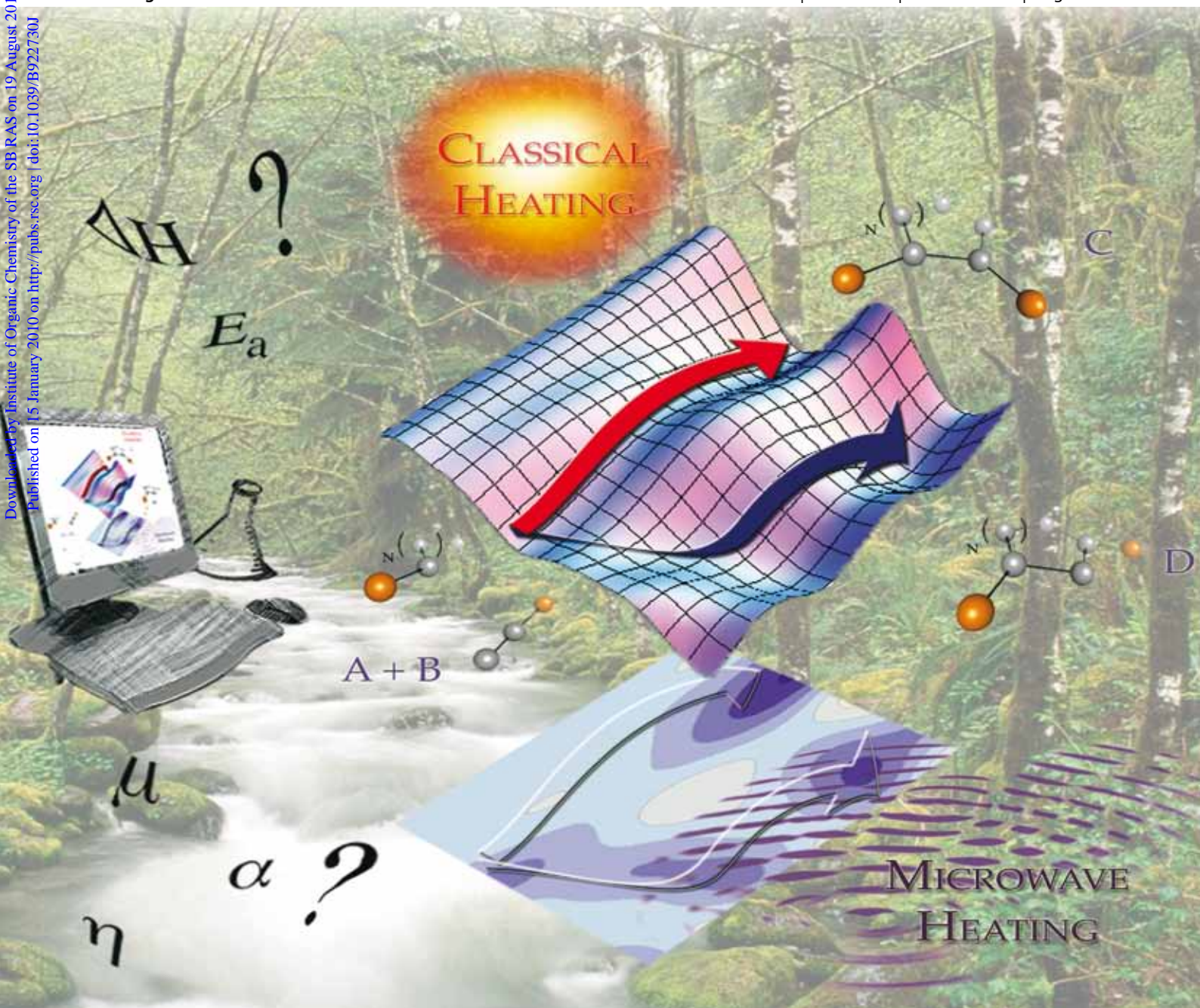


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FULL PAPERPilar Prieto *et al.*

Computational calculations in microwave-assisted organic synthesis (MAOS). Application to cycloaddition reactions

PERSPECTIVERai-Shung Liu *et al.*

Carbo- and heterocyclisation of oxygen- and nitrogen-containing electrophiles by platinum, gold, silver and copper species

Computational calculations in microwave-assisted organic synthesis (MAOS). Application to cycloaddition reactions†‡

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Computational calculations represent a very useful tool to study separately the occurrence of thermal and non-thermal effects of microwave irradiation through the determination of the thermodynamic and kinetic parameters of the reaction. In this paper, we approach the computational study of two previously reported cycloaddition reactions. All of the outcomes indicate the presence of a thermal effect alone for the microwave irradiation that produces changes in the regioselectivity or in the reaction mechanism.

Introduction

Microwave radiation is a non-conventional energy source, and its popularity and synthetic utility in organic chemistry has increased and developed considerably during the last two decades. Since the first published reports on the use of microwave irradiation to accelerate organic chemical transformations,¹ more than 3500 articles have been published in this field, which today is generally referred to as microwave-assisted organic synthesis (MAOS).^{2,3}

This technique is characterised by the spectacular accelerations produced in many reactions. Moreover, it has been shown that milder reaction conditions, shorter reaction times, higher yields and enhanced product purities can be achieved by reducing unwanted side reactions. The combination of solvent-free conditions and microwave irradiation has several advantages in the eco-friendly approach termed green chemistry.^{4,5}

It was reported that the selectivity (chemo-, regio- and stereoselectivity) of a reaction can be modified in relation to that obtained with conventional heating.⁶ These results showed that microwave irradiation can be used as an alternative to conventional heating to obtain different results to those afforded by classical methods.

The use of microwave irradiation in chemistry has increased in the scientific community and it seems reasonable that, in a few years, most chemists will use microwave energy to heat chemical reactions on a laboratory scale.⁷

Despite the relatively large body of published work in this area, the exact reasons why microwave irradiation is able to enhance chemical processes remain unknown.

The results obtained by microwave exposure arise from material-wave interactions. It has been claimed that these interactions lead to thermal effects and specific (not purely thermal) effects. A combination of these two contributions is thought to be

responsible for the effects observed. The main debate has dealt with the question of what actually alters the outcome of the synthesis. Is it merely an effect of the thermal heat generated by the microwaves or is it a specific (non-thermal) effect for microwave irradiation?

