Understanding MAOS through Computational Chemistry

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The importance of microwave irradiation in Organic Synthesis today is unquestionable, but in many cases the nature of these improvements remains unknown. Exploiting the benefits that microwave irradiation has in chemistry is still hindered by a lack of understanding of the physical principles of the interaction of microwave irradiation with the components of a reaction. Moreover, dielectric properties vary with temperature and along the reaction coordinate and this makes the situation more complex. Experimental determinations employed to date in Microwave-Assisted Organic Chemistry (MAOS) are characterized by the importance of thermal heating. In this way the separation of thermal heating from any other effect of the elecromagnetic radiation is completely impossible. This review provides an overview of the use of Computational Chemistry in MAOS to provide a theoretical understanding of the factors that can be used to explain the improvements in MAOS and how computational calculations can be used as a predictive tool.

1. Introduction

Since the introduction of the first commercial household microwave oven into the market in 1954 a new heating technology was introduced in our lives. More than three decades later, in 1986, with the seminal papers from Giguere and Gedye[1,2] on the use of domestic ovens in Organic Synthesis, microwave irradiation has burst into the chemistry laboratory as new heating technology. Since then microwaves have emerged as a useful methodology to introduce energy into chemical reactions.[3-5]

Many reactions have been improved under microwave irradiation with a reduction in reaction times when compared to conventional heating (microwave flash heating), improvements in product purity and reductions in the levels of side products. In many cases, modification of the selectivity with regard to conventional heating has been achieved[6] and, in some cases, very difficult reactions[7,8] or reactions with sensitive compounds[9] that do not occur at all under classical conditions have been successful under microwaves. This methodology is particularly useful to perform autoclave experiments, because the temperature profiles achieved are very difficult, if not impossible, to reproduce using standard conditions. Today, many authors believe that microwave irradiation should be the first choice to perform organic synthesis and describe this technology as "the Bunsen burner of the XXI century".[10]

Microwave-Assisted Organic Synthesis (MAOS) is defined as the "preparation of organic compounds from accessible starting materials via some (multistep) procedures involving microwave irradiation" and, in this regard, multistep sequences using microwave irradiation exclusively have been reported.[11,12] Thousands of publications, review articles and books show the utility of this technique and highlight an interesting alternative for heating chemical reactions that offers considerable advantages.

Microwave heating differs from conventional heating in many respects. Understanding the differences in the transmission of energy by both techniques is essential to take advantage of the use of microwave irradiation. In conventional heating, the reaction mixture is heated from the surface of the reaction vessel; it requires a contact between the vessel and the heating source and the heating mechanism involves conduction. Microwave heating produces an efficient internal heating by direct coupling of microwave energy with polar substances. It is volumetric, it proceeds throughout the whole reaction mixture, and the heating mechanism involves dielectric polarization and conduction and does not require a physical contact between the sample and the heating source.

1.1. Interaction between the electromagnetic field and the matter

The effect of heating in a chemical reaction is well known. The situation with microwaves is very different and more complex since there is no external source of heat but external electromagnetic radiation, with heating dependent on the

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x capacity of the sample to absorb the radiation and the in-core transformation of the electromagnetic radiation into heat.[13]

Many excellent original papers and reviews (for instance, ref 13) cover the fundamentals of microwave-matter interaction and heating and, consequently we will not cover this subject. In brief, polar molecules absorb microwaves efficiently and can be easily heated, while apolar molecules are transparent and are not heated. Two main polarization mechanisms are used to describe the material-wave interaction and heating: Dipolar rotation and ionic conduction. In the first mechanism, permanent or induced dipoles are aligned with the electromagnetic field. The electromagnetic field leads to rotation since the field changes orientation 4.9×10^9 times per second, heat is produced as a result of agitation and intermolecular friction between molecules when the mutual orientation of the dipoles changes at each alternation of the electric field. In ionic conduction, microwaves induce charge redistribution and, once again, the reorientation increases molecular motion and results in more solute collisions, thus producing efficient heating and enhanced reactivity (Figure 1).

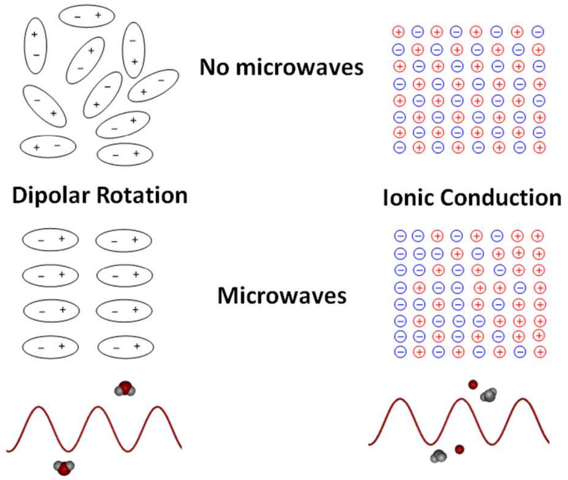


Fig. 1 Principal polarization mechanisms under microwave irradiation.

1.2. Thermal and non-thermal effects

Regardless of the significant developments and applications of microwave-assisted chemistry, there is an ongoing debate in the scientific community concerning the effects of microwave irradiation. In many pioneering reports in this field, some of the improvements observed in microwave organic synthesis were attributed to a so-called "non-thermal" effect.

Today it is generally accepted that in many cases the observed enhancements in microwave-heated reactions are in fact the result of purely thermal/kinetic effects. In this sense, Kappe and col.[14,15] performed critical reinvestigations of some previous results that claimed the existence of "non-thermal" effects. They showed that, in most cases, the observed differences between experiments performed under conventional and microwave heating conditions are in fact the result of inaccurate temperature measurements or inefficient stirring of the reaction mixture.

Nowadays it is accepted that under the action of microwave irradiation reactions can be affected by inverted temperature gradients,[16] overheating,[17] formation of macro-[18] and microscopic hot-spots[19] and selective heating of a component in the reaction, solvent,[20] catalysts[21] and reagents.[22,23]

Non-thermal microwave effects do not require the transfer of microwave energy into thermal energy. Instead, microwave energy itself directly couples to energy modes within the sample. They are highly controversial and have caused great debate among experts in microwave chemistry.

The Eyring equation (Eq. 1) relates the rate constant of a reaction with the temperature and the free energy of activation.

$$k = \frac{k_B T}{h} e^{-\Delta G^{\#}/RT} \qquad \text{Eq. 1}$$

Several authors have postulated non-thermal effects related to the temperature, considering that the bulk temperature is not representative of the temperature of the reaction. When materials absorb energy from an external time-dependent field energy accumulates in the slower configurational degrees of freedom. This nonequilibrium system is formally described by introducing rotational temperature or "effective temperature", which is higher than the translational temperature and produce an increase in the rate constant.[23-26]

A reduction of the activation energy by stabilization of polar intermediates and transition states has also been postulated. Finally, considering the Arrhenius equation $k = A\exp\left(-\frac{Ea}{RT}\right)$several authors have postulated that under microwave irradiation the pre-exponential factor increases. The two later hypotheses will be discussed in sections 2.1.3 and 2.1.1, respectively.

Recently, the use of an electrical potential to accelerate a Diels–Alder reaction has been described.[27] However, it is difficult to justify a non-thermal effect using a system that is designed to produce heating. The question arises: Is it necessary to obtain a non-thermal microwave effect to justify microwave chemistry? The clear answer is no, it is not necessary to present microwave effects in a scientific disguise.[28] The situation is also complicated since the energy delivered by heating is much larger than that of the electromagnetic radiation and because the transformation of the electromagnetic radiation into heat is very rapid. As a consequence, the separation of thermal and non-thermal effects experimentally is practically impossible.

The physical principles and the factors that determine the use of microwave technology in chemical synthesis are unfamiliar to chemists. Electric field theory is generally taught in engineering or physics rather than in chemistry. As a consequence, the way in which microwave reactors operate is not widely understood, and this had led to many misconceptions about the interaction between electromagnetic waves and chemical systems. Therefore, further studies are needed on the physical factors that can guide improvements in the design of microwave instruments and the use of microwave radiation.

1.3. Computational calculations

Computational chemistry[29] is a branch of chemistry that uses computer simulations to assist in solving chemical problems. This approach uses methods of theoretical chemistry, incorporated into efficient computer programme, to calculate the structures and properties of molecules as well as reaction mechanisms. This discipline has become a powerful tool in chemistry and it has now entered the toolkit of many chemists, including those mainly oriented towards synthesis. The tremendous development of computer science, which has led to a significant increase in the accuracy and efficiency of numerical calculations and simulations, has boosted the application of Quantum Theory to Chemistry. As a consequence, this approach has had a great impact on our current understanding of Organic Chemistry and this methodology has played a significant role in developing new theories and providing important supporting evidence for experimentally derived insights. This area has undergone spectacular development in recent decades. A good indicator of the increasing importance of computational methods for organic chemists is the large number of articles published in this time, and the award of two Nobel Prizes to researchers in this field.[30]

Experimental determinations used to date in MAOS are hindered by the interference of thermal heating and the inaccuracies in the determination of the reaction temperature. Moreover, it is still extremely difficult to design procedures that accurately reproduce, with either microwave or conventional heating, the same conditions considering the different characteristics of the two methods of heating. In this sense, computational calculations provide a useful tool to study the influence of microwave irradiation in Chemistry. This discipline has also contributed to the chemistry toolkit by providing chemical concepts that are not experimentally measurable, for instance aromaticity, reactivity, and molecular orbital topology, amongst others.

In this sense, this methodology allows to calculate parameters that play an important role in microwave chemistry but they are scarcely used in conventional synthesis, e.g. polarity, polarizability, together with intermediates and transition states in order to elucidate the reaction mechanism. As well as, it is possible to determinate other parameters, as activation energy and enthalpy, those also can be measured experimentally.

The use of Density Functional Theory (DFT),[31] developed by Kohn and Hohenberg, is stablished as an effective tool in the study of chemical reactions. The broader application of computational chemistry is partially based on the development of computer efficiency. Further developments in computer accuracy led to the development of several functionals (such as B3LYP, PBE, etc.)[32] that have been extensively used in the study of organic reactions. The expansive use of DFT initiated with its implementation on multiple accessible codes or programs, making thus more accessible for the chemistry community.

An important contribution of Computational Chemistry is its ability to be used as a predictive tool. This aspect is very important because this discipline can predict the structural and electronic properties of systems before they are synthesized, thus allowing the design of useful products and avoiding the synthesis of unnecessary ones, which contributes to the sustainable development of chemistry.

Numerous papers include microwave-assisted organic synthesis and computational studies,[33-38] but very few concern computational studies as a tool to clarify the influence of microwave irradiation in the reaction.

2. Results and discussion

In order to gain further insights into MAOS, this review aims to provide an overview of the use of Computational Chemistry in the microwave field by considering selected examples. The results are classified according to the factors that may influence the effect of microwave irradiation.

