Theoretical study on the reaction between 4,6-dimethyl-1,2,3-triazine and enamines

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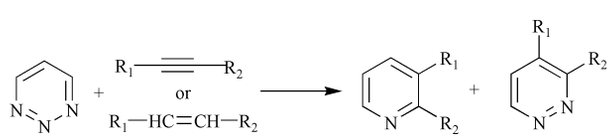
Received (in Cambridge, UK) 17th April 2002, Accepted 28th May 2002
First published as an Advance Article on the web 13th June 2002

The reaction between 4,6-dimethyl-1,2,3-triazine and cyclopentanone pyrrolidine enamine has been studied using *ab initio* SCF-MO computational methods. Solvent effects have also been taken into account. The reaction is predicted to be a concerted Diels–Alder cycloaddition. Self-consistent reaction field methods based on multipole expansions of the free energy of solvation tend to overestimate the stability of zwitterionic intermediates at the Hartree–Fock level. This overestimation results in a stepwise mechