

The issue of ‘molecular radiators’ in microwave- assisted reactions. Computational calculations on ring closing metathesis (RCM)[†]

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A DFT computational mechanistic study of the ring closing metathesis (RCM) reaction of diallyl ether or N,N-diallyl-p-toluenesulfonamide catalyzed by a second generation Grubbs-type ruthenium carbene complex has been carried out. This study was performed at the PCM(CH₂Cl₂)-B3LYP/6-311+G(2d,p)// B3LYP/SDD theory level. The aim of this work was to shed light on the influence that microwave irradiation has on these reactions and to gain insight into the so-called ‘molecular radiator’ effect. The outcomes obtained indicate that thermal effects induced by microwave irradiation decrease the catalytic induction period. The presence of a polar reagent and/or polar species in the reaction that increases the polarity of the medium may enhance this thermal effect.

Introduction

Microwave (MW) radiation is an unconventional energy source whose applications in organic synthesis are well established.¹ MW irradiation is a method to introduce energy into reactions by exploiting the ability of some compounds (liquids or solids) to transform electromagnetic energy into heat.²

The use of microwave irradiation has led to a significant added value in chemistry and also to the introduction of new concepts, mainly because the absorption and transmission of the energy is completely different from the conventional mode of heating. Conventional forms of heating are rather slow and inefficient methods for transferring energy into a reaction mixture. In contrast, MW irradiation produces efficient internal heating by direct coupling of MW energy with the molecules that are present in the reaction mixture. The magnitude of the energy transfer is dependent on the dielectric properties of the molecules; as a guide, compounds with high dielectric constants tend to absorb the MW energy whereas less polar substances and highly ordered crystalline materials are poor absorbers. In this way, absorption of the radiation and heating may be performed selectively.

Microwave-assisted organic synthesis (MAOS) has found broad applications as a very efficient way to accelerate the course of many organic reactions. This approach can produce high yields and, in some cases, modifications in the selectivity, lowering of side products and, consequently, easier work-up and purification of products.³

The question arises: if only polar substances absorb microwave irradiation, what would happen if there are no polar compounds in the reaction medium? In this case, polar additives or passive heating elements, called susceptors, can be employed. Susceptors⁴ are inert compounds that efficiently absorb microwave irradiation and transfer thermal energy to a medium that absorbs poorly, thus increasing the absorbance level of the medium. Solid catalysts, graphite (under solvent-free or heterogeneous conditions),^{5a} silicon carbide⁵ and ionic liquids (used both in solution and under heterogeneous conditions) have been widely used as susceptors.⁶

The use of susceptors is also related to the concept of selective heating. This concept has been proposed when a component in the reaction, e.g. the solvent or the catalyst, is very polar and can be heated selectively under microwave irradiation. This situation is not reproducible under conventional heating and leads to results that are hardly achievable under classical conditions.

In relation to selective heating, the proposed ‘molecular radiators’ should be taken into consideration. They are believed to be formed when a polar reactant is irradiated in a nonpolar medium. It has been suggested that ‘molecular radiators’ can directly couple microwave energy and thus create microscopic hot spots at the molecular level. However, this hypothesis is difficult to prove experimentally.

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The concept of ‘molecular radiators’ was proposed by Larhed and colleagues⁷ and it is relatively new in microwave assisted synthesis. These authors described the molybdenum-catalyzed allylic alkylation of (E)-3-phenyl-2-propenyl acetate. The reaction occurs with complete conversion, high yield (87%) and excellent enantiomeric excess (98% ee) in only a few minutes. It was postulated that the high temperature achieved (220 °C) was not only a consequence of increased boiling points at elevated pressure but also because of a significant contribution from sustained overheating.

This new concept was also described in two papers by Kappe and co-workers. These authors successfully employed microwave irradiation to perform rapid and racemization-free Mitsunobu inversions in the cases where the conventional protocol failed.⁸ They also demonstrated that the heating profile of the pure solvent differed significantly from that of the reaction mixture. Since THF does not effectively couple with microwave irradiation, it is evident that the bulk of the microwave energy was absorbed by the substrate and reagents. It is also possible that the ionic intermediates formed during the Mitsunobu reaction act as ‘molecular radiators’. Similar findings were obtained in other studies related to metathesis reactions. Recently, a debate has started concerning the influence of highly polar ionic species in microwave irradiation.⁹

The advantages of using controlled microwave heating for synthetic purposes are now undisputed. Although in most cases the reasons why a given chemical process is improved under microwave irradiation are thermal effects, in other processes the influence of microwave is still unknown. In this context, our research group uses computational chemistry tools in an effort to identify and quantify the parameters necessary to perform reactions under microwave activation.¹⁰ It is well known that one of the main problems encountered when comparing reactions performed under conventional heating and with microwaves is to reproduce the reactions under the same conditions because the transfer of energy is completely different. This problem could be overcome by using theoretical calculations. This methodology can be efficiently used to estimate the influence of microwave irradiation on chemical processes.

In order to shed light on the activation mechanisms associated with microwave irradiation we performed several computational studies in which we quantified aspects such as the activation energy required,¹¹ the polarity of the species, and the influence of ionic liquids or intermediates that exist in triplet states.¹² As an extension of our previous studies, in this paper we focus our attention on the computational study of the presence of ‘molecular radiators’ in the reaction medium and have used the metathesis process as a model.