Thermal effects can be determined by temperature measurements. These effects are a consequence of a different heating profile, which arises from the overheating of polar solvents, the presence of “hot spots”—particularly in heterogeneous systems—and the selective heating of solvents, catalysts or reagents.

In most examples, the specific microwave effects claimed can be attributed exclusively to thermal effects and reactions are reproducible under conventional heating when the temperature is accurately measured and controlled. Some authors have reinvestigated previous reports employing more accurate measurement systems and all agree with the absence of specific microwave effects.⁸

Recently, Schminck and Leadbeater⁹ showed using *in situ* Raman spectroscopy that while microwave energy may interact with polar molecules to a greater extent than with non-polar ones, conversion of electromagnetic energy into kinetic energy is slower than conversion of kinetic energy into thermal energy. It was concluded that localized superheating does not exist. Kappe *et al.*¹⁰ described a new technology to evaluate separately thermal and non-thermal effects by using SiC vials. SiC absorbs microwave irradiation very efficiently and can heat the sample while eliminating the electromagnetic field in the reaction mixture. In all of the reactions studied, only bulk temperature effects are responsible for the observed enhancements and the electromagnetic field does not have a direct influence on the reaction pathway.

However, some recent publications still contain results that cannot be explained by thermal effects alone, including heterogeneous reactions,¹¹ enzymatic catalysis,¹² glycosidation and anomeric equilibria,¹³ and radical reactions.¹⁴ The use of microwaves at 1 GHz¹⁵ and hybrid systems (combining conventional heating and microwave irradiation)¹⁶ have also provided some results that cannot be easily explained by thermal effects.

Justifications for the existence of non-thermal effects have been very broad¹⁷ and is still a matter of debate. The possibilities range from modifications of the pre-exponential factor¹⁸ to enhanced diffusion,¹⁹ and even the occurrence of surviving radicals in radical reactions.²⁰

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† Dedicated to Professor Antonio García Martínez on the occasion of his retirement.

‡ Electronic supplementary information (ESI) available: Supplementary tables and cartesian coordinates of all stationary points. See DOI: 10.1039/b922730j

The determination of non-thermal effects is hindered by thermal energy, which is in most cases the most important effect and it is distributed rapidly throughout the sample.^{21,22}

Perreux and Loupy stated that if the polarity of a system increases from the ground state to the transition state, microwave irradiation produces an acceleration of the reaction.²³ Computational calculations of the polarity of initial products and transition states support this statement.²⁴ We have also shown that the selectivity in competitive reactions can be related to the polarizability and hardness of the transition state, with the harder and less polarizable transition structure favoured under microwave irradiation.²⁵ Subsequent reports from Conner and Tompsett,²⁶ and Elander *et al.*²⁷ confirmed our results. Moreover, Huang *et al.* showed that the electrical conductivity (EC) of aqueous sodium chloride solutions is modified under microwave irradiation.²⁸

In this regard, as we have previously reported,²⁹ we consider that computational calculations can be useful tools to predict and confirm the possible occurrence of thermal and non-thermal microwave effects. Experimental determinations used to date are hindered by the interference of thermal heating, inaccuracies produced in the determination of the reaction temperature, and the need for specially designed set-ups to obtain comparable reaction conditions under microwave irradiation and conventional heating that are almost impossible to achieve considering the different characteristics of these two methods of heating.^{7c} In this sense, computational calculations can efficiently overcome these drawbacks through the determination of the thermodynamic and kinetic parameters of the reaction.

In this paper, we have selected two previously reported cycloaddition reactions that were claimed to show non-thermal microwave effects: (i) cycloaddition of azidomethylphosphonates and enamines,³⁰ in which the regioselectivity was modified, and (ii) cycloaddition of fulvenes with various dienophiles where microwave irradiation led to the formation of structurally unrelated products to those obtained under conventional heating.³¹

Calculation methods

All calculations included in this paper were carried out using the GAUSSIAN 03³² series of programs, with the standard 6-31G* basis set.³³ In order to include electron correlation at a reasonable computational cost, density functional theory (DFT)³⁴ was used. In this study, these calculations were carried out by means of the three-parameter functional developed by Becke *et al.*,³⁵ which is usually denoted as B3LYP. Zero-point vibrational energies (ZPVEs) were computed at the B3LYP/6-31G* level and were not scaled. All transition structures and minima were fully characterized by harmonic analysis. For each located transition structure, only one imaginary frequency was obtained in the diagonalized Hessian matrix, and the corresponding vibration was found to be associated with nuclear motion along the reaction coordinate. Reaction paths were checked by intrinsic reaction coordinate (IRC) calculations.³⁶ Solvent effects were estimated by means of polarization continuum models (PCM)³⁷ or the Onsager model^{38,39} using toluene and DMF as solvents, respectively.

The molecular hardness (η) of each species was computed according to the following approximate expression (eqn 1)

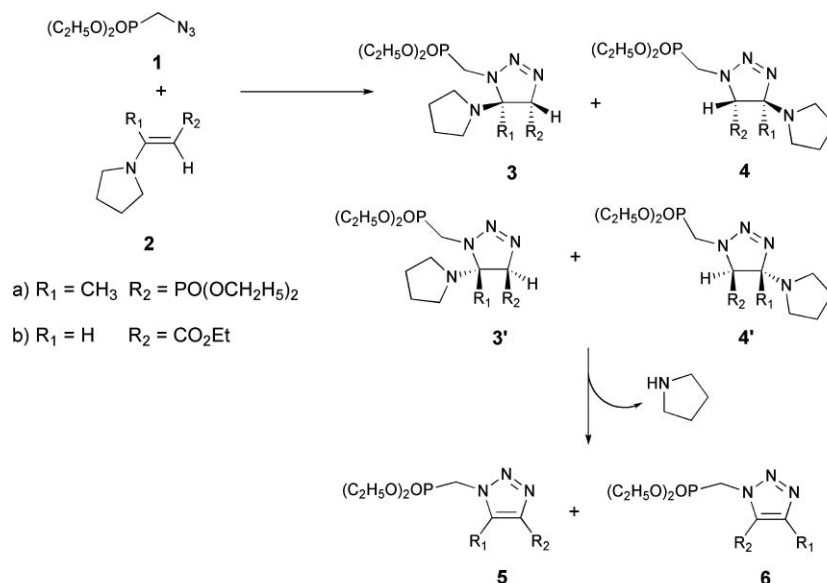
$$\eta = \frac{1}{2}(\varepsilon_L - \varepsilon_H) \quad (1)$$

where ε_L and ε_H are the energies of the LUMO and HOMO, respectively.

