the route that involves polar intermediates or transition states could be favoured. It is widely accepted today that the solvent has a strong influence on the kinetics and selectivity of a reaction¹⁰¹—a polar solvent will stabilize a polar transition state or intermediate and thus favour this

route. There is also an interesting discussion about the effect of magnetic fields in relation to the origin of life, particularly regarding the origin of enantioselectivity in nature^{102,103} and, consequently, how circularly polarized magnetic fields can induce stereoselectivity in a chemical reaction.^{104–106} However, many people still consider that the presence of highly polarizing radiation, such as microwaves, has no influence at all on a chemical reaction. For example, it has been postulated that “while the existence of a “specific microwave effect” cannot be completely ruled out, the effect appears to be a rarity and of marginal synthetic importance”.¹⁰⁷

The effect of microwave irradiation on a chemical reaction is very complex in nature and involves thermal (e.g. hot spots, superheating) and non-thermal (e.g. molecular mobility, field stabilization) effects. Today many of these parameters have been measured and are well known, but the effect of the magnetic field has not been elucidated conclusively. More experimentation, computational calculations and the development of theories, similar to those described for ultrasound or solvents, are still required.

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