Olefin metathesis was discovered in the 1950s but only recently has acquired importance as an efficient method for the formation of carbon–carbon double bonds.¹³ Nowadays, this reaction is extensively used in organic synthesis. The applications include cross-metathesis (CM), ring-closing metathesis (RCM), ring-opening metathesis (ROM), ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis polymerization (ADMET). Ring-closing metathesis warrants

special attention because it is a powerful method for the synthesis under mild conditions of highly functionalized carbocycles and heterocycles with a wide range of sizes. Numerous groups have executed elegant syntheses of complex natural products based on RCM reactions.¹⁴ Although some computational studies have been carried out on metathesis reactions,¹⁵ very few concern RCM.¹⁶ Computational studies have been carried out extensively on, for example, the strength of ligand binding and the mode of coordination (bottom or side bound). Complex systems of special synthetic interest are also described but studies on full systems of general interest and importance are rare.¹⁷ Despite all this activity, systematic studies on the relationship between the structure and the reactivity remain scarce.

Our goal in this paper is to clarify how microwaves influence the ring-closing metathesis (RCM) reaction and we attempt to compare these outcomes with results from previous experimental studies. DFT studies allow determining parameters such as the activation energy or polarity of all species involved. The latter is difficult to measure experimentally. It is noteworthy that the effect of the solvent is also taken into account in order to obtain good quality results.

Computational procedures

All the computational calculations reported here were performed with the Gaussian 09 series of programs.¹⁸ The PES was computed by means of density functional calculations¹⁹ using the nonlocal hybrid Becke’s three-parameter exchange functional denoted as B3LYP.²⁰ The basis set employed was the standard 6-31G(d)²¹ for all atoms except ruthenium, for which the triple-zeta basis with the Stuttgart/Dresden effective core potential (SDD)²² was used. Normal coordinate analysis was performed at the same level for all stationary points to characterize the TSs (one imaginary frequency) and equilibrium structures (no imaginary frequency) and to calculate zero point energy (ZPE) and thermal corrections. Single point energy calculations were performed with a more extended basis set (6-311+G(2d,p)) for all atoms except Ru. It is well documented that the use of the 6-311+G(2d,p) basis set combined with SDD correlates well with experimental values when the Ru atom participates in the mechanism.²³ To take into account the possible solvent effect on the reaction, we performed single point calculations at the same theoretical level, employing the polarized-continuum model (PCM)²⁴ using dichloromethane (DCM) as the solvent. It has been previously reported that full geometry optimization taking into account the solvent has often a very limited effect on the computed energies.²⁵ However, to test that this was the case in our systems, we performed full PCM-B3LYP/6-31G(d) calculations of the precatalytic steps and no differences between these values and the single point energy results were obtained (see ESI†). For this reason, single point calculations using PCM for the total reaction path were performed. Gibbs free energies discussed throughout the work were calculated using the triple zeta single point energies, and then adding the corresponding ZPE and thermal corrections, and solvation energies.

The electrostatic potential maps and the dipolar moment vector of all the species involved in the mechanism were obtained using the SPARTAN 10 program.²⁶

Results and discussion

Experimental background

Ring-closing metathesis (RCM) has been reported to be improved under microwave irradiation. Different arguments have been used to explain the improvement. Kiddle and co-workers²⁷ reported the RCM of diallyl derivatives using ruthenium-based catalysts (Scheme 1).

These authors observed a significant improvement under microwave irradiation vs. conventional heating. The reaction can be rapidly conducted either in an IL, such as 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF₄]), or in a microwave-transparent solvent (MTS) such as dichloromethane. In both cases, the reaction successfully improved under microwave irradiation. The best results were obtained on using the IL. Using dichloromethane as the solvent a dramatic decrease in reaction time was not observed probably due to that the temperature did not exceed 33 °C. The authors suggested that microwave energy produced non-thermal effects that may involve direct coupling to one or both reactants in these transformations. However, they could not ascertain which component was coupled with the microwave energy or if other factors related to the medium were influencing the microwave heating.

On the other hand, careful comparisons performed by Kappe and co-workers²⁸ indicated that the observed rate enhancements were not the result of a non-thermal microwave effect. When *N,N*-diallyl-*p*-toluene-sulfonamide is employed they confirmed experimentally the selective heating of diene under microwave irradiation. They found a dramatic change in the heating profile of a 0.05 M solution of the diene in dichloromethane in comparison with the pure solvent. In contrast, the absorption of the Grubbs catalyst, even at a concentration of 10 mol% (0.005 M solution), was negligible, as was that of the solvent. DCM is weakly microwave absorbing ($\tan \delta = 0.042$). The heating profile for the reaction mixture was very close to the profile for the diene. In order to mimic the rapid heating reaction profile achieved through microwave irradiation, Kappe and colleagues preheated the diene solution in DCM to 60 °C in an oil bath before a solution of the metathesis catalyst was added using a syringe through the Teflon septum. Under these conditions, the reaction results were almost identical to those obtained by microwave heating. Therefore, they concluded that the comparatively rapid

metathesis transformations could be rationalized by taking into account solely thermal effects (Arrhenius equation).

Other authors postulate that microwave heating results in higher conversions in shorter reaction times either by overcoming catalyst decomposition or by increasing catalyst turnover in the metathesis reaction.²⁹

Computational study of the PES

In order to clarify the reasons for the improvement in the RCM and as a continuation of our previous studies, our initial goal was to complete a computational study of the Potential Energy Surface (PES) of the RCM and to determine the polarity of all the species involved in the PES. A high polarity for any species should be an indication of its probable behaviour as a molecular radiator.