2.1. Polarity

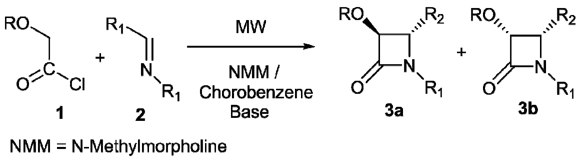
The polarity of the species that take part in the reaction is an important factor to be considered in MAOS. Polarity and the dielectric constant, ε', determine the ability of a material to store electromagnetic energy through polarization. This parameter is related to the dielectric loss factor (ε''),[39] which represents the ability to convert the stored energy into heat. The ratio $\varepsilon''/\varepsilon'$, which is known as the loss tangent ($\tan \delta$), can be used to assess the general ability of a material to be heated in a microwave field. Materials with low $\tan \delta$, at a given frequency, are considered to be transparent to microwaves and they do not undergo significant heating, whereas materials with high $\tan \delta$ are heated very efficiently. Although $\tan \delta$ is a helpful parameter when comparing the heating rates of a series of compounds with similar chemical and physical characteristics, it is not very useful in assessing chemical transformations. In order to determine $\tan \delta$ in a reaction, and consequently to calculate the heating rate reliably, more complex expressions are required that take into account the complexity of the electric field pattern, the heat capacity of the compound and its density.[40] Furthermore, $\tan \delta$ depends strongly on the temperature and will vary throughout the course of the reaction. Therefore, the polarity is a more indicative parameter to evaluate the influence of microwave heating. There are three aspects to highlight: The polarity of the species involved in the reaction, the polarity of assistant substances (susceptors) and the evolution of polarity along the reaction path.

2.1.1. Polarity of the species involved in the reaction

The polarities of all components present in the reaction medium play an important role in the heating rate under microwaves. The ability of highly polar substrates to absorb microwave energy efficiently has been used to heat reactions under microwave irradiation. Furthermore, several reports suggest that the electric component of microwaves leads to orientation effects of dipolar molecules or intermediates and hence changes the pre-exponential factor (A) or the activation energy terms in the Arrhenius equation,[41,42] thus leading to an improvement in the reaction.[43]

In this regard, the dielectric properties are group properties and cannot be modelled by an interaction between a single dipole and an electric field.[44] Considering that the reagents are in a homogeneous reaction mixture, the presence of a polar reagent might increase the polarity of the medium and hence the absorption of microwave irradiation.

In contrast to the above, when these species are in a non-polar medium or in a heterogeneous medium they could act as "molecular radiators". It was suggested that such compounds could directly couple with microwaves, thus creating microscopic hot spots that improve the absorption of microwave radiation.

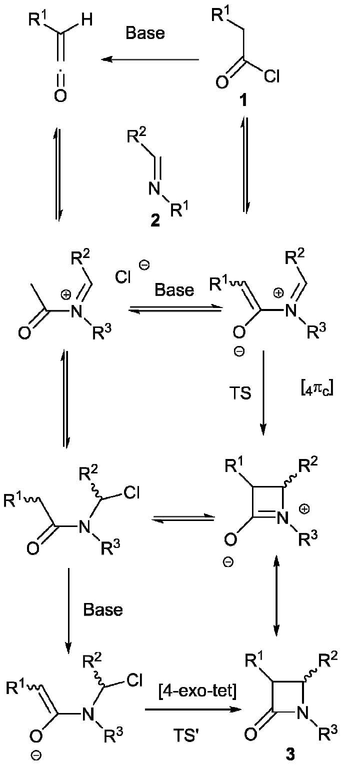


Scheme 1 Formation of substituted β-lactams **3** in the reaction between acid chlorides **1** and imines **2**.

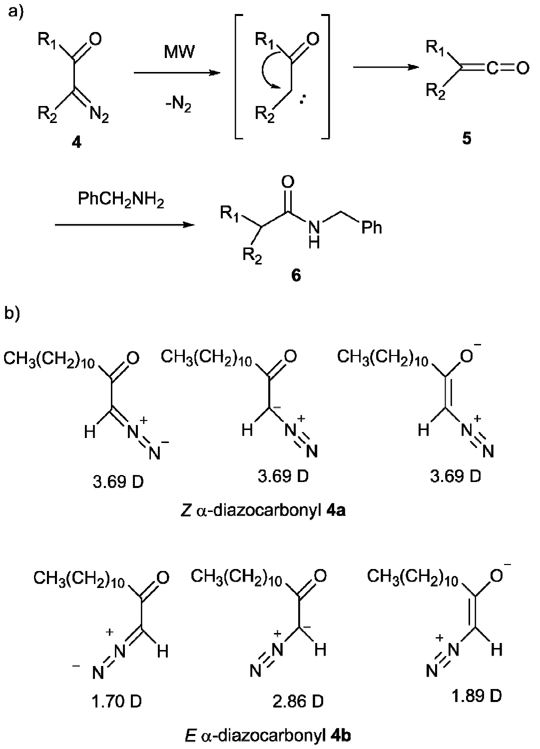
Within this framework – and using computational chemistry – several studies concluded that the polarity of a given species is a determinant factor in improving reactions under microwave irradiation. Regarding the reactions carried out in homogenous media, the following contributions should be highlighted:

Bose described the Staudinger reaction between acid chlorides **1** and Schiff bases **2** where the stereoselectivity depends on the order of addition of the reagents (Scheme 1).[45-47] When the condensation was conducted by a 'normal addition' sequence (*i.e.*, acid chloride last), only the *cis* β-lactam **3b** was formed. However, if the 'inverse addition' technique (triethylamine last) was used, 30% *cis* and 70% *trans* β–lactams **3** were obtained under the same conditions. Additionally, when the reaction was performed under microwave irradiation using chlorobenzene as the solvent, 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 **3a** did not occur.

Cossío employed density functional theory (DFT, B3LYP/6-31G* level) to explain the stereodivergent outcome observed in this reaction.[48] He computed the reaction path postulated by Lynch et al.[49] (Scheme 2). Under microwave irradiation the more polar route, *i.e.*, direct reaction between the acyl chloride **1** and the imine **2**, is favoured over the ketene-imine



Scheme 2 Two possible reaction paths computed by Cossío at B3LYP/6-31G* theory level.[48]



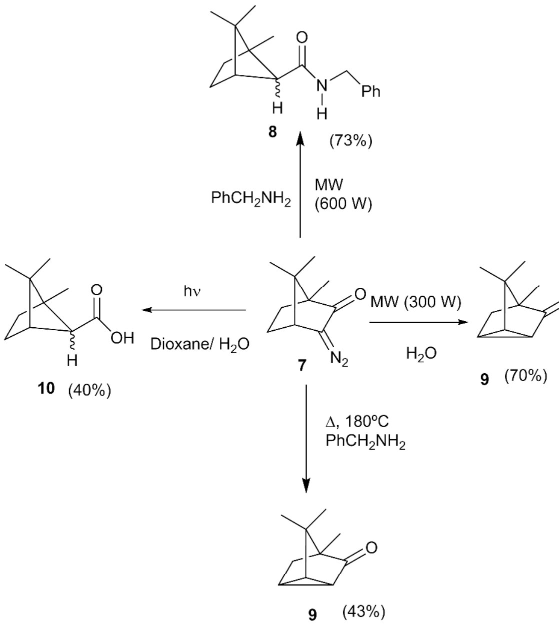
Scheme 3 a) General Wolff Rearrangement reaction. b) *Z*-type resonance conformers **4a** and *E*-type resonance conformers **4b** of α-diazocarbonyl compounds.

reaction pathway. Both competitive processes are subject to torquoelectronic effects and the polarity of the solvent enhances the diastereomeric excess of the reaction.

On the basis of their results, Hu et al. claimed that specific microwave non-thermal effects do not exist in the Staudinger reaction.[50] They attributed the different diastereoselectivities between thermal and microwave-assisted Staudinger reactions to temperature gradients generated in the microwave-assisted reaction because reactants and intermediates are more polar than solvents.

Sonawane and col.[51] demonstrated that microwave irradiation of α-diazoketones **4** efficiently promotes a Wolff rearrangement (Scheme 3). This effect is due to the high electric dipole moments of these compounds as a consequence of the dipolar nature of the diazocarbonyl functional group. Vectorial analysis of both conformers, performed at the PM3 theory level, indicates that the *Z*-type resonance conformers **4a** have higher dipole moments than the corresponding *E*-type ones **4b** (Scheme 3b).

Given this background, the authors performed the Wolff rearrangement under microwave irradiation and under classical heating in order to find possible different behaviours (Scheme 4).[51] Microwave irradiation (600 W) of 3-diazocamphor **7** in benzylamine at 600 W for 18 minutes gave exclusively a diastereomeric mixture (45:55) of the ring-contracted bicyclic benzyl amide **8** in 73% yield. In comparison, a solution of α-diazoketone **7** in benzylamine was heated under reflux for 15 minutes and this afforded product **9** (43%) arising from intramolecular C–H insertion. An aqueous dioxane solution of **7** submitted to UV light (λ = 300 nm) for 3 hours yielded a diastereomeric mixture (85:15) of the ring-contracted carboxylic acid **10** in 40% yield.



Scheme 4 Different reaction conditions and reaction paths for 3-

These outcomes indicate that under conventional heating the reaction occurs predominantly through the thermodynamically more stable conformer, while the conformer with the highest dipole moment is preferred under microwave conditions. In contrast, when the reaction of 3-diazocamphor (**7**) was performed under microwave irradiation (300 W) in the presence of water, the same product **9** as obtained under conventional heating was observed. These results indicate that water is a superior microwave absorber than an α-diazoketone and they strongly suggest the occurrence of a through-solvent heating process.

Moreover, these results suggest than the *Z* configuration is the preferred orientation to align with the electric field of the microwaves, owing to the higher dipolar moment when compared to the *E* configuration, and this enables the reaction.

Contrary to the general assumption that more polar molecules are more active under microwave irradiation, Asakuma and col.[52] described the preparation of biodiesel under microwave irradiation by transesterification of lipids with methanol. They stated that the planar triolein formed under microwave irradiation has a higher reactivity, lower dipole moment, lower activation energy and stronger vibration around the carboxyl group than the triolein with a higher dipole moment (Figure 2). Computational calculations performed at the HF/STO-3G level indicate that the triglyceride conformer in which the three oxygen atoms of C=O bonds point in different directions (**11a**) has a lower dipole moment (1.12 D) than the conformer in which the three C=O groups point in the same direction (7.29 D) (**11b**). However, calculations predict that the less polar species produce a planar conformation that is 26.9 Kcal mol^{-1} more stable than the more polar conformer. Moreover, the planar structure is more prone to the attack of the methoxy group.

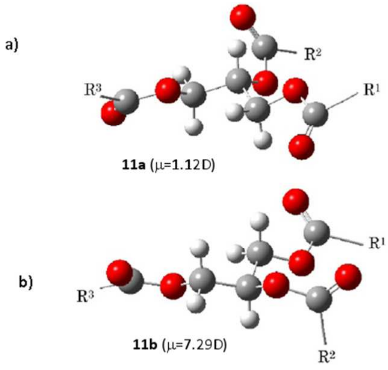
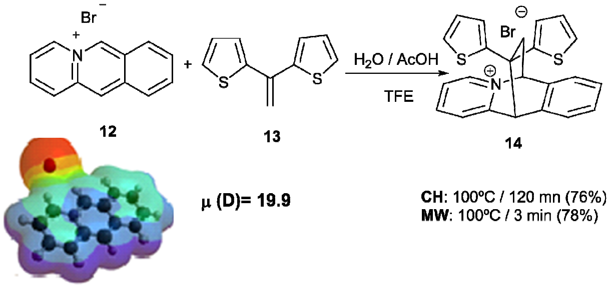


Fig. 2 Optimized conformational isomers of triglyceride (**11a** and **11b**) calculated at HF/STO-3G level of theory. Dipole moments (μ) in Debyes (D) are reported in parenthesis. Reproduced from ref. 52 with permission from Elsevier, copyright 2011.