Results and discussion

Cycloaddition reaction between azidomethylphosphonates and functionalized enamines

Loupy *et al.*³⁰ described the 1,3-dipolar cycloaddition of azidomethylphosphonate (**1**) and functionalized enamines (**2a**, **2b**) in solvent-free conditions under microwave irradiation (Scheme 1 and Table 1).



Scheme 1 Cycloaddition reaction between azidomethylphosphonate (**1**) and functionalized enamines (**2a–b**).

Table 1 Reaction of azidomethylphosphonate (**1**) and enamines (**2a–b**)³⁰

Entry	Dipolarophile	<i>T</i> /°C	<i>t</i> /min	Solvent	Technique	Yield (%)	5 : 6
1	2a	110	2880	Toluene	C.H. ^a	60	100 : 0
2	2a	100	3600	—	C.H. ^a	70	100 : 0
3	2a	90	20	—	C.H. ^a	0	0
4	2a	90	5	—	MW ^b	30	85 : 15
5	2b	110	2880	Toluene	C.H. ^a	63	100 : 0
6	2b	100	3600	—	C.H. ^a	86	100 : 0
7	2b	90	20	—	C.H. ^a	0	0
8	2b	90	20	—	MW ^b	55	85 : 15

^a C.H. conventional heating. ^b MW microwave irradiation (120 W).

The process required long reaction times and high temperature because the dipolarophilic character of the enamines is reduced by the introduction of electron-withdrawing groups. In this sense, the enamino-phosphonate (**2a**) or -ester (**2b**) did not behave as acrylic acid derivatives but as enamines. The best yields were obtained in solvent-free conditions at 100 °C with very long reaction times (60 h) (Table 1, entries 2 and 6). Triazole **5** was obtained exclusively in good yields.

In contrast, under microwave irradiation a mixture of both regioisomers (**5** and **6**) was obtained (Table 1, entries 4 and 8). The authors postulated that modification of the regioselectivity under microwaves is a consequence of dipolar polarization, which favours the interactions between two mutually oriented dipoles.

We carried out a computational study of this reaction in order to clarify the effect of microwave irradiation on the regioselectivity of the cycloaddition.

All possible intermediates and transition states were optimized for these reaction paths at the B3LYP/6-31G* level and the solvent effect was determined at the B3LYP(PCM)/6-31G* level, considering toluene as the solvent. In order to minimize the computational cost, we replaced the ethyl groups by methyl groups in the azide. The cycloaddition reaction can give two regioisomers, **3** and **4**, as stereoisomeric mixtures. Subsequent elimination of pyrrolidine leads to the corresponding triazoles **5** and **6** (Scheme 1). We optimized the cycloaddition reaction exclusively, since aromatization should not influence the selectivity.

The calculated activation and reaction energies are collected in Tables 2 and 3, and in Fig. 1 and 2.

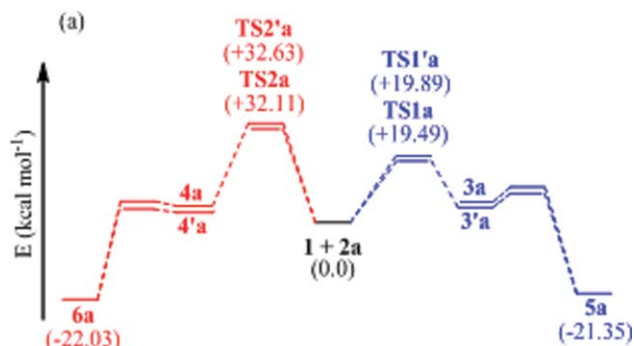
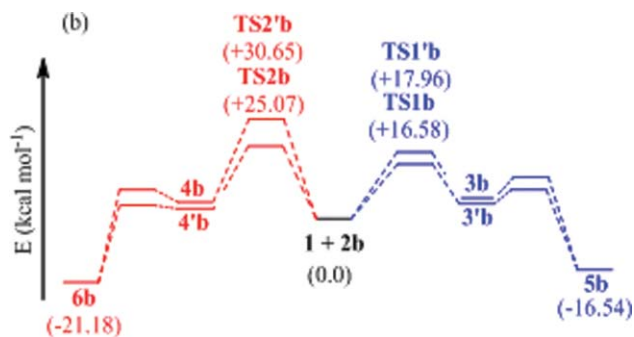
Our results indicate that cycloadducts **3** should be produced under kinetic control (Table 2, entries 1, 2, 5 and 6). In contrast, the activation energy for cycloadducts **4** is higher (Table 2, entries

Table 2 Reaction of azidophosphonate (**1**) with enamines **2a** and **2b**. Activation energies (ΔE_a , kcal mol⁻¹) computed at the B3LYP/6-31G*+ Δ ZPVE and B3LYP(PCM)/6-31G*+ Δ ZPVE levels

Entry	Reaction	ΔE_a /kcal mol ⁻¹	
		Gas phase	Solution
1	1 + 2a → 3a	17.72	19.49
2	1 + 2a → 3'a	18.16	19.89
3	1 + 2a → 4a	29.05	32.63
4	1 + 2a → 4'a	30.10	32.11
5	1 + 2b → 3b	13.59	16.58
6	1 + 2b → 3'b	15.64	17.96
7	1 + 2b → 4b	21.61	25.07
8	1 + 2b → 4'b	27.33	30.65

Table 3 Reaction of azidophosphonate (**1**) and enamines **2a** and **2b**. Reaction energies (ΔE_{rxn} , kcal mol⁻¹) computed at the B3LYP/6-31G*+ Δ ZPVE and B3LYP(PCM)/6-31G*+ Δ ZPVE levels

Entry	Reaction	ΔE_{rxn} (kcal mol ⁻¹)	
		Gas phase	Solution
1	1 + 2a → 5a	-21.78	-21.35
2	1 + 2a → 6a	-23.29	-22.03
3	1 + 2b → 5b	-23.73	-16.54
4	1 + 2b → 6b	-24.13	-21.18

**Fig. 1** Reaction profile of the reaction between **1** and **2a**.**Fig. 2** Reaction profile of the reaction between **1** and **2b**.