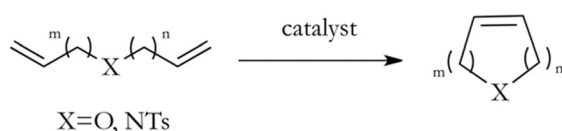
Cavallo reported³⁰ that only the full-size DFT system is able to reproduce the experimental results because simpler model systems disregard the steric interaction between the mesityl group and the olefin. For example, the dissociation energy for the PCy₃ of the real system and the model one (PH₃) differs by 8.9 kcal mol⁻¹. For this reason we computed the PES by taking into account the full system, without structural simplifications. In the forthcoming discussion low barriers for computational changes with respect to activation barriers for bond-forming/breaking steps in the catalytic cycle are assumed.

The postulated mechanism for the ring-closing olefin metathesis involving the Grubbs-type ruthenium carbene complex is shown in Scheme 2. As can be seen, precatalytic steps are required in order to achieve coordination of the diene to the catalyst to give the first species in the catalytic cycle (5). These precatalytic steps may result in an induction period in the reaction kinetics.³¹

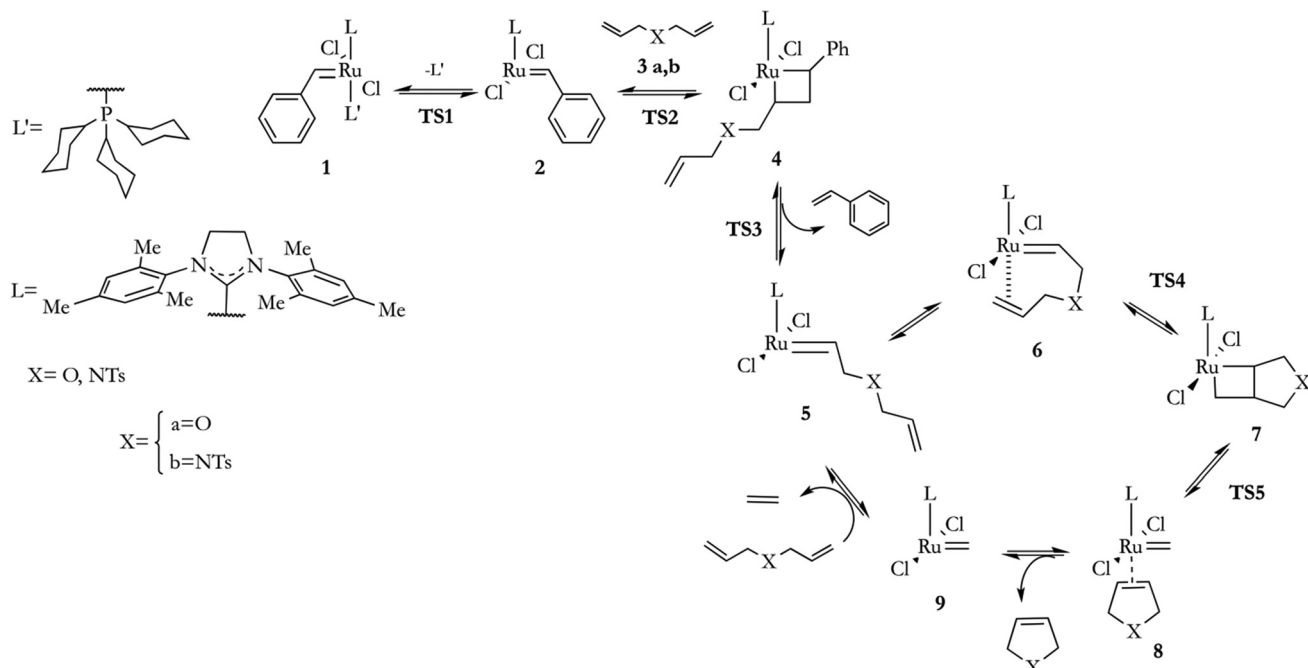
Diallyl ether (3a) and *N,N*-diallyl-*p*-toluene-sulfonamide (3b) were chosen as the dienes. The latter has been extensively studied by Kappe²⁸ and colleagues in their comparative study, who demonstrated that it acts as a “molecular radiator”. In order to extend the study in this work we have selected another diene studied experimentally such as diallyl ether.

The connection between computational and experimental results is not always obvious, as the languages of these disciplines are different. A bridge between computational and experimental regimes is provided by the energetic span model. This model constitutes a fundamental tool for computational chemists in the world of catalysis.³² As a result, this energetic model was taken into account in our discussion of the computational results.

In many catalytic cycles, only one transition state and one intermediate determine the TOF (Turnover Frequency). These are called the TOF-Determining Transition State (TDTS) and the TOF-Determining Intermediate (TDI). The energy difference between the TDI and the TDTS, i.e. the so called energetic span (ΔE), is the apparent activation energy of the catalytic cycle that determines the catalytic efficiency. So, in a catalytic cycle there are no rate determining steps, but rather rate determining states should be considered. According to this principle we calculated the Gibbs energies for all the species that



Scheme 1 General scheme for RCM of diallyl derivatives.