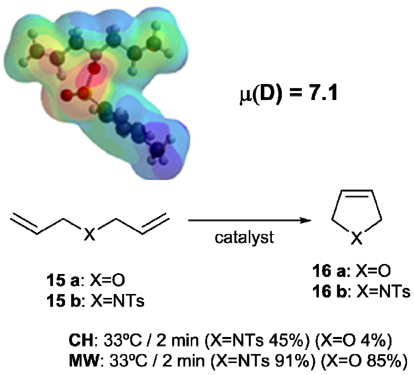
Recently, Prieto and col. determined the parameters that play a decisive role in microwave-assisted reactions.[53] For this purpose they selected a variety of previously reported reactions and the outcomes indicated that polarity is one of the most influential factors.

The first reaction studied was the Diels–Alder cycloaddition between azoniaanthracene (**12**) and 1,1-bis-2-thienylethene (**13**), which yields 6,11-ethanobenzo[*b*]quinolizinium bromide (**14**). This reaction, which was described by Sasaky and col., was performed in a domestic microwave oven with trifluoroethanol (TFE) or 10% acetic acid in TFE as solvent. Under conventional heating the reaction took place in two hours; in contrast, the reaction was highly accelerated under microwave irradiation (3 min) to give product **14** in good yields (78%) (Scheme 5).[54] A computational study performed at the B3LYP/6-31+G* level indicated that this process is exothermic but with a high activation energy (41.8 kcal mol^{-1}). These harsh conditions can be overcome owing to the high polarity of azoniaanthracene (μ = 19.9 D). As a result, the presence of a very polar reagent leads to an increase in the absorption of microwaves.



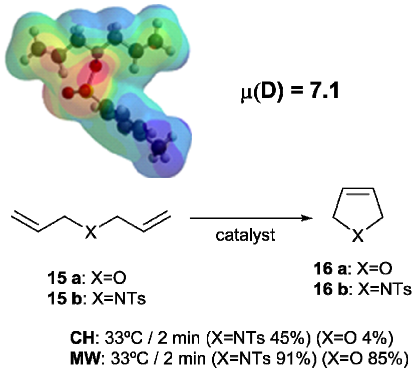
Scheme 5 Diels–Alder cycloaddition between azoniaanthracene (**12**) and 1,1-bis-2-thienylethene (**13**)

A second example concerns a ring-closing metathesis (RCM) reaction of diallyl derivatives **15** using ruthenium-based catalysts (Scheme 6). The reaction was successfully improved under microwave irradiation.[55] The authors suggested the existence of non-thermal effects. They postulated that this improvement could be due to coupling between microwave energy with one or both reactants. However, they could not



ascertain which component was responsible for the microwave heating. Careful comparisons by Kappe and col.[56] confirmed experimentally that the diene showed significant microwave absorption, while the absorption of the Grubbs catalyst was negligible. The heating profile of the reaction mixture was very similar to that of the diene. However, the authors did not find any evidence for a significant non-thermal microwave effect.

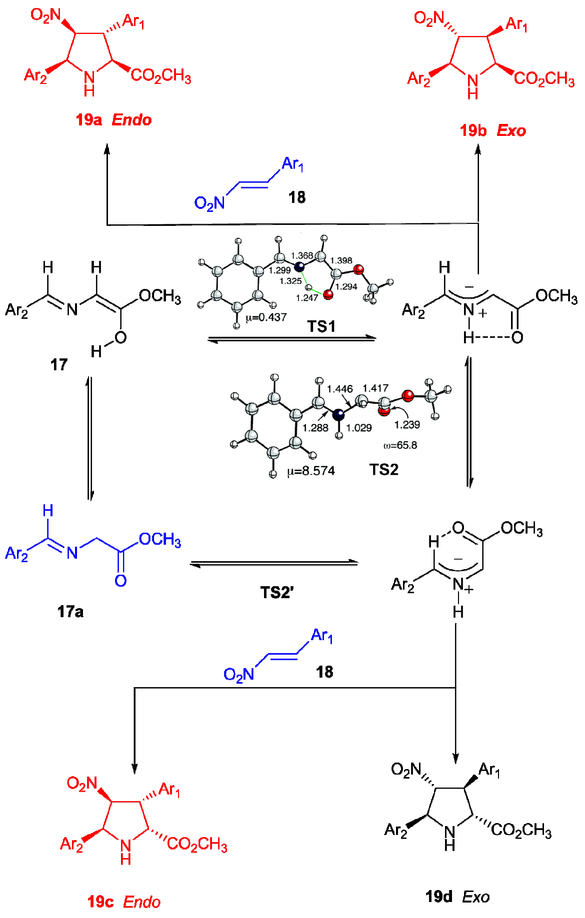
Prieto and col. carried out a DFT computational mechanistic study at the B3LYP/6-311+G(2d,p)//B3LYP/SDD theory level for this reaction path between diallyl ether (**15a**) or *N*,*N*-diallyl-*p*-toluenesulfonamide (**15b**), catalyzed by second generation Grubbs-type ruthenium carbene complexes.[57] The outcomes were completely in agreement with Kappe's postulates and indicated that the polarity of the species plays an important role in this process. For example, *N*,*N*-diallyl-*p*-toluenesulfonamide (**15b**) is much more polar (7.1 D) than diallyl ether (**15a**) (1.7 D). However, this trend is not observed exclusively for diene **15b**, but is consistent for all species present in the reaction path in which the tosyl group is involved. Thus, as stated above, the improvement under microwave irradiation may be a consequence of the presence of molecular radiators. Futhermore, the high activation energy in the precatalytic step explains the improvement in this reaction under microwave irradiation.



Scheme 6 General scheme for the ring-closing metathesis of diallyl derivatives (**15a**, **15b**).

The polarities of intermediates and transition states in solvent-free conditions have been used by Díaz-Ortiz and Cossio[58] to explain some different results obtained under microwave irradiation in solvent-free conditions. They studied the 1,3-dipolar cycloaddition of imines derived from α-aminoesters (**17**) with β-nitrostryrenes (**18**) in the absence of solvent to prepare nitroprolines (**19**) (Scheme 7).

Conventional heating with toluene as solvent afforded isomers **19a** and **19b**, as expected, by *endo* and *exo* approaches, respectively. However, in the absence of solvent a new compound (isomer **19c**) was obtained both under classical heating conditions and under microwave irradiation. Results obtained in DFT studies at the B3LYP/6-31G(d) level indicated that isomer **19c** is produced by an *endo* approach, which arises from thermal isomerization of the imine by rotation of the carboxylic part of the ylide. This fact indicates that formation of the second dipole should be related to its higher polarity. Isomer **19d**, although it is the thermodynamically most stable isomer, is not formed because it requires a very high energy of activation.

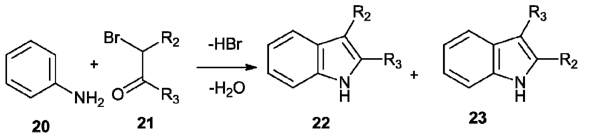


Scheme 7 Mechanism of the 1,3-dipolar cycloaddition of imines derived from α-aminoesters (**17**) with β-nitrostryrenes (**18**) calculated at B3LYP/6-31G(d)+ΔZPE level. Reactants and observed products are depicted in blue and red, respectively. Reaction intermediates and cycloadducts that are not observed are represented in black.

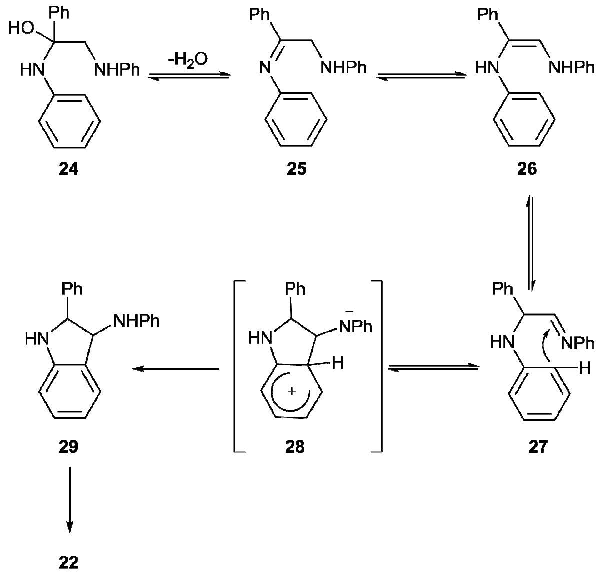
In this context, the scope and regioselectivity of the Bischler–Möhlau reaction between aromatic amines (**20**) and α-bromoketones (**21**) has been studied by computational and experimental techniques by Cossío and col. (Scheme 8).[59] They found that in many cases yields were improved under microwave irradiation in the absence of solvent.

Computational studies at the B3LYP/6-31G(d)+ΔZPVE theory level indicated that the mechanism shown in Scheme 9 is the preferred one for the formation of substituted 1*H*-indoles (**22**), at least in the presence of an excess of aniline.

It was postulated that this reaction is a suitable candidate for microwave-assisted acceleration, even in the absence of solvent with large loss tangent values,[39,60,61] due to the involvement of very polar reaction intermediates and transition structures in the mechanism.



Scheme 8 General Bischler–Möhlau reaction between aniline (**20**) and α-bromoketones (**21**).



Scheme 9 Accepted mechanism for the synthesis of substituted indoles from intermediate imines.

2.1.2. Microwave susceptors

What happens in cases where all the components of the reaction have low polarity?. Could these reactions be carried out under microwave irradiation?. In these cases, the addition of small amounts of agents that strongly absorb microwaves (microwave susceptors),[62] such as ionic liquids,[63] tetrabutylammonium bromide,[64] silicon carbide plugs[65] or graphite,[65] changes the dielectric properties of the reaction mixture. These “doping agents” interact very efficiently with microwaves through the ionic conduction mechanism and they allow the process to be performed successfully.

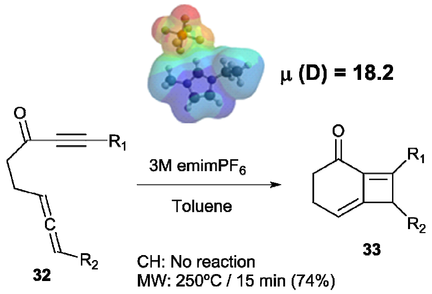
As an example, the intramolecular hetero-Diels–Alder cycloaddition of alkenyl-tethered 2(1*H*)-pyrazinones **30** (Scheme 10) was studied by Hoornaert and col.[66] The reaction mixture was irradiated in a sealed vessel in a single-mode microwave cavity using a preselected maximum temperature of 170 °C (300 W maximum power) with dichloroethane (DCE) as the solvent and 0.035 mmol of 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) as susceptor. The reaction took place within 10 minutes and afforded compounds **31** in good yield (67–77%), which represents a considerable decrease in the reaction time as compared to the 1–2 days required under conventional reflux conditions in chlorobenzene (131 °C).