3, **4**, **7** and **8**), although in all cases **4** led to triazoles **6**—the thermodynamic control products (Table 3, entries 1 vs. 2 and 3 vs. 4).

Under conventional heating, only the kinetic product **5** is obtained; by contrast, under microwave irradiation, a mixture of the kinetic **5** (85%) and the thermodynamic **6** (15%) product is obtained. As a consequence, theoretical calculations are in complete agreement with the experimental results. As shown

previously,^{29a,c} these results confirm that reactions with a high activation energy (20–30 kcal mol⁻¹) can be performed successfully under microwave irradiation due to thermal effects (overheating or hot spots).

Secondly, we calculated the hardness, polarity and hyperpolarizability of intermediates and transition states in order to find indications of a possible non-thermal microwave effect. Previous studies indicated that the microwave efficiency should be higher in reactions with transition states that are hard, polar and have low polarizability.

The main features of the transition structures of the reaction between azidomethylphosphonate **1** and enamines **2** are shown in Fig. 3 and 4.

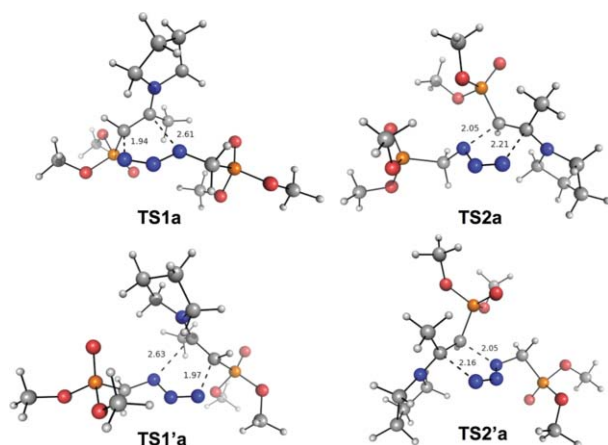


Fig. 3 Main features of the transition states computed at the B3LYP/6-31G* level of theory corresponding to the reaction between azidomethylphosphonate **1** and enamine **2a**.

From a structural viewpoint, it can be observed that critical distances (N1–C5 and N3–C4) are more similar in **TSs 2** than in **TSs 1**. The latter are thus more synchronous than the former. Similarly, N3–C4 distances were shorter in **TSs 1** than in **TSs 2**. Thereby, **TSs 1** are reagent-like transition states as they are formed earlier, while **TSs 2** are product-like transition states.

These observations are consistent with the calculated energy profile. Activation barriers are always lower for the formation of cycloadducts **3**.

Table 4 Reaction between **1** and **2a**. Dipole moments (μ , D), hardnesses (η , eV) and average polarizability volumes (α'_{av} , Bohr³) of reagents, transition structures and products

	1	2a	TS 1a	TS 1'a	TS 2a	TS 2'a	5a	6a
μ/D	1.63	4.73	5.3	4.09	4.1	2.16	5.35	1.33
α'/Bohr^3	77.42	133.94	219.87	220.81	216.36	220.0	153.98	153.52
η/eV	0.110	0.107	0.079	0.077	0.067	0.069	0.122	0.113

Table 5 Reaction between **1** and **2b**. Dipole moments (μ , D), hardnesses (η , eV) and average polarizability volumes (α'_{av} , Bohr³) of reagents, transition structures and products

	1	2b	TS 1b	TS 1'b	TS 2b	TS 2'b	5b	6b
μ/D	1.63	6.99	6.01	6.17	5.06	4.08	3.12	2.33
α'/Bohr^3	77.42	102.47	188.47	188.19	180.4	170.85	123.77	121.90
η/eV	0.110	0.193	0.161	0.162	0.137	0.137	0.239	0.214

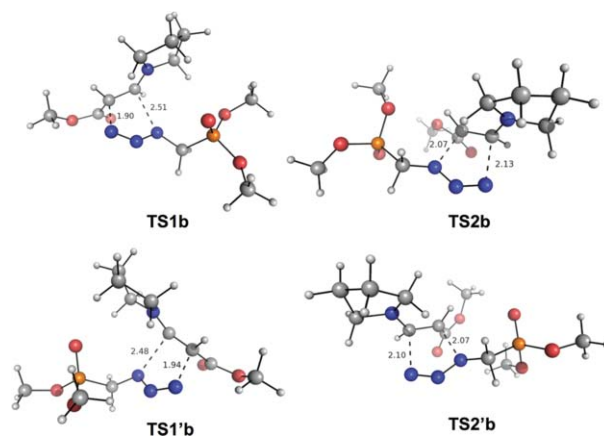


Fig. 4 Main features of the transition states computed at the B3LYP/6-31G* level of theory corresponding to the reaction between azidomethylphosphonate **1** and enamine **2b**.

Loupy proposed that the position of the transition state along the reaction coordinate should be considered in relation to the Hammond postulate. If a reaction only needs a small activation energy, the TS is more similar to the ground state and only weak specific microwave effects can be foreseen under these conditions. By contrast, a more difficult reaction implies a higher activation energy and the TS therefore occurs later along the reaction path. In this respect, in product-like TSs, specific microwave effects should be more pronounced, a situation in agreement with the Hammond postulate.

Hardness, polarity and polarizability values for all the species involved in the reaction are collected in Tables 4 and 5.

TS2 leads to triazole **6** (observed exclusively under microwave irradiation) and is less polar, hard and polarizable than **TS1**, although it occurs late in the reaction coordinate. This is not surprising since this is an isopolar reaction and the TS differs little or not at all in charge separation or charge distribution from the reactants. Moreover, a decrease in the polarity occurs from the ground to the transition state. Accordingly, non-thermal microwave effects should not be expected in this reaction.