Scheme 2 General mechanism of the RCM reaction of diallyl derivatives.

participate in a whole catalytic cycle using the scheme described in the computational procedure section.

The structural features of all the species, the reaction profiles and the energy values are collected in Fig. 1 and 2. The energy values computed at PCM-B3LYP/6311+G(2d,p)//B3LYP/

SDD are normalized to compound 5 in the catalytic cycle. The energy difference between both compounds 5 in the reaction profile corresponds to the reaction energy involved in each catalytic cycle, i.e., the difference between the energies of products and reactants.

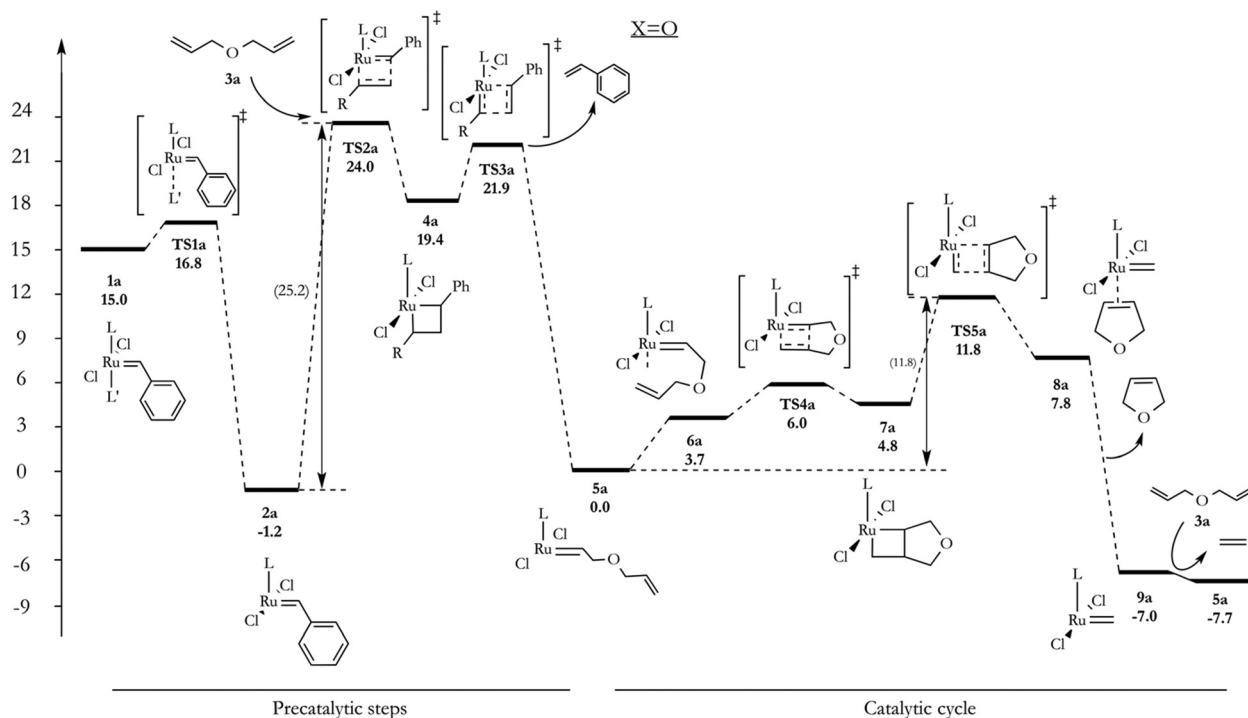


Fig. 1 Computed reaction pathway for the RCM of diallyl ether (3a) at the PCM-B3LYP/6-311+G(2d,p)//B3LYP/SDD theory level. Gibbs free energies computed for all species.