The potential energy surface of this reaction was explored at the B3LYP(PCM)/6-31G*+ΔZPVE level using DCE as solvent by Prieto and col.[67]

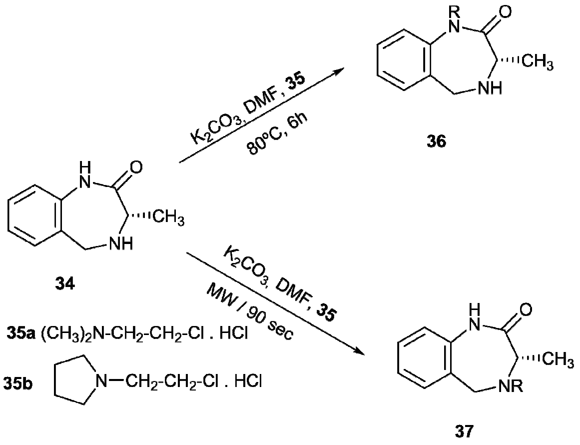
The outcomes indicated that the process shows high activation energies (25.7–28.3 kcal mol^{-1} when n = 2 and 37.2–39.7 kcal mol^{-1} when n = 3), low Gibbs energy and it is moderately exothermic. Moreover, the polarity of the reactants is moderate (μ = 5.1–5.2 D) and only increases slightly from the ground to the transition state. Given these characteristics, this reaction should not occur under microwave irradiation.

The addition of small amounts of a strongly microwave absorbing ionic liquid as a ‘doping agent’ changes the dielectric properties of the reaction mixture due to their efficient interaction with microwaves through the ionic conduction mechanism. In this case the addition of 0.035 mmol of [bmim][PF_6] (18.2 D, computed polarity value) (Scheme 10) clearly improved the reaction. The loss tangent of ionic liquids increases with temperature and, as a result, rapid heating (less than one minute) to 190 °C is possible – a heating rate that cannot be achieved under classical heating. This higher temperature allows more effective ionic movement and the ionic mechanism, which leads to more energy dissipation, is more effective.

Intramolecular [2π+2π] cycloaddition of alkynyl allenes (**32**) under microwave heating within 15 minutes at 250 °C afforded the corresponding bicyclomethylenecyclobutenes (**33**) in high yields (74%).[68] The high temperature necessary for the reaction was achieved by doping the solvent (toluene) with an ionic liquid (1-ethyl-3-methylimidazolium hexafluorophosphate, [emim][PF_6]) (Scheme 11).

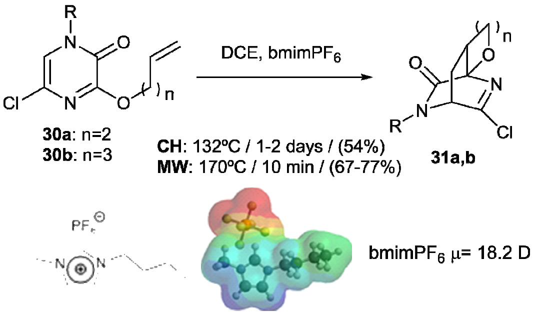


Scheme 11 Microwave irradiation of alkynylallenes **32** leads to bicyclomethylenecyclobutenes **33** through an intramolecular [2π+2π] cycloaddition.



Scheme 12 Aminoalkylation of 1,4-benzodiazepin-2-one (**34**) by conventional heating and under microwave irradiation.

The computed activation energy (29.7 kcal mol^{-1}) and enthalpy (28.8 Kcal mol^{-1}) at B3LYP/6-31G(d) level indicates that this reaction requires very harsh conditions. The computed dipolar moment of the ionic liquid (18.2 D) once again shows that the presence of an ionic liquid enables efficient coupling with microwaves and provides the harsh conditions under which the reaction can be carried out.



Scheme 10 Intramolecular hetero-Diels–Alder cycloaddition of alkenyl-tethered 2(1*H*)-pyrazinones **30**.

It is worth highlighting that our recent computational study on the influence of the polarity in MAOS[53] allowed us to quantify the dipolar moment of a species necessary for an improvement of the reaction under microwave irradiation and this was between 7 and 20 D.

2.1.3 Evolution of polarity along the reaction path

Loupy postulated that improvements caused by microwaves are related to the enhancement of polarity along the reaction path from the ground state towards the transition state.[69] This effect is particularly important in solvent-free conditions or in a non-polar medium. If the ground and transition states show identical polarities and charges are not developed during the reaction path, the MW effect would be negligible. On the other hand, if a polar mechanism occurs, and the polarity of the TS is higher than the polarity of ground state (GS), an enhancement of reactivity by a decrease in the activation energy could be expected.[70] This effect would be similar to that observed with a polar solvent that stabilizes a polar transition state, since microwave radiation is a highly polarizing field. Moreover, the magnitude of a specific microwave effect could be indicative of a polar mechanism or a polar rate-determining step in a procedure involving several steps.

Panda and col.[71] described the chemoselective aminoethylation of 1,4-benzodiazepin-2-one (**34**) on changing the energy source to furnish either the *N*-1 or *N*-4 aminoethylated products. Treatment of **34** with different aminoalkylating agents (**35**) under conventional heating led exclusively to *N*-1 substituted products (**36**). In contrast, when the same reaction was carried out under microwave irradiation *N*-4 substituted products (**37**) were formed exclusively (Scheme 12).

Computational calculations performed at the MP2/6-31G*//HF/6-31G* level of theory explained satisfactorily the chemoselectivity of the aminoalkylation by considering the extent of the polarity of the transition state and on the basis of the rate-determining step involved under both conventional heating and microwave conditions.

Two possible routes for the formation of **36** and **37** are shown in Scheme 13.

Anion **38**, generated by abstraction of a proton at *N*-1, allows the charge to be delocalized into the carbonyl group. Thus the *N*-1 centre can be regarded as a soft anionic centre. There is a small change in polarity between the ground state (GS) and the transition state (TS) and the reaction requires a small activation energy, with the nucleophilic substitution being the rate-determining step. In contrast, anion **39** – generated by abstraction of a proton at *N*-4 – is localized due to the absence of conjugation and this can be regarded as a hard anionic centre with a high charge density, with deprotonation being the rate determining step.

The reaction profiles for both products are depicted in Figure 3 and the calculated dipole moments are collected in Table 1.

The thermal pathway adopts the lower energy profile and this results in the preferential formation of **36** (Figure 3). In contrast, microwave irradiation facilitates the formation of anion **37** by deprotonation at *N*-4, although this has higher energy due to its higher dipole moment. Once **37** is formed, the subsequent step is very rapid and the modification of the chemoselectivity is established. It is noteworthy that the MW pathway has a much more negative free energy of reaction than the thermal reaction, thus indicating that the MW effects are substantial in stabilizing that route.

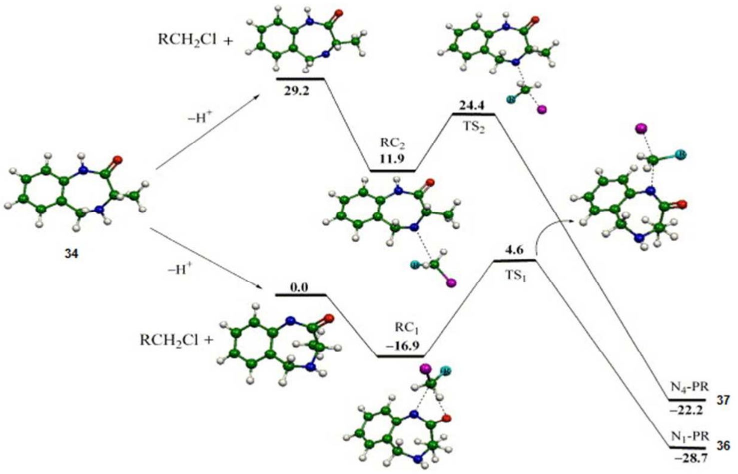
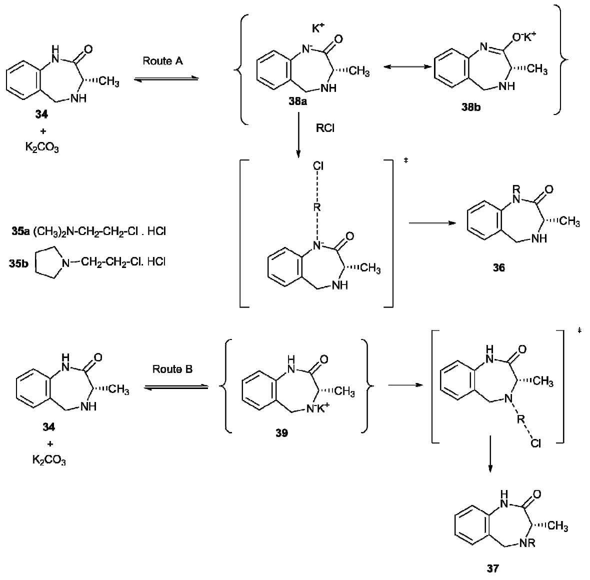


Fig. 3. Reaction profile of products **36** and **37** computed at the MP2/6-31G*//HF/6-31G* level of theory. Reproduced from ref. 71 with permission from Elsevier, copyright 2006.



Scheme 13. Two computed reaction paths for the synthesis of **36** and **37**.

Table 1 Calculated dipole moments (μ) in Debyes (D) of reactants, reaction complex and transition states computed at the MP2/6-31G*//HF/6-31G* level of theory.

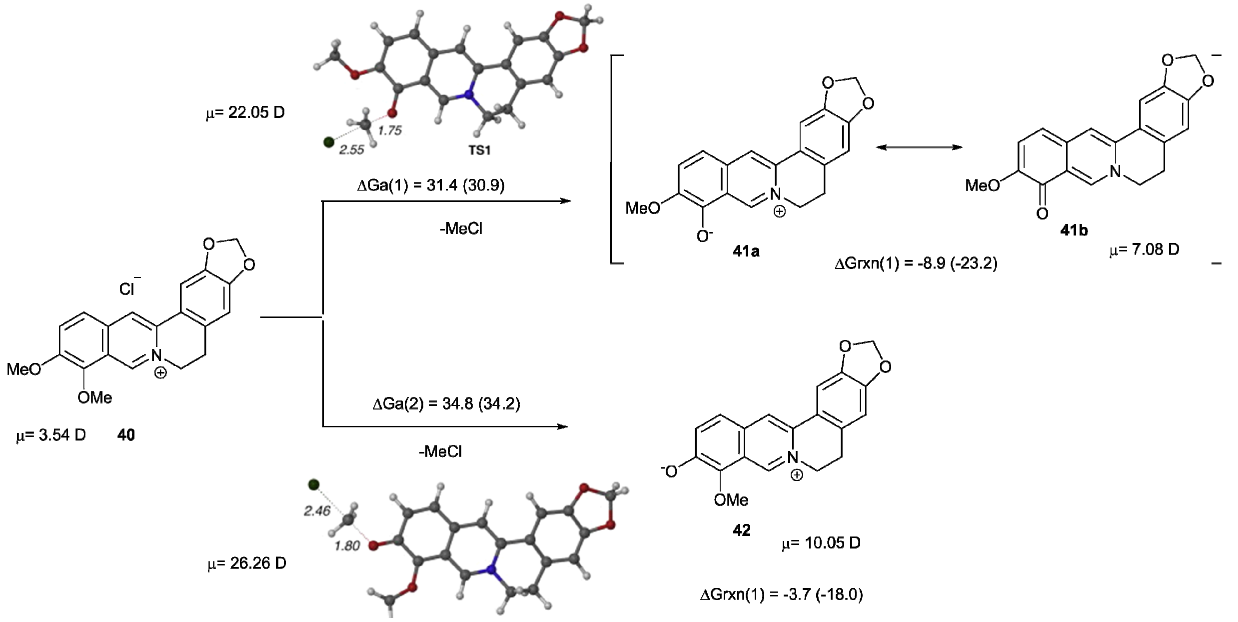
Compound		Dipole Moment (Debye)
Reactants	**34**	3.4
	38 (N-1 anion)	6.5
	39 (N-4 anion)	7.1
Reaction complex	**36a**	2.1
	36b	4.1
	37a	3.2
	37b	5.1
Transition states	**36a**	8.4
	36b	8.5
	37a	8.0
	37b	8.4

Barberrubine (**41**) has been synthesized by microwave-assisted selective demethylation of berberine (**40**).[72] Reactions were performed in two cycles at 130 °C/180 °C for 5/10 min, respectively, under 300 W to give 85% yield (Scheme 14). Although there are two possible products [berberrubine (**41**) and thalifendine (**42**)], only compound **41** was obtained.