Finally, reactants are very polar, 6.36 Debyes (1.63 D of **1** and 4.73 of the enamine **2a**) for reaction (a) and 8.62 in reaction (b) (1.63 D of **1** and 6.99 of the enamine **2b**), so they absorb

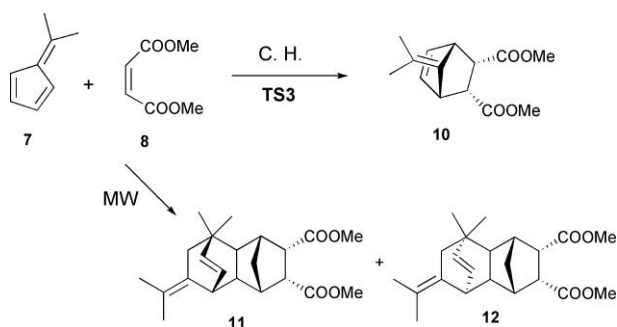
microwaves efficiently and can be heated rapidly. Furthermore, this effect is even more important in solvent-free conditions.

As a result, the experimentally observed modification of selectivity in the cycloaddition of azides **1** with enamines **2** is a consequence exclusively of thermal effects and non-thermal effects can be excluded.

Cycloaddition reactions of 6,6-dimethylfulvene (**7**)

Hong *et al.*³¹ reported the reaction of 6,6-dimethylfulvene (**7**) with alkenes and alkynes promoted by microwave irradiation. These processes resulted in the formation of intriguing polycyclic ring systems. The final result depended on the alkene and the heating source, *i.e.* microwaves or conventional heating. These results suggest that microwave irradiation can in fact alter the reaction pathway. We considered two selected examples to perform a computational study; the reactions of 6,6-dimethylfulvene (**7**) with dimethyl maleate (**8**) and maleic anhydride (**9**).

In the first example (Scheme 2), 6,6-dimethylfulvene (**7**) reacts with dimethyl maleate (**8**) under conventional heating (C₆H₆, 80 °C, 8 h) to afford the Diels–Alder adduct **10** (Table 6, entries 1 and 2). In contrast, under microwave irradiation in DMSO, products **11** and **12** were obtained (Table 6, entries 3 and 4).



Scheme 2 Reaction of 6,6-dimethylfulvene (**7**) and dimethyl maleate (**8**).

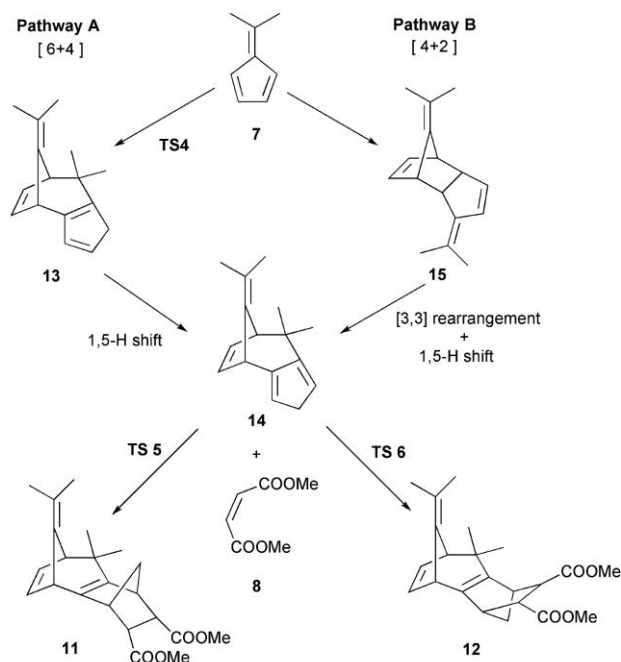
A plausible mechanism for the formation of **11** and **12** under microwave irradiation involves dimerization of fulvene **7** through a [6 + 4]-cycloaddition to give dimer **13**, isomerization of which led to the reactive diene **14** (Scheme 3, Pathway A).

Alternatively, dimerization of fulvene **7** by a [4 + 2]-cycloaddition affords adduct **15**, which would be transformed to dimer **14** through a [3,3]-sigmatropic rearrangement and a 1,5-hydrogen shift (Scheme 3, Pathway B).

Table 6 Reaction of 6,6-dimethylfulvene (**7**) and dimethyl maleate (**8**). Experimental results³¹

Entry	Heating source	Conditions	Yield (%) [prod]
1	C.H.	DMSO/60 min/150 °C	65 [10]
2	C.H.	DMSO/480 min/80 °C	84 [10]
3	MW	DMSO/60 min/150 °C	30 [11 + 12]
4	MW	DMSO/60 min/150 °C	65 [11 + 12] ^a

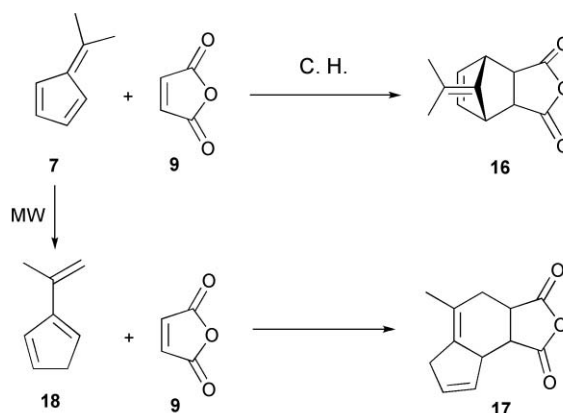
^a 2 equiv. of 6,6-dimethylfulvene (**7**) were used.



Scheme 3 Reaction of 6,6-dimethylfulvene (**7**) and dimethyl maleate (**8**) under microwave irradiation. Mechanism proposed by Hong.³¹

Subsequently, [4 + 2]-cycloaddition of **14** with dimethyl maleate generates adducts **11** and **12**.

In the second example, the reaction of 6,6-dimethylfulvene (**7**) with maleic anhydride (**9**) under conventional heating produced the Diels–Alder adduct **16** (Scheme 4). By contrast, under microwave heating the [4 + 2]-cycloadduct **17** was obtained by cycloaddition with the exocyclic diene. A possible mechanism for the formation of **17** involves microwave-induced isomerization of 6,6-dimethylfulvene (**7**) to 2-isopropenylcyclopenta-1,3-diene (**18**) followed by trapping with maleic anhydride (**9**) in a [4 + 2]-cycloaddition.