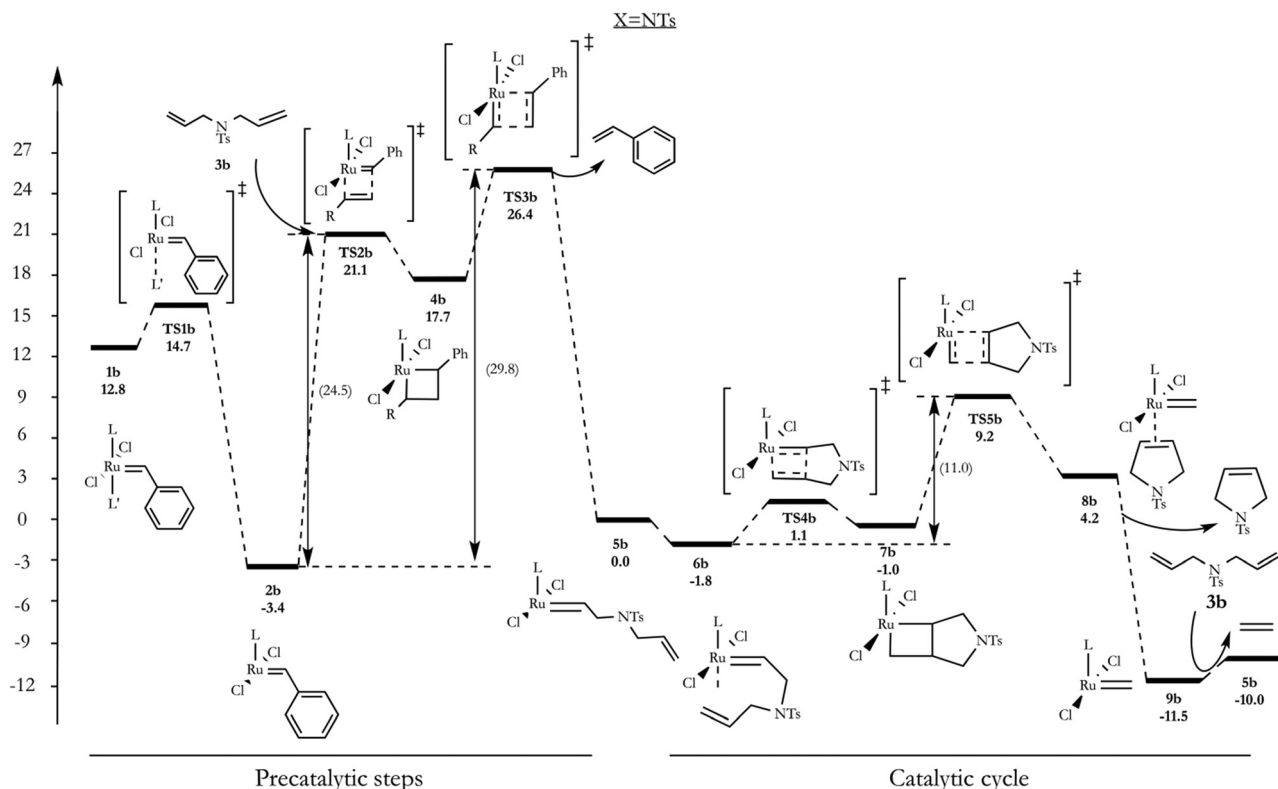


Fig. 2 Computed reaction pathway for the RCM of *N,N*-diallyl-*p*-toluenesulfonamide (**3b**) at the PCM-B3LYP/6-311+G(2d,p)//B3LYP/SDD theory level. Gibbs free energies computed for all the species.

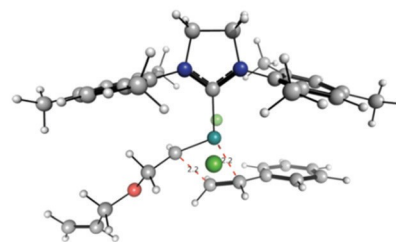
Catalyst **1** possesses an ancillary *N*-heterocyclic carbene ligand that lies perpendicular to the Ru-Cl-Cl(benzylidene) plane. The reaction begins through several pre-catalytic steps, in which dissociation of the phosphane from the metal centre occurs to give a coordinated Ru carbene complex (**2**) (Fig. 1 and 2). This mechanism is widely accepted in the literature.³³ The 14 electron-propagating ruthenacyclobutane complexes **4** are formed by an endothermic reaction between **2** and the corresponding diene. The activation energies of these steps are similar in both reaction pathways (25.2 vs. 24.5 kcal mol⁻¹).

Complexes **4** release styrene through TS3 to form **5**. The activation energy is higher when X = NTs than when X = O (8.7 vs. 2.5 kcal mol⁻¹). This fact can be explained in terms of steric hindrance to release styrene in the case where X = NTs. As depicted in Fig. 3, when X = O the release of styrene is easier and steric hindrance is minimal.

In both 14e⁻ alkylidene complexes (**5**) the orientation of the Ru-CH bond causes the hydrocarbon chain to project into free space, which brings the alkylidene proton into close contact with the N-C(aryl) carbon, as reported previously. This H-C contact lies between 2.41 and 2.44 Å and thus it might result in an attractive interaction.

In both cases the TDI is the intermediate **2**, but the TDTs is different. This one is TS2 when X = O and TS3b if X = NTs. So, the energetic span in these precatalytic steps is 25.2 kcal mol⁻¹ when X = O and 29.8 kcal mol⁻¹ in the case where X = NTs.

X=O



X=NTs

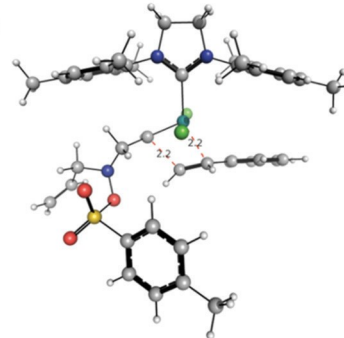


Fig. 3 Geometric features of TS3a and TS3b.

After the step outlined above, the catalytic cycle begins. Compounds **5** evolve to the intermediates **6**. These intermediates possess a bottom-bound coordination (Fig. 4). This fact is also taken into account in the results reported by Correa and