DFT calculations performed at the B3LYP-D3/6-31G* level of theory showed that the activation barrier associated with the formation of berberrubine (**41**) is lower than that of thalifendine (**42**) (*ca.* 3 kcal mol^{-1}) and the former is the most exergonic process. Therefore, the generation of berberrubine (**41**) is both kinetically and thermodynamically favoured. In both cases, the high activation barriers computed (31.4 and 34.8 kcal mol^{-1}, respectively) agree well with the harsh experimental reaction conditions required (Scheme 14). In addition, the polarity increases on going from the reactant (μ = 3.54 D) to the transition structure (μ = 22.05 D), thus explaining the suitability of microwave irradiation as a heating source.

In contrast, in isopolar reactions the ground and transition states present *a priori* similar polarities and exhibit negligible microwave effects. Nevertheless, if a stepwise process or asynchronous one is involved, a specific microwave effect could intervene as charges are developed in the transition state.

Loupy studied some irreversible Diels–Alder cycloadditions in solvent-free conditions in order to justify his postulate concerning the influence of microwaves in processes with an enhancement of polarity (Scheme 15).[73] In the first case, the reaction of 1-ethoxycarbonylcyclohexadiene (**43**) with ethyl propiolate (**44**), the regioselectivity is identical under conventional and microwave heating. Likewise, only a slight modification of selectivity was observed in the reaction of 3-ethoxycarbonyl-α-pyrone (**46**) with phenyl acetylene (**47**). Finally, the selectivity is markedly affected in the reaction of 2-methoxythiophene (**49**) with dimethyl acetylenedicarboxylate (DMAD) (**50**) in acetic acid. Under microwaves, the Michael adduct is highly predominant over the Diels–Alder adduct.



Scheme 14 Two possible reaction pathways for the formation of berberrubine (**41**) and thalifendine (**42**). Activation and reaction Gibbs free energies at 298 K, 1 atm and 498 K, 0.01 atm (in parentheses) computed at the B3LYP-D3/6-31G* level of theory.

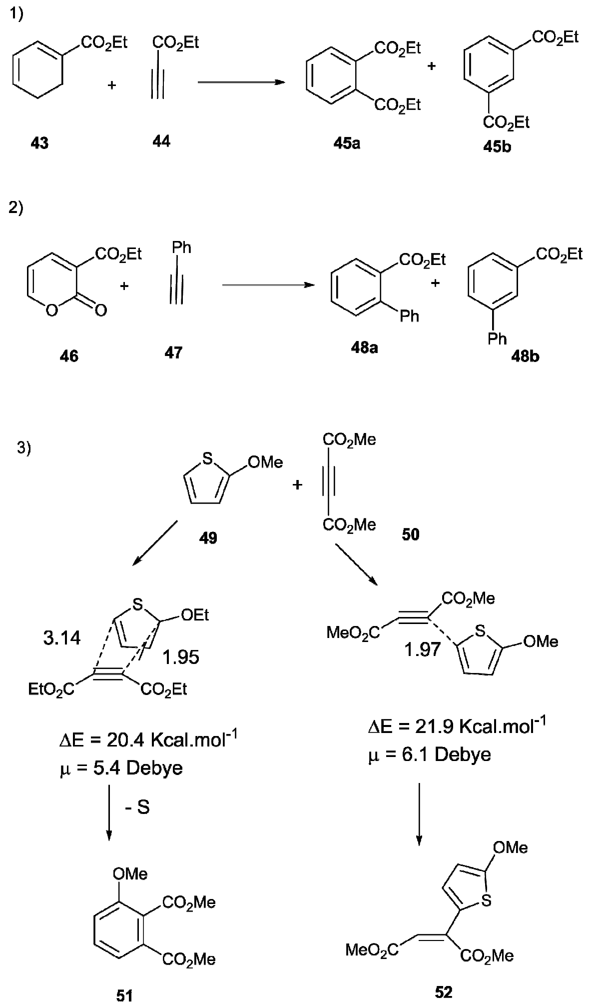
These results were justified in the basis of *ab initio* calculations at the B3LYP/6-31G(d) level of theory, taking into account the activation energies, the dissymmetry in TS geometries and enhancements in the dipole moment from the ground state (GS) to the transition state (TS). In this sense, the absence of MW effects in the reaction of 1-ethoxycarbonylcyclohexadiene (**43**) (Scheme 15.1) is due to a synchronous transition state, without the development of charge along the reaction path. Subsequently, the regioselectivity of the reaction depicted in Scheme 15.2 is slightly affected under microwave irradiation due to the occurrence of an asynchronous transition state with the development of charges. The large enhancements in dipole moments from the ground to the transition state in the reaction between 2-methoxythiophene and DMAD (Scheme 15.3) could explain the influence of microwave irradiation. So, the asynchronous Diels–Alder cycloaddition is strongly favoured under MW conditions when performed in an aprotic solvent. The calculations of the relative activation energies ΔEa are clearly in agreement with the experimental results. The calculated values are, respectively, 20.4 and 21.9 kcal mol^{-1} for Diels–Alder *versus* Michael reactions. In contrast, when the process is carried out in a protic solvent the Michael addition is favoured due to the high polarity of its TS.

Finally, Díaz-Ortiz and col. reinvestigated five solvent-free reactions previously carried out in domestic ovens, with the aim of demonstrating the reproducibility and scalability of solvent-free reactions.[74] The authors translated the reactions into a single-mode microwave reactor and then scaled them up in a multimode oven. The results show that most of these reactions can be easily scaled in microwave reactors using temperature-controlled conditions. Moreover, computational calculations performed at B3LYP(PCM)/6-31G(d) theory level using bromobenzene at solvent, showed that reactions involving a moderate or medium increase in polarity in the reaction path are relatively easy temperature-controlled processes under microwave irradiation. However, large increases in polarity during the reaction path give rise to extreme absorptions of microwave energy and this makes these processes more difficult to control. This situation was observed in the oxidation of alkyl halides **54** to carbonyl compounds **56** with pyridine *N*-oxide (**53**), due to the high polarity of the *N*-benzyloxypyridinium bromide intermediate (**55**) (Scheme 16).

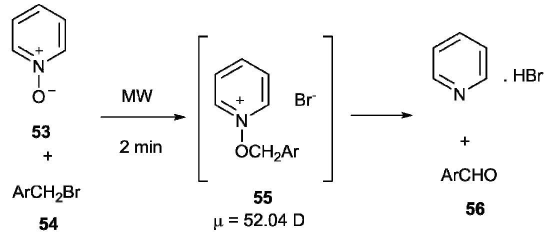
2.2. Activation energy

The Activation Energy is a good indicator to assess the improvement of a reaction under microwave conditions. Some proposed microwave effects have been explained in terms of the Arrhenius law.[35] Several reports suggest that the electric component of microwaves leads to orientation effects of dipolar molecules or intermediates and hence changes the activation energy terms in the Arrhenius equation, which means an increase in the rate constant.

Loupy explained this effect by using the Hammond postulate.[75] Thus, if the polarity is only slightly modified between the GS and TS, and the reaction only requires a small activation energy, only weak microwave effects can be expected. In contrast, a more difficult reaction implies a higher activation energy. In this case, the TS occurs late in the reaction path



Scheme 15. Reactions of 1-ethoxycarbonylcyclohexadiene (**43**), 3-ethoxycarbonyl-α-pyrone (**46**) and 2-methoxythiophene (**49**) with acetylenic dienophiles.



Scheme 16. Oxidation of benzylic bromides **54**.

(product-like transition state) and the influence of polarity may be significantly higher. This statement is consistent with a remark by Lewis, who stated that "slower reacting systems tend to show a greater effect under microwave radiation than faster reacting ones".[76] Once again, microwave effects are most noticeable in the absence of solvent.

Recently, Prieto and col. performed a computational study on previously described reactions in order to determine the influence of activation energy and enthalpy in MAOS.[53]

Taking in account the outcomes obtained in this computational study they classified the reactions into different types, which are collected in Table 2.

Table 2 General classification of different reactions considering the influence of microwave irradiation.[53] (All the calculations were carried out at B3LYP/6-31G(d) level)

Reaction	Ea	ΔH	Conclusion
Type I	< 20 kcal mol^{-1}	< 0	Not improved
Type II		> 0	Improved
Type III	20-30 kcal mol^{-1}	< 0	Improved
Type IV		> 0	Improved
Type V	> 30 kcal mol^{-1}	< 0	Improved with susceptors
Type VI		> 0	Do not occur

A careful analysis of the outcomes indicates that exothermic reactions, with low activation energies (type I), proceed well under conventional heating and improvements should not be expected under microwave irradiation. However, the corresponding endothermic reactions (type II) can be improved slightly under microwave irradiation.

Endothermic and exothermic reactions with moderate or high activation energies (type III and IV) can be improved under microwave irradiation in the presence of a polar component (reagents, solvent, catalyst).

Finally, reactions with very high activation energies that do not occur under conventional heating can be performed by microwave heating when two requirements are fulfilled: they are exothermic (type V) and a polar component is present. In contrast, endothermic reactions (type VI) do not take place under either microwave irradiation or conventional heating.

The findings provide evidence that slower processes tend to show better effects under microwave irradiation if a polar solvent, reagent or support, which allows a strong coupling with the radiation, is present in the media. This characteristic may lead to selective heating profiles. It is noteworthy that this fact is particularly important in heterogeneous systems, where it could also generate microscopic hot spots or selective heating.

Furthermore, the presence of small amounts of a strongly microwave absorbing 'doping agent' or 'susceptor' such as an ionic liquid may be beneficial since it leads to very efficient interactions with microwaves through the ionic conduction mechanism.

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Furthermore, the presence of small amounts of a strongly microwave absorbing 'doping agent' or 'susceptor' such as an ionic liquid may be beneficial since it leads to very efficient interactions with microwaves through the ionic conduction mechanism.

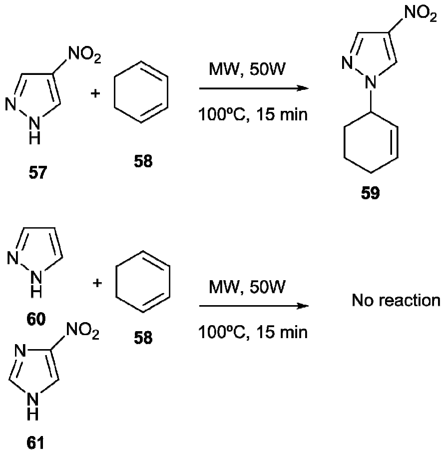
It is worth highlighting that we have also determined that an activation energy of 20–30 kcal mol^{-1} is required to obtain improvements under microwave irradiation.

De la Hoz and col.[77] performed the microwave-assisted reaction of 4-nitropyrazole (**57**) with cyclohexadiene (**58**) (Scheme 17) to afford 80% yield of product **59**. However, the more nucleophilic pyrazole (**60**) and 4-nitroimidazole (**61**) did not react, despite them having higher pKa values (pKa = 14.2 and 14.4, respectively) than 4-nitropyrazole (pKa = 9.64).