Scheme 4 Reaction of 6,6-dimethylfulvene (**7**) and maleic anhydride (**9**).

Reaction of 6,6-dimethylfulvene (**7**) and dimethyl maleate (**8**)

We explored the potential surface of this reaction at the B3LYP(LIA1)/6-31G* level. Initially, we isolated the transition state (TS3) corresponding to a normal Diels–Alder reaction

(Scheme 2), which occurred under conventional heating. The main features of **TS3** are depicted in Fig. 5.

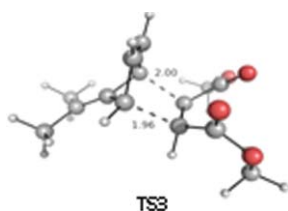


Fig. 5 Main features of the transition state **TS3** computed at the B3LYP(LIA1)/6-31G* level of theory.

Regarding the reaction under microwave irradiation, evidence for a transition state corresponding to a [3,3]-rearrangement was not found (Scheme 3, Pathway B).

The main features of transition states involved in Pathway A are depicted in Fig. 6. Dimerization of fulvene **7** in a [6 + 4]-cycloaddition pathway to give the dimer **13** takes place through **TS4**. This cycloadduct undergoes a 1,5-H shift to yield the reactive diene **14**. Subsequently, **TS5** and **TS6** lead to the formation of **11** and **12** through a [4 + 2]-cycloaddition of **14** with dimethyl maleate (**8**) in *endo*-supra and *endo*-infra approaches, respectively.

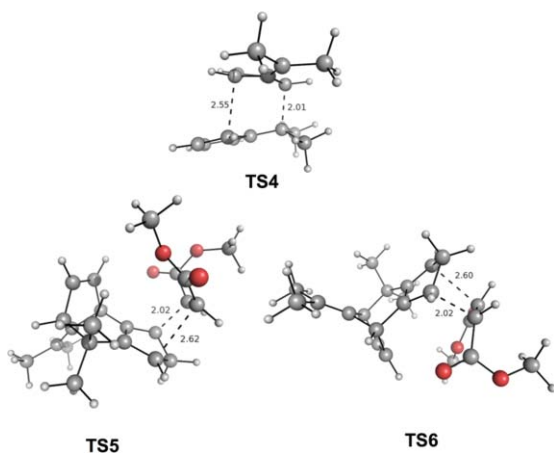


Fig. 6 Main features of the transition states **TS4–6** computed at the B3LYP(LIA1)/6-31G* level of theory.

Similarly we determined the reaction and activation energies for these mechanisms (Table 7) and polarities, polarizabilities and hardness of the species involved (Table 8).

These outcomes indicate that under conventional heating, the kinetic control product was obtained again. In contrast, under microwave heating, the thermodynamic products (**11** and **12**) were obtained through a modification of the reaction pathway (Table 7, entries 2 and 3). Once again, activation energies close

Table 7 Reaction of 6,6-dimethylfulvene (**7**) with dimethyl maleate (**8**). Activation and reaction energies (kcal mol⁻¹) computed at the B3LYP(LIA1)/6-31G*+ΔZPVE level

Entry	Heating source	ΔE _{a1}	ΔE _{a2}	ΔE _{rxn}	Prod.
1	C.H.	24.6	—	-0.2	10
2	MW	28.2	21.2	-12.9	11
3	MW	—	18.2	-19.0	12

to 30 kcal mol⁻¹ are surpassed exclusively under microwave irradiation.

Reaction of 6,6-dimethylfulvene (**7**) with dimethyl maleate (**8**) followed pericyclic processes under either conventional heating or microwave irradiation. In mechanism B, there is no change in polarity during the limiting step. Thus, non-thermal effects were not expected to occur.

In conclusion, thermal effects were the only ones responsible for the modification of the reaction pathway under microwave irradiation.

Reaction of 6,6-dimethylfulvene (**7**) and maleic anhydride (**9**)

Finally, we performed computational calculations on the reaction of 6,6-dimethylfulvene (**7**) and maleic anhydride (**9**) (Scheme 4), where microwave irradiation again leads to structurally different products.

Under conventional heating, product **16** was obtained exclusively through a Diels–Alder cycloaddition between the cyclopentadienyl system of 6,6-dimethylfulvene (**7**) and maleic anhydride (**9**). Under microwave irradiation, isomerization of 6,6-dimethylfulvene to 2-isopropenyl-cyclopenta-1,3-diene (**18**) followed by a [4 + 2]-cycloaddition with maleic anhydride (**9**) occurred (Scheme 4).

We propose two pathways for the isomerization process. The first involves 6,6-dimethylfulvene (**7**) exclusively (Scheme 5, Pathway C) and involves a 1,7-hydrogen shift through either a unimolecular or a bimolecular process (Scheme 5). The second pathway involves 6,6-dimethylfulvene (**7**) and maleic anhydride (**9**) (Scheme 6, Pathway D). The main features of these TSs are depicted in Fig. 7 and the energies associated with these processes are collected in Table 9.