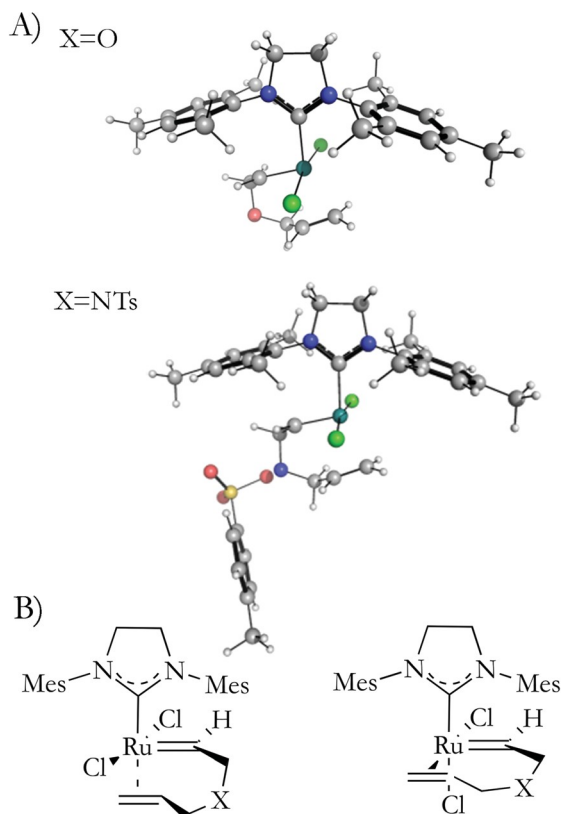


Fig. 4 (A) Geometrical features of intermediates 5. (B) Schematic structures of bottom-bound (left) and side-bound coordination (right).

Cavallo.^{15a} They demonstrated computationally that when a bulkier and ‘real life’ substrate, such as system 6, was considered, the increased steric pressure results in an increased preference for the bottom-bound versus the side-bound geometry (Fig. 4B).

In compounds 6 coordination of the ω -alkene brings the two π -bonds into alignment in readiness for metallacyclobutane formation (Fig. 4B). If $X = NTs$ the stabilization of compound 6b is much higher than in the case where $X = O$ (6a) (3.7 vs. $-1.8 \text{ kcal mol}^{-1}$). These results are in agreement with Cavallo’s conclusions,³⁰ which established that the steric interaction between the mesityl group and the olefin is assumed to be one of the driving forces for the faster olefin metathesis by second-generation ruthenium carbene catalysts.

The reaction continues towards the metallacyclobutanes 7 through TS4. In complexes 7, the cyclopentane ring adopts an envelope conformation to reduce these eclipsing interactions, but this increases the angle strain ($C-O-C = 105-106^\circ$). The coordination adopted means that the protons of the metallacyclobutane ring are eclipsed. The geometric features of TS4 and 7 are depicted in Fig. 5. Although the metallacyclobutanes 7 have been viewed as the pivotal species on the RCM energy surface, in our case this step takes place easily. The activation energy is 2.3 or 2.9 kcal mol^{-1} (Fig. 1 and 2) depending on the nature of X. If $X = NTs$, this intermediate is in a potential minimum. This fact is in close agreement with the findings of

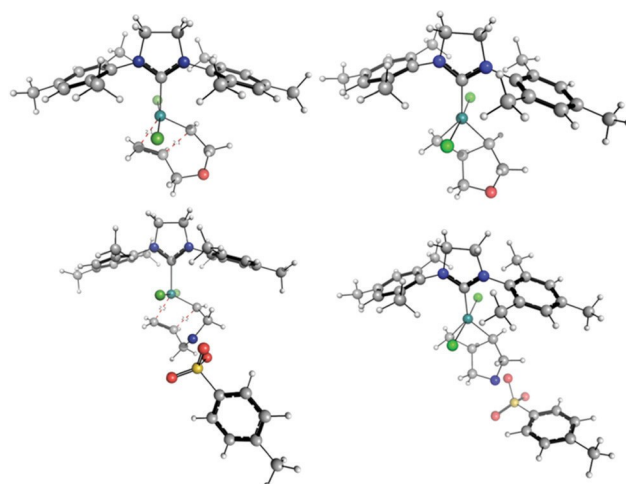


Fig. 5 Geometric features of TS4a and TS4b (left) and intermediates 7a and 7b (right).

a previous study,³⁰ which highlighted that the stabilization of the metallacyclobutane intermediate is even more pronounced in carbene complexes with NCH ligands. These kinds of ligands are strong σ donor ligands and only weak π acids. In our case, the electrostatic potential map of this species (see ESI†) shows a more extended charge delocalization when $X = NTs$. As a result, intermediate 7b is more stable than 7a.

As described by Hillier,³⁴ the transition structures for metallacyclobutane fragmentation (TS3 and TS5) are consistently the highest points on the energy surface and they are therefore of critical importance for appreciation of the barriers that determine the turnover rate. Unlike previous studies,^{15a} we were unable to find transition structures for the release of cycloalkene from the methyldene complex. The geometric features of TS5 and 8 are shown in Fig. 6.

Finally, the $14e^-$ alkylidene complexes 9 release ethylene and, after coordination with a new ω -diene, the catalytic cycle is closed.

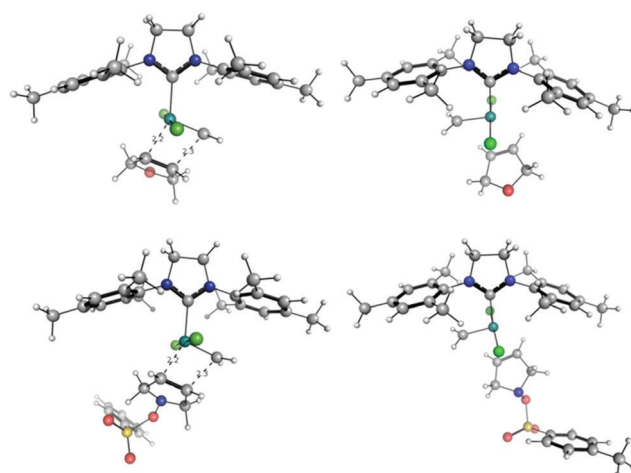


Fig. 6 Geometric features of TS5a and TS5b (left) and complexes 8a and 8b (right).