Computational calculations, carried out at B3LYP(PCM)/6-31G(d) level, showed that the addition of pyrazole is a concerted process with an activation energy of 29.5 kcal mol^{-1} (type IV reaction) and this can be improved under microwaves. However, the addition of imidazole follows a stepwise mechanism with activation energies of 40.4 and 35.3 kcal mol^{-1} (type VI reaction) and this does not occur (Scheme 18).

In many microwave-assisted reactions computational calculations have been performed to justify the result and the selectivity considering the activation energy. However, such calculations are not used as a predictive tool or to justify the improvement of the reaction under microwave conditions and they are therefore beyond the scope of this review.[78-83]

2.3. Thermodynamic control

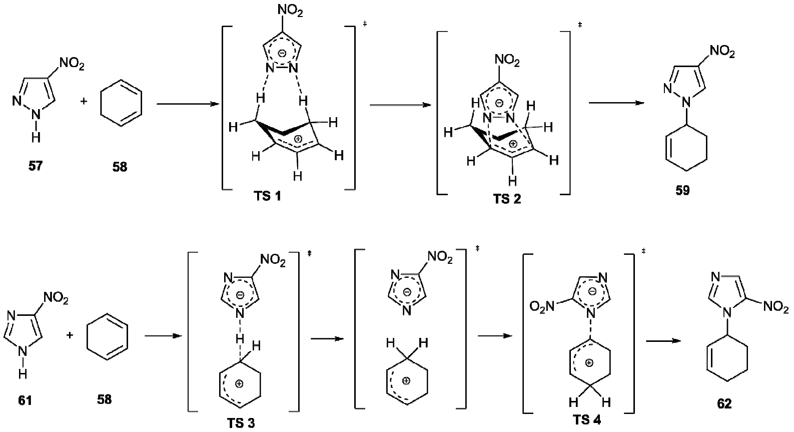


Scheme 17. Reaction of different azoles and cyclohexadiene (**58**)

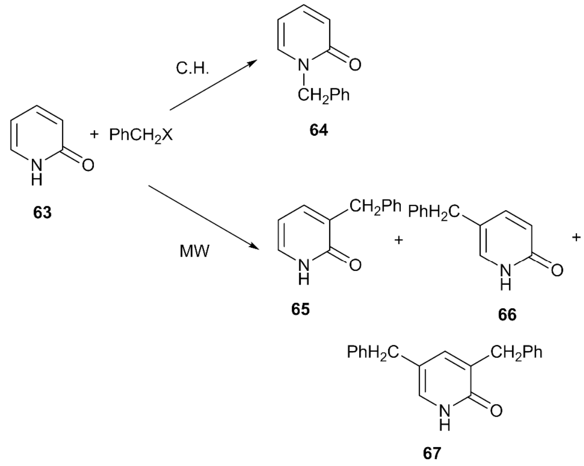
dition of

Microwave irradiation may favour thermodynamically controlled products. In this sense, de la Hoz and col.[84] described the benzylation of 2-pyridone (**63**) in solvent-free conditions in the absence of base under conventional heating and microwave irradiation (Scheme 19).

The regioselectivity of this reaction depends on the heating mode and on the leaving group (Table 3). When benzyl chloride was employed, *N*-alkylation was the exclusive process regardless of the heating source (Entries 1 and 2). In contrast, with benzyl iodide the selectivity depends on the heating source. Under microwave irradiation *C*-alkylation was obtained exclusively (Entry 6) and under classical heating only traces of *N*-alkylation were detected (Entry 7). Finally, with benzyl bromide the selectivity depends again on the mode of heating and on the power applied. Conventional heating leads to *N*-alkylation exclusively (Entry 5), while microwave irradiation at 150 W produced *N*-alkylation (entry 3), and at 450 W only *C*-alkylation was observed (Entry 4).



Scheme 18. Two reaction mechanisms computed at the B3LYP(PCM)/6-31G* theory level using benzene as solvent.



Scheme 19 Benzylation of 2-pyridone (**63**) under solvent-free conditions

Table 3 Benzylation of 2-pyridone (**63**) using conventional heating and microwave irradiation under solvent-free conditions and in the absence of base.

Entry	X	Conditions	Time (min)	Temp. (°C)	N/C Ratio
1	Cl	MW, 780 W	5	198	100:0
2	Cl	CH	5	176	100:0
3	Br	MW, 150 W	5	81	100:0
4	Br	MW, 450 W	2.5	180	0:100
5	Br	CH	5	196	100:0
6	I	MW, 150 W	5	146	0:100
7	I	CH	5	180	Traces:0

In an attempt to understand the modification in selectivity, a computational study was performed using the semiempirical AM_1/SM5.2 model.[85] The results show that by classical heating *N*-alkylation occurs through an S_N2 mechanism, because this is the kinetically favourable process and it has the lowest activation energy. In contrast, under microwave irradiation the thermodynamic control product (*C*-alkylation) is obtained.

Moreover, under microwave irradiation *N*-alkylation could occur through an S_Ni mechanism. In this case, the activation energies for *N*- and *C*-alkylation are similar, while the increase in polarity is more marked in the S_Ni mechanism.

Similarly, Díaz-Ortiz and Cossío[86] reported the cycloaddition of pyrazolylimines **69** with 2-chloroacrylonitrile (**68**) as a dienophile to afford pyrazolo[3,4-*b*]pyridines (Scheme 20). The regioselectivity depended on the substitution on the imine. Thus, pyrazolylimine **69a** yielded exclusively regioisomer **70a** while **69b** led to **71b**.

Ab initio calculations at the B3LYP/6-31G(d)//HF/3-21G(d)+ΔZPVE level of theory for both reaction pathways (Table 4) proved that microwaves induce the thermodynamically controlled product, although a higher energy of activation is required.

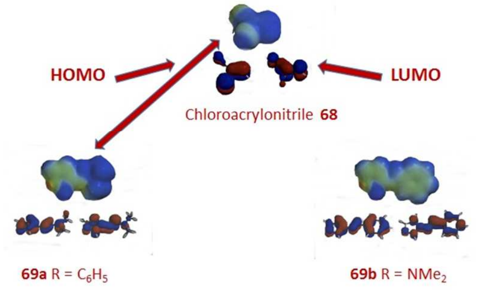


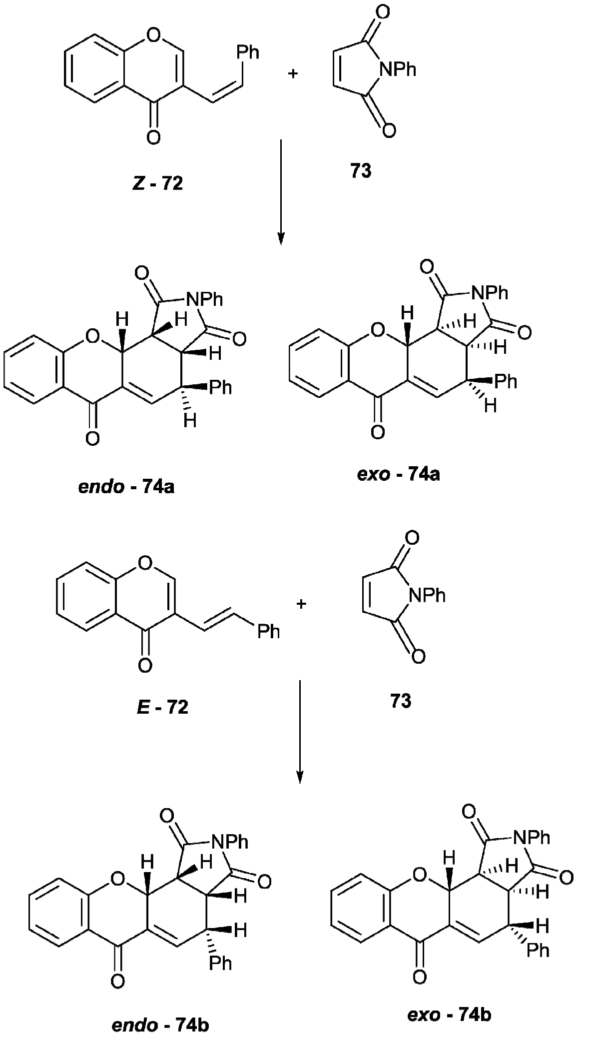
Fig. 4 Frontier molecular orbitals (FMOs) of reactants and the electrostatic potentials mapped on the electron density surfaces. Reproduced from ref. 86 with permission from Elsevier, copyright 2000.

Table 4 Computed Activation Energies[a] (ΔE_a, kcal mol^{-1}) and Reaction Energies[a] (ΔE_{rxn}, kcal mol^{-1}) for the transformations depicted in Scheme 20

Comp.	R	ΔE_a		ΔE_{rxn}	
		ε=1.00	ε=36.64	ε=1.00	ε=36.64
70a	**C_6H_5**	39.31	40.62	–6.81	–4.40
70b	**NMe_2**	45.17	47.51	+3.71	+8.97
71a	**C_6H_5**	34.54	43.73	–4.56	–1.89
71b	**NMe_2**	29.69	32.17	–5.11	–10.27

[a] Single-point energies computed at B3LYP/6-31G(d)//HF/3-21G(d)+ΔZPVE in gas phase and at B3LYP(L1A1)/6-31G(d)//HF/3-21G(d)+ΔZPVE in acetonitrile solution (ε = 36.64), respectively.

The explanation for this behaviour can be found by examining of the frontier molecular orbitals (FMOs) (Figure 4) of the reactants as well as the electrostatic potentials mapped on the electron density surfaces. From the shape of the FMOs it is clear that in both cases formation of product **71a** is expected if only orbital control is considered, and this is in good agreement with the activation barriers computed *in vacuo*. In contrast, the electrostatic interactions between the reactants favour the formation of regioisomers **70a** and **71b**, respectively. Therefore, if the electrostatic contribution of the solution energy is considered, the regiocontrol of the reaction is determined by Coulombic interaction rather than by FMO overlap.



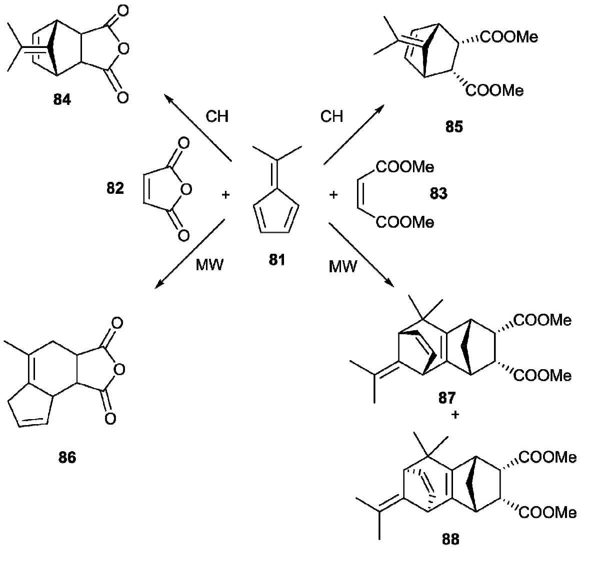
Scheme 21 Diels–Alder cycloaddition reactions of 3-styrylchromones ***Z/E*-72** with *N*-phenylmaleimide (**73**).