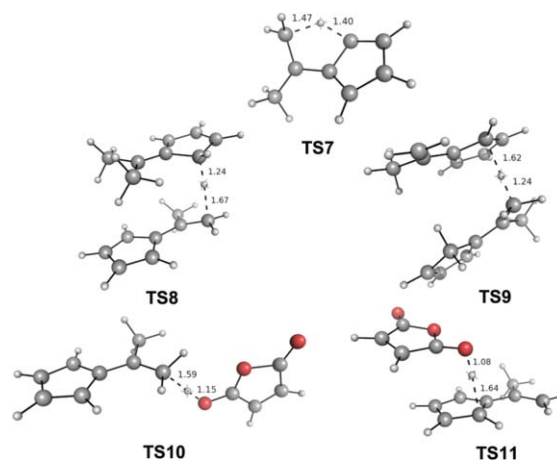
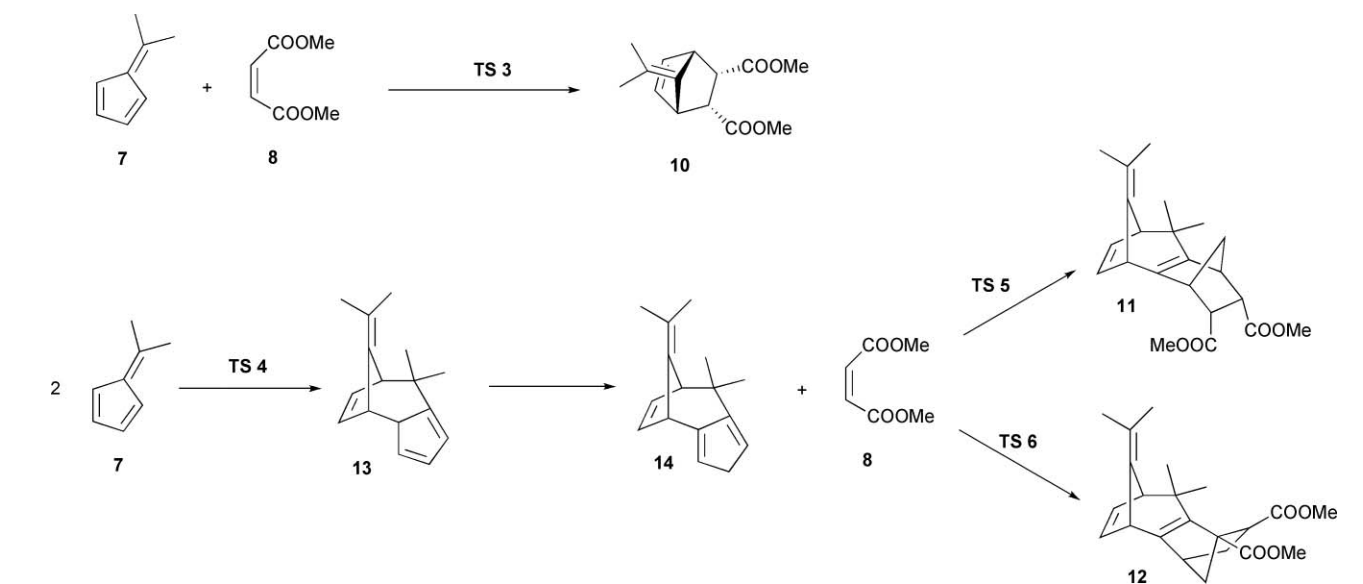


Fig. 7 Isomerization of 6,6-dimethylfulvene (**7**). Main features of transition states computed at the B3LYP(LIA1)/6-31G* level.

These outcomes indicate that a bimolecular mechanism is involved in the isomerization process (Table 9, entries 2 and 3), because a difference of 0.9 kcal mol⁻¹ between the two activation energies is not sufficient to rule out one of the mechanisms. Thus, bimolecular Pathway C (two molecules of fulvene) or Pathway D, which involves a molecule of 6,6-dimethylfulvene (**7**) and another of maleic anhydride (**9**), must be the mechanisms to account for the isomerization.

Table 8 Reaction between **7** and **8**. Dipole moments (μ , D), hardnesses (η , eV), average polarizability volumes (α'_{av} , Bohr³) of reagents, transition structures and products (B3LYP(LIA1)/6-31G*+ Δ ZPVE)



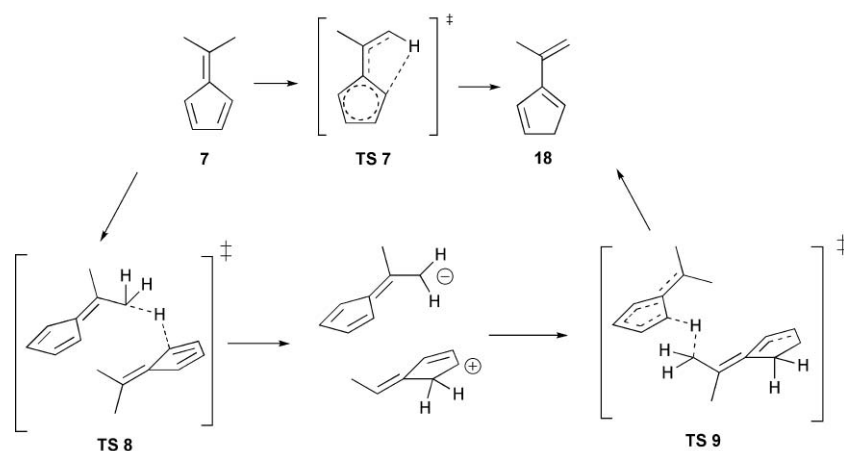
Conventional Heating Mechanism

	μ/D	α'/Bohr^3	η/eV	$\Delta\mu/D$
7	2.32	105.44	0.072	
8	8.32	86.20	0.102	
TS3	10.09	205.05	0.094	
10	8.97	176.33	0.111	-0.55

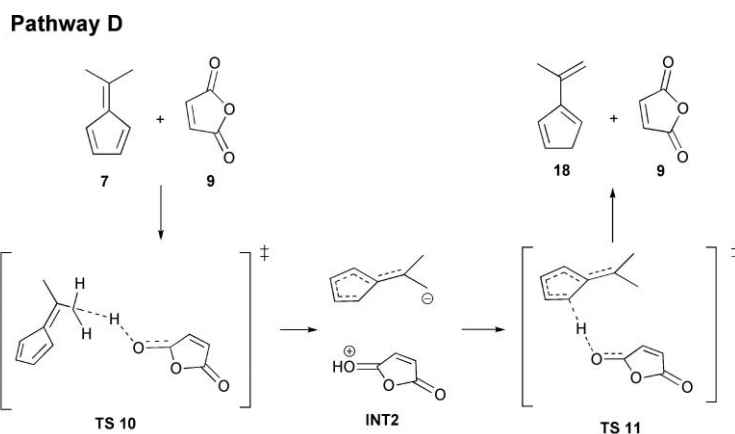
Microwave Heating Mechanism

	μ/D	α'/Bohr^3	η/eV	$\Delta\mu/D$
7	2.32	105.44	0.072	
TS4	4.64	236.85	0.048	0
13	0.74	195.08	0.097	
14	0.11	163.76	0.097	
8	8.32	86.20	0.102	
TS5	2.79	299.64	0.072	-5.64
TS6	7.31	296.13	0.064	-1.12
11	2.78	266.72	0.102	
12	9.07	279.91	0.101	

Pathway C



Scheme 5 Proposed mechanism for the isomerization of dimethylfulvene (Pathway C).