It is remarkable that compound 5 appears in the energy profile with different relative values of energy at the beginning and at the end of the catalytic cycle. This difference corresponds to the energy release during the overall reaction.

From an energetic point of view, we can conclude that both reactions have low activation energies, as one would expect for a catalyzed reaction. The energetic spans of both catalytic cycles are 11.8 kcal mol⁻¹ if X = O and 11.0 kcal mol⁻¹ if X = NTs. These results are consistent with those obtained in previously reported studies. Although the turnover-determining step may be different for different catalysts, substrates and pathways, it was reported^{16b} that the turnover-determining step is either the olefin insertion (for phosphane-containing catalysts) or the reverse reaction of ruthenacycle cleavage (for NHC-containing catalysts), as in our case.

Insights into microwave effects on the RCM reactions

Despite the fact that the catalytic cycles have low activation energies, the energy gaps corresponding to the induction periods are high (25.2 and 29.8 kcal mol⁻¹). This fact is due to the high stability of the 14e⁻ complex 2 and the barriers of formation and breaking of cyclobutanes.

It is known that the positive effect of microwaves is more pronounced when harsh reaction conditions are required. In this sense, previous results from our research group have quantified that reactions with activation energies from 20 to 30 kcal mol⁻¹ can be improved under microwave irradiation without the use of harsh reaction conditions.¹¹ Thereby, reactions with activation energies below 20 kcal mol⁻¹ occur easily by conventional heating and improvements are not expected under microwave irradiation. In view of the energetic outcomes and by comparison with our previous findings, we can conclude that the experimental results reported previously are in agreement with the computational outcomes. The results suggest that the main mechanism of microwave activation consists of accelerating the formation of the active catalyst species promoting the initiation stage and reducing the induction period. This would be a purely thermal effect reproducible by careful assembly with a thorough control of the temperature.

In order to determine whether the diene can act as a 'molecular radiator' we analyzed other molecular parameters of the reaction intermediates and TSs. We also computed the polarities of all the species involved in the reaction profile. These results are collected in Table 1.

These outcomes are in complete agreement with Kappe's postulates.²⁸ The polarity values indicate that diene 3b (dipole moment 7.2 D) is much more polar than diene 3a (dipole moment 1.7 D). However, this feature is not only shown by diene 3b but is associated with all the species that bear the tosyl group (Table 1). In this regard, it could be postulated that these species might be acting as 'molecular radiators' as they can absorb microwave irradiation very efficiently. In contrast, the dipole moment of the Grubbs catalyst is 1.6 D and this value confirms its negligible absorption.

These polar species appear to act as ionic liquids and allow weakly absorbing solvents such as DCM to absorb microwave

Table 1 Dipole moments for all intermediates and TSs involved in both reaction pathways (μ , D)

Compound	μ	
	X = O	X = NTs
1	1.6	1.6
TS1	5.7	5.7
2	7.3	7.3
TS2	6.4	12.8
3	1.7	7.2
4	6.7	12.5
TS3	5.4	6.4
5	6.8	13.1
6	6.1	6.3
TS4	6.1	11.8
7	7.1	12.3
TS5	5.4	7.6
8	6.5	12.6
9	8.5	8.5

energy considerably faster than the neat solvent, thus leading to very rapid conversions. This situation should be considered as a thermal effect. It should be noted that in order to mimic the rapid heating reaction profile achieved through microwave irradiation, Kappe and colleagues preheated the diene solution in DCM to 60 °C in an oil bath before a solution of the metathesis catalyst was added using a syringe through the Teflon septum.

Finally, we focused our attention on the analysis of the electrostatic potential surface (EPS) and the molecular dipole moment vectors of all these species. Some of the dipole moment vectors are collected in Fig. 7 (see ESI† for more details). The different polarities for the two RCM pathways are in agreement with the electronic nature of O vs. NTs. As can be seen in the EPS, when X = O the electronic density is higher around the two chloride atoms and the oxygen of the diene. However, when X = NTs the highest electronic density is located on the oxygen atoms of the tosyl group. It is worth noting the significant decrease in the electronic density on the chlorine atoms and on the mesityl group in the latter case. This situation is in agreement with the higher electron-withdrawing character of the N-tosyl group vs. the oxygen atom.

It is remarkable that, with reference to the EPS when X = NTs, the molecular dipole vector modifies its direction more than in the case where X = O. As previously stated, in the case where X = O, the chlorine atoms possess higher electron density (Fig. 7). This part of the structure remains mostly intact during the course of the reaction. Therefore, the variation of the dipole moment vector is less important. In contrast, in the case where X = NTs, the electronic density is mostly located around the tosyl group. This part of the molecule experiences a higher mobility along the reaction path.

We previously observed a similar variation in a cyclotrimerization reaction.¹² In this context, the relationship between the mobility of the dipoles and the ability to orient them according to the direction of the electric field is currently under investigation by our group.