Similarly, a DFT study of the Diels–Alder cycloaddition of 3-styrylchromones (**Z/E-72**) with *N*-phenylmaleimide (**73**) under microwave irradiation in solvent-free conditions showed that (*Z*)-3-styrylchromones produce *endo* cycloadducts (***endo*-74a,b**) (kinetically and thermodynamically favoured) while (*E*)-3-styrylchromones produce *exo* cycloadducts (***exo*-74a,b**) (thermodynamically controlled) (Scheme 21).[87] The reaction profiles were computed at B3LYP/6-31G(d)//HF/3-21G(d)+ΔZPVE theory level.

Prieto and col.[88] attempted to assess computationally the occurrence of thermal or non-thermal microwave effects by studying two previously reported cycloaddition reactions that were reported to occur with non-thermal microwave effects. The first reaction was the cycloaddition of azidomethylphosphonates (**75**) and enamines (**76**),[89] in which the regioselectivity can be modified under microwaves (Scheme 22).

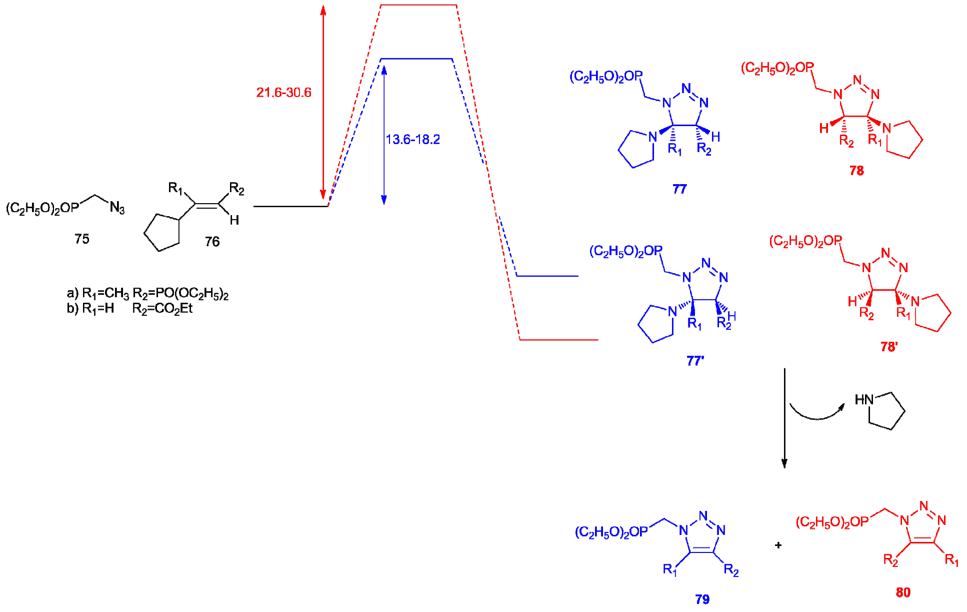
Experimentally, triazole **79** was obtained in good yields (70–86%) by conventional heating in solvent-free conditions at 100 °C but very long reaction times were required (6 hours). Under these conditions the reaction is 100% regioselective. For shorter times (20 minutes) there was no reaction under classical heating, but the reaction did give 55% yield under microwave irradiation, albeit with lower regioselectivity (**79**:**80** ratio, 85:15).

Computational calculations carried out at the B3LYP(PCM)/6-31G* level using toluene as solvent showed that cycloadduct **79** is the kinetically controlled regioisomer; the activation energy for this isomer lies between 13.6 and 18.2 kcal mol^{-1}. In contrast, the activation energy for cycloadducts **80** is higher (21.6–30.6 kcal mol^{-1}), although this regioisomer is thermodynamically more stable (Scheme 22). In agreement with the predictive model, formation of **79** corresponds to a type I reaction (Table 2) that is not improved under microwave heating.[53] In contrast, the synthesis of **80** involves a type III process that is favoured under microwave irradiation.



Scheme 23 Reaction of 6,6-dimethylfulvene (**81**) and maleic anhydride (**82**) or dimethyl maleate (**83**) under conventional heating and under microwave irradiation.

The second reaction considered is the cycloaddition of 6,6-dimethylfulvene (**81**) with alkenes, as reported by Hong,[90] that led to different polycyclic ring systems depending on the heating source (Scheme 23).

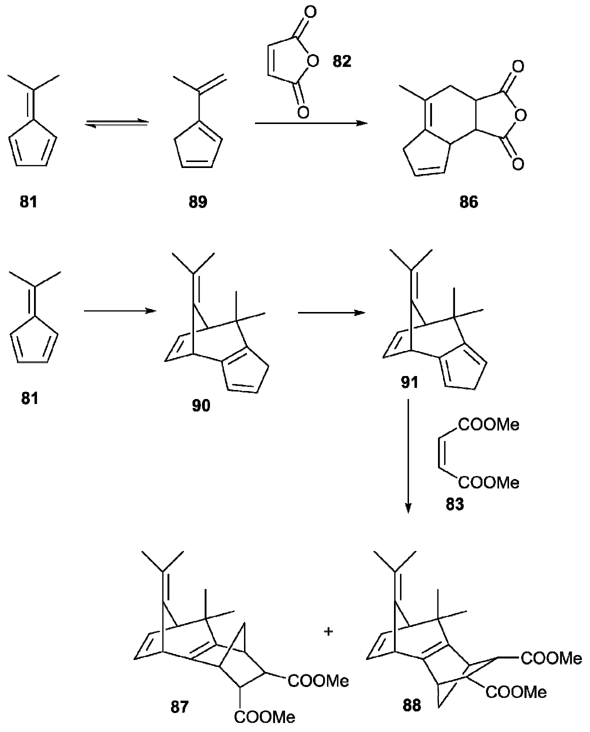


Scheme 22 Calculated reaction path for the cycloaddition reaction of azidomethylphosphonate (**75**) and functionalized enamines (**76**) at B3LYP(PCM)/6-31G(d)+ΔZPVE theory level using toluene as solvent.

Computational studies performed at the B3LYP(L1A1)/6-31G* level[88] indicate that under conventional heating, Diels–Alder cycloadditions between the cyclopentadienyl system of 6,6-dimethylfulvene (**81**) and the different dienophiles takes place exclusively. This pathway is kinetically controlled.

In contrast, microwave irradiation alters the reaction path, resulting in the formation of intriguing polycyclic ring systems. In the first example, the reaction between **81** and maleic anhydride (**82**) leads to the formation of a [4+2]-cycloadduct (**86**) by cycloaddition with the exocyclic diene. The computational findings show that the mechanism involves a microwave-induced isomerization of 6,6-dimethylfulvene (**81**) to 2-isopropenylcyclopenta-1,3-diene (**89**) followed by trapping with maleic anhydride (**82**) (Scheme 24). In the second reaction, microwave irradiation leads to dimerization of fulvene **81** through a [6+4]-cycloaddition to give dimer **90** and isomerization to the reactive diene **91**. Subsequently, [4+2]-cycloaddition of **91** with dimethyl maleate (**83**) generates adducts **87** and **88** (Scheme 24).

In both cases the thermodynamic product is preferred. The reactions required a high activation energy that can be achieved exclusively under microwave irradiation and not under conventional heating. Therefore, computational calculations showed that the modification of selectivity is the result exclusively of thermal effects and non-thermal effects can be excluded.



Scheme 24 Computed mechanisms for 6,6-dimethylfulvene (**81**) with maleic anhydride (**82**) and dimethyl maleate (**83**) under microwave irradiation.

2.4. Polarizability

It is known that microwaves interact with a charge distribution through the Lorentz force (Eq. 2):

$$F = qE + q\frac{v\ x\ B}{c} \qquad \text{Eq. 2}$$

Where q is the charge of a single particle, E is the electric field, *v* is the velocity of the charged particle, and B is the magnetic flux density. Only the electric component of the microwave field will take part in the energy transfer between an EM field and the charge distribution because the magnetic component Lorentz force F is perpendicular to the velocity of the charged particle.

The presence of permanent and/or electric field-induced dipoles will create a polarization current when the sample is perturbed by an oscillating electromagnetic field. Two kinds of polarization are possible.[44] The first has an electric charge redistribution nature that creates the induced dipoles; the second kind of polarization current corresponds to the hindered motion of the dipoles in the liquid or solid substrate.

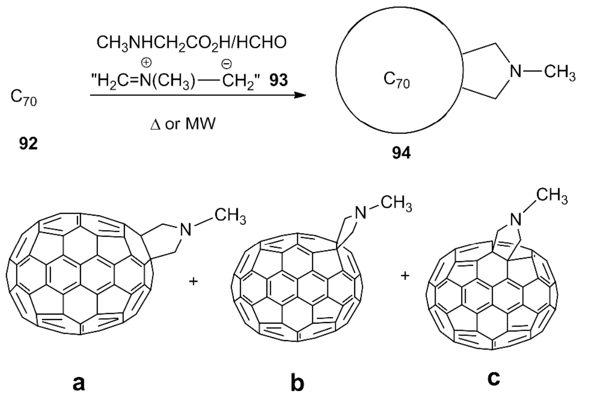
The relation between the applied electric field component, E, and the resulting induced polarization, P_{ind}, for a given orientation of the molecules is:

$$P_{ind} = \alpha \varepsilon_0 E \qquad \text{Eq. 3}$$

Where α is polarizability and ε_0 the dynamic electric permittivity of a sample exposed to an electric field.[91]

Therefore, the polarizability is another factor that may play a role in microwave heating. However, very few studies have been published on this topic.

Langa[92] described how the cycloaddition of *N*-methylazomethine ylides (**93**) to C_{70} (**92**) gave three isomers **94a–c** by attack at the 1-2, 5-6 and 7-21 bonds, respectively (Scheme 25).



Scheme 25 Isomers obtained in the cycloaddition of C_{70} and *N*-methylazomethine ylides, **94a** (1-2), **94b** (5-6), **94c** (7-21).

Under classical heating isomer **a** was found to predominate and isomer **c** was formed in a low proportion. The use of microwave irradiation in conjunction with ODCB as the solvent led 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 (Figure 5).

The computational study performed at RHF/PM3 on the mode of cycloaddition showed that the reaction is not concerted but stepwise. The computational outcomes indicated that purely thermal arguments predict the predominance of isomer **a** under microwave irradiation since this isomer has a lower ΔG° at higher temperatures (Table 5, last column). However, this is the opposite to the result found experimentally. Therefore, the relative ratio of isomers **a–c** can be explained by considering that, under kinetic control, microwave irradiation favours the formation of the product corresponding to the hardest and least polarizable transition state (Table 5 and Figure 6) and isomer **94c** – with the negative charge delocalized in the C_{70} sphere – is not formed.

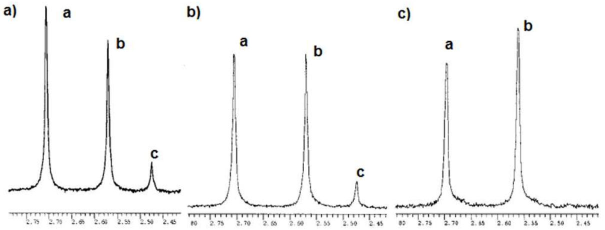


Fig. 5 ^{1}H NMR region of the methyl group: (a) classical heating in toluene as solvent, (b) classical heating in ODCB as solvent, and (c) microwave irradiation in ODCB at 180 W, 30 min. Reproduced from ref. 92 with permission from the American Chemical Society, copyright 2000.