Scheme 6 Proposed mechanism for the isomerization of dimethylfulvene (Pathway D).

Table 9 Isomerization of 6,6-dimethylfulvene (**7**). Activation energies (ΔE_a , kcal mol⁻¹) computed at the B3LYP(L1A1)/6-31G*+ Δ ZPVE level

Entry	Mechanism		ΔE_{a1}	ΔE_{rxn}
1	Pathway C	Unimolecular	53.2	6.1
2		Bimolecular	35.2	
3	Pathway D	Bimolecular	34.3	

Table 10 Diels–Alder cycloaddition of maleic anhydride (**9**) with 6,6-dimethylfulvene (**7**) and with 2-isopropenylcyclopenta-1,3-diene (**18**), respectively. Activation energies (ΔE_a , kcal mol⁻¹) (B3LYP(L1A1)/6-31G*+ Δ ZPVE)

Entry	Heating source	ΔE_1	ΔE_{rxn}
1	C.H.	16.1	-6.1
2	MW	11.8	-22.6

Next, we studied the Diels–Alder cycloaddition of maleic anhydride (**9**) with 6,6-dimethylfulvene (**7**) and 2-isopropenylcyclopenta-1,3-diene (**18**), respectively. The main features of the transition states and the activation energies for both reactions are depicted in Fig. 8 and Table 10.

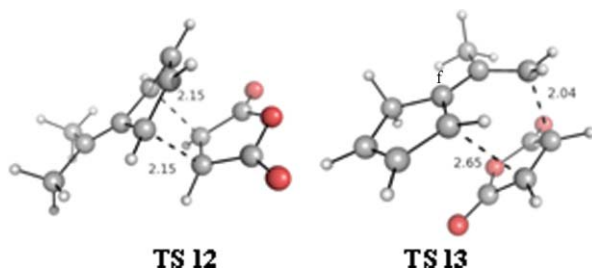


Fig. 8 Diels–Alder cycloaddition of maleic anhydride (**9**) with 6,6-dimethylfulvene (**7**) or 2-isopropenylcyclopenta-1,3-diene (**18**). Main features of the transition states computed at the B3LYP(L1A1)/6-31G* level.

As in the previous examples, microwave irradiation enabled the thermodynamic control product to be obtained. It should be noted that the formation of product **17** requires a prior isomerization process that occurred with a high activation energy (34.3 or 35.2 kcal mol⁻¹), which is only reached with microwave heating.

Table 11 Reaction between **7** and **9**. Dipole moments (μ , D), hardnesses (η , eV), average polarizability volumes (α_{av} , Bohr³) of reagents, transition structures and products (B3LYP(L1A1)/6-31G*+ Δ ZPVE)

Pathway A				
	μ/D	$\alpha/Bohr^3$	η/eV	$\Delta\mu/D$
7	2.32	105.44	0.072	
9	4.75	52.88	0.092	
TS12	9.61	170.50	0.091	2.54
16	6.69	145.51	0.073	
Pathway C (Bimolecular)				
	μ/D	$\alpha/Bohr^3$	η/eV	$\Delta\mu/D$
7	2.32	105.44	0.072	
9	4.75	52.88	0.092	
TS8	0.38	299.22	0.033	-4.26
TS9	0.50	259.89	0.040	
18	0.91	104.23	0.082	
TS13	6.82	176.73	0.065	3.58
17	5.42	144.66	0.101	
Pathway D (Bimolecular)				
	μ/D	$\alpha/Bohr^3$	η/eV	$\Delta\mu/D$
7	2.32	105.44	0.072	
9	4.75	52.88	0.092	
TS10	26.55	237.50	0.050	19.48
Int 2	3.81	258.00	0.044	
TS11	4.43	272.35	0.038	
18	0.91	104.23	0.082	
TS13	6.82	176.73	0.065	3.58
17	5.42	144.66	0.101	

We also computed the polarities, polarizabilities and hardnesses of the species involved (Table 11).

In these reactions, an increase in the polarity is observed from the ground to the transition state. This effect is especially important for **TS10**. This outcome must be considered with caution because the ONSAGER solvent model, despite being the most developed model, is not adequate for very large structures like **TS10** and **TS11**. As a result, we performed a single point calculation of these two structures using the SCI-PCM method⁴⁰ and similar values were obtained.

Thereby, we can conclude that microwave irradiation again favours the thermodynamic product **17**, although a high activation energy is required. In this case, it is possible that the high polarity increase calculated for pathway D allows the formation of a new product under microwave irradiation.

Conclusions

We have shown the utility of computational calculations in assessing the effect of microwave irradiation in chemical synthesis by determining the thermodynamic and kinetic parameters of the reaction. This methodology can be efficiently used to estimate thermal and non-thermal effects without the need to repeat reactions and design experimental set-ups with exactly the same conditions under conventional heating and microwave irradiation. Finally, theoretical results can be used as a useful tool to predict possible modifications in the reaction under microwave irradiation.

Computational calculations on two previously reported cycloaddition reactions, which were claimed to show non-thermal microwave effects, demonstrated that thermal effects alone can account for the results obtained. First, the cycloaddition of azidomethylphosphonates **1** and enamines **2** in which the regioselectivity is modified. Second, the reaction of fulvene **7** with different dienophiles; the use of microwave irradiation instead of conventional heating leads to the formation of structurally unrelated products.

In this regard, the theoretical outcomes show that modification of selectivity in the reactions with isopolar transition states is a consequence of thermal microwave effects. Non-thermal microwave effects could not be detected. In all the examples the thermodynamic product is favoured under microwave irradiation. These results are in agreement with our previous results and show that reactions with high activation energy (20–30 kcal mol⁻¹) can be successfully performed under microwave irradiation without the use of harsh reaction conditions (for example, high pressure or pyrolysis).

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