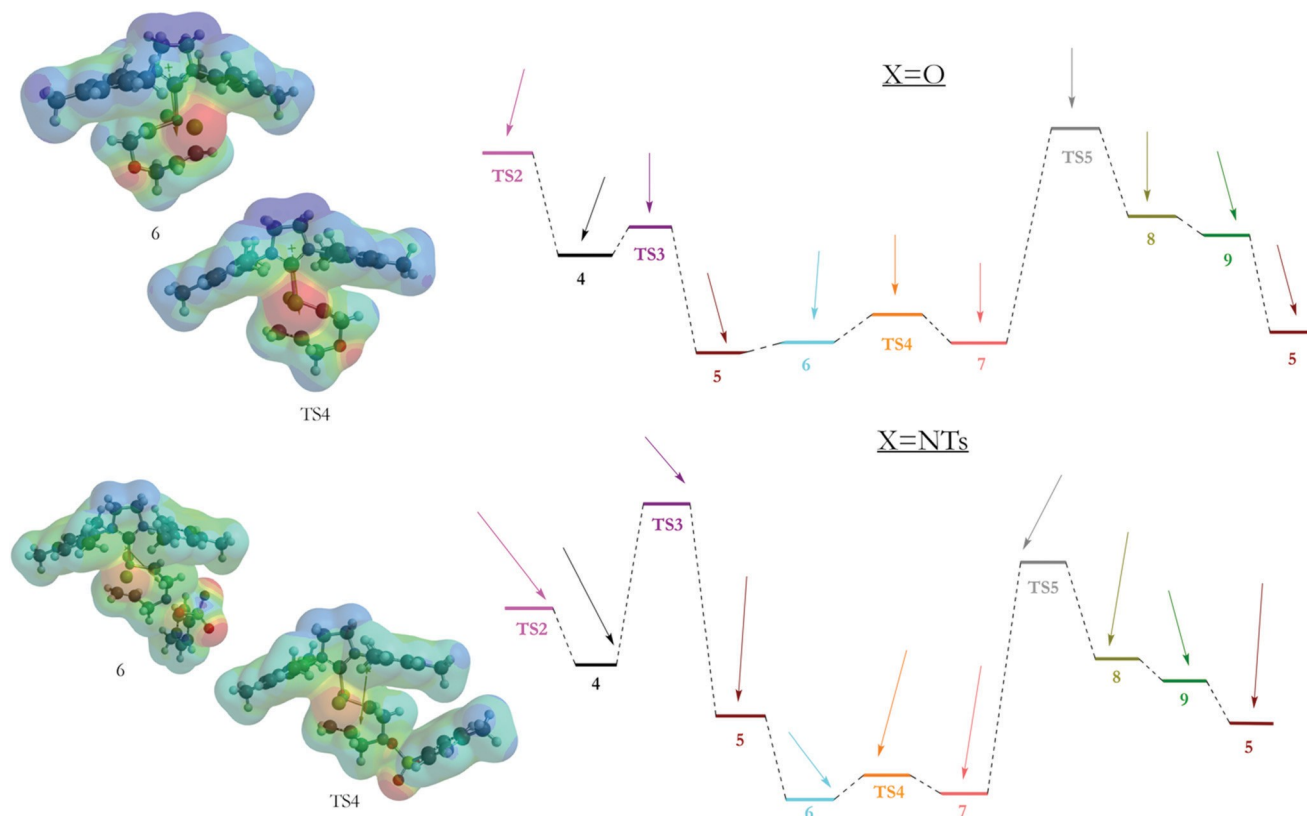


Fig. 7 Variation of the molecular dipole vector for all the intermediates and TS computed for both pathways. Arrows indicate the direction of the dipolar moment. As an example, the EPS of intermediates 6a and 6b, TS4a and TS4b is shown.

Conclusions

We have performed a complete computational study of the RCM of diallyl ether and N,N-diallyl-p-toluenesulfonamide catalyzed by a second-generation Grubbs-type ruthenium carbene complex. The geometric features of all the calculated species and some energy findings are in agreement with the results of other similar studies.

Although the activation energies of the elementary steps of the catalytic cycle are low, microwave thermal effects do indeed affect the induction period of the catalytic kinetics, since the energy gap in the pre-catalytic steps amounts to ca. 30 kcal mol^{-1} . This will result in a shorter induction period by increasing the catalyst turnover and therefore an enhancement in the conversion rate of the reactants.

Furthermore, the presence of polar species, whether a susceptor, solvent, catalyst, reagent or substrate, may increase the polarity of the medium and may lead to rate enhancements through thermal microwave effects independently of the activation energy. This situation occurred when N,N-diallyl-p-toluenesulfonamide was employed as the diene.

As far as the proposed 'molecular radiators' are concerned, we agree with Kappe that far from being a non-thermal effect or a selective absorption that creates microscopic 'hot spots', this represents an example of the modification of the polarity of the reaction that improves the absorption of microwave

radiation and may improve the reaction through a thermal effect. Dielectric properties are group properties and cannot be modelled by an interaction between the single dipole and the electric field. A group of dipoles interacting themselves could be considered.

Finally, in this paper we have exposed how this kind of microwave effect can be evidenced by a computational treatment of the catalytic reaction pathway, showing the complementarity of experimental and theoretical studies.

Acknowledgements

Financial support from the DGICYT of Spain through project CTQ2011-22410/BQU, from the Consejería de Educación y Ciencia, JCCM through project PII2I09-0100 and technical support from the High Performance Computing Service of the University of Castilla-La Mancha is gratefully acknowledged. A.M.R. gratefully acknowledges the MEC for the FPU fellowship.

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