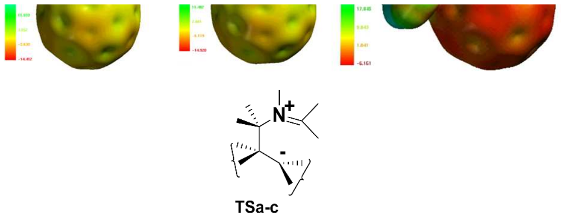
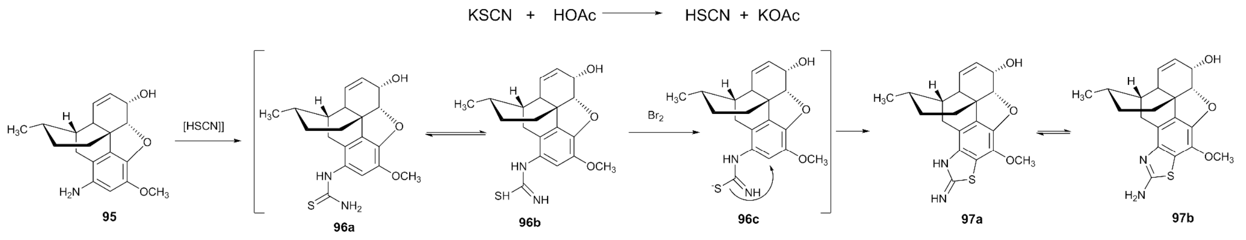


Fig. 6 Electrostatic potentials mapped onto electron densities for transition structures **TSa–c**. Red and blue colours denote negative and positive charges, respectively. All values have been computed at the RHF/PM3 level and are given in kcal mol^{-1}. Reproduced from ref. 92 with permission from the American Chemical Society, copyright 2000.

Table 5 Dipole moment (μ, D), Hardness (η, eV). Average Polarizability Volumes (α'_{AV}, Å^3) and Free Energies (ΔG^0, kcal mol^{-1}) of Transition Structures **Ts a–c** computed at RHF/PM3.

TS	μ	η	α'_{av}	ΔG^o		
				384 K	**405 K**	**454 K**
Ts a	4.880	2.492	91.51	855.70	850.95	838.00
Ts b	4.812	2.505	91.21	855.69	850.94	839.00
Ts c	5.298	2.488	92.76	858.41	853.75	842.00

In this context, Elander[91,93] described a quantum chemical model of an S_N2 reaction ($Cl^- + CH_3Cl \rightarrow$) in order to study the effect of a microwave field on the reactivity. Once again, a



Scheme 26. Proposed mechanism for the formation of thiazole **97**

variation of the polarizability was observed. However, while the perpendicular component is practically unchanged during the reaction, the polarizability component parallel to the reaction coordinate increased dramatically from $\alpha_{||}$ = 34 au in the starting materials to 92 au for the transition state geometry. This significant increase occurs just after the van der Waals' minimum, where the potential energy starts to increase and the most important chemical transformation develops.

The authors emphasize the importance of solvent effects and, in addition, the following conclusions were established:

(i) In the gas phase reaction 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) Solvation shells were included in order to study the non-gas phase environment. 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.

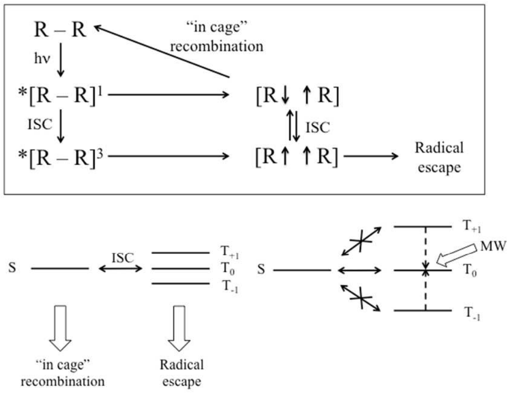
Taking these points into account, it was concluded that absorption of microwave photons may play an important role in this type of reaction.

2.5. Radicals and triplet state

Microwave irradiation (MW) has been applied successfully in the development of reactions that take place via radical intermediates.[94,95] Sipos and col.[96] developed a novel strategy for the synthesis of ring A-fused thiazolomorphinans and ring D fused thiazoloaporphines. The conventional thermal thiazole-forming reaction was replaced by microwave initiation. DFT calculations performed at the B3LYP/6-31+G* level indicated that the ring closure mechanism occurs with the presence of radical intermediates (Scheme 26).

Numerous organic reactions involve the formation of transient radical ion pairs, which are initially formed in a singlet state and develop triplet character as a function of time and vice versa (Intersystem Crossing). Occasionally, a triplet pair escapes the solvent cage and reacts independently at a later stage (Figure 7).

It is generally accepted that a static magnetic field can affect intersystem crossing in biradicals (magnetic field effect, MFE),[97] so a strong internal perturbation on a radical pair may be produced by a magnetic field related to microwave radiation.[98] Application of a strong magnetic field to the singlet-born radical pair leads to an increase in the probability of recombination that can be controlled by microwave irradiation. It has been postulated that when the radical ions are separated to distances of the order of 10 Å, the internal magnetic fields in the radical ions are capable of perturbing this correlation. These microwave-induced spin dynamics can be considered as an archetypical non-thermal MW effect.[99]



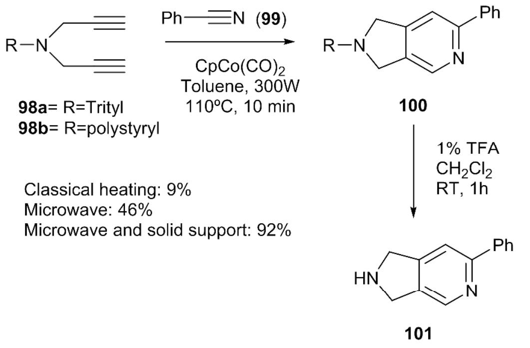
(a) Zero external magnetic field (b) Non-zero external magnetic field

Fig. 7 Schematic illustration of magnetic field and MW effects in radical-pair chemistry.

Wasielewski et al.[97] observed that the duration of photosynthetic charge separation could be controlled by using microwave radiation. The large increase in the lifetime of the radical pairs by the initial microwave pulse shows the importance of spin dynamics in prolonging charge separation. This fact is useful in solar energy conversion, molecular electronics and spintronics applications.[99]

Some chemical reactions, which involve a change in the spin-state, are formally forbidden.[100] In these cases the reactivity is determined by two factors. The first factor is the critical energy necessary for the reaction to occur, which in spin forbidden reactions is often defined by the relative energy of the Minimum Energy Crossing Point (MECP) between potential energy surfaces corresponding to different spin states. The second factor is the probability of hopping from one surface to the other in the vicinity of the crossing region, which is defined by the spin-orbit coupling matrix element between the two electronic wavefunctions.

Recently, we reported a computational study at the B3LYP/6-31+G*(d) level on the [2+2+2] cyclotrimerization reaction between trityl-protected dipropargylamine **98** and benzonitrile (**99**) that used $CpCo(CO)_2$ as a catalyst to obtain the fused pyridine **101** (Scheme 27).[101] This reaction is markedly improved under microwave irradiation.[102]



Scheme 27 [2+2+2] Cyclotrimerization reaction between trityl-protected dipropargylamine **98** and benzonitrile (**99**) using $CpCo(CO)_2$.

The widely accepted mechanism is depicted in Scheme 28.

In the first step, coordination of bispropargylamine to the cobalt complex and spontaneous oxidative coupling gives the intermediate **102**, which relaxes to the triplet state in a key step of the mechanism. At this point, this species may follow three different reaction paths: (i) Coordination with an excess of CO and subsequent intermolecular [4+2] cycloaddition (path a); (ii) the triplet cobaltacyclopentadiene coordinates benzonitrile to afford an intermediate, which can follow an intramolecular metal-assisted [4+2] cycloaddition (path b) or; (iii) undergo an insertion into the Co–C bond (path c).

The outcomes indicate that intermediate **102** evolves through the more kinetically favourable path b. It is noteworthy, that an inversion of the dipolar moment vector in the intermediate **102** was detected (Figure 8). So, microwave irradiation can increase the triplet lifetime, thus promoting the reaction and producing higher yield.

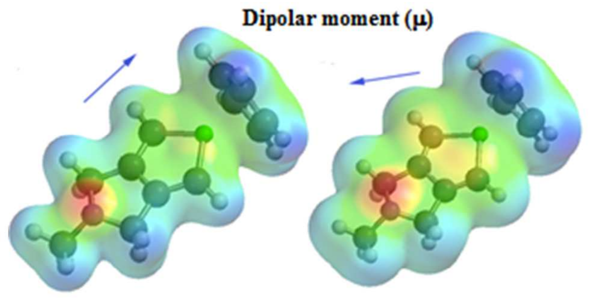
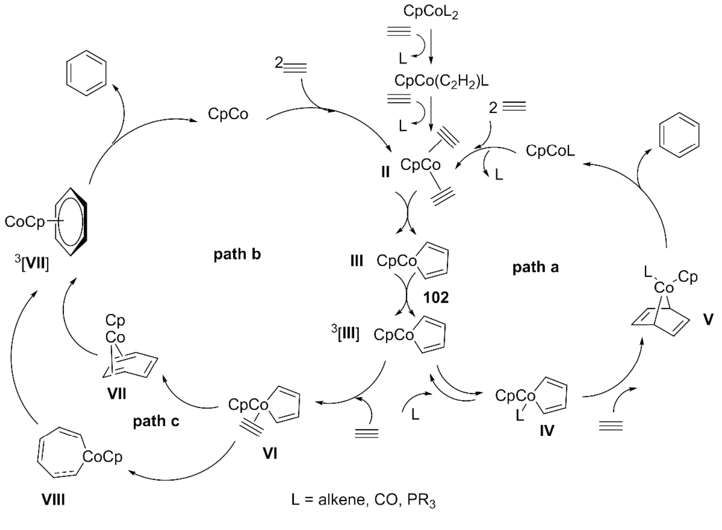


Fig. 8 Dipolar moment vector in the ESP surface of both singlet and triplet species of the intermediate. Reproduced from ref. 101 with permission from John Wiley & sons, copyright 2012.

Conclusions

Computational chemistry has been used successfully to justify the improvements and modifications in the selectivity observed in MAOS. With this methodology it is possible to determine the parameters that play a decisive role in microwave chemistry. These factors can be summarized in terms of the polarity of the species that participate in the reaction (reactants, intermediates, solvents and susceptors) and the evolution along the reaction coordinate. The activation energy and the enthalpy of the reaction have a decisive role and it was possible to classify the reactions into six types according to these parameters and relate them with the possible improvements under microwave irradiation. It is also worth noting that an activation energy of 20–30 kcal mol^{-1} and a polarity of 7–20 D for the species involved in the process is required to obtain improvements under microwave



Scheme 28 General mechanism for the CpCo-catalysed [2+2+2] cyclotrimerization of alkynes.

irradiation.

Polarizability and hardness of the transition structure have been used to justify the selectivity in some reactions, with the harder transition structure being the most favoured under microwaves. Finally, reactions with radicals have been significantly improved under microwaves and microwave irradiation has been reported to stabilize radicals in the triplet state.

In conclusion, computational calculations allow the determination of the thermodynamic parameters and the polarity, dipolar moment and polarizability of the components that take part in a reaction. Taking into account these parameters it is possible to predict if a proposed reaction could be improved under microwaves and even if the selectivity could be modified in relation to conventional heating. The only requirement is to analyse adequately the influence of these parameters that have a decisive role in microwave chemistry. The results presented in this review provide a guide for these processes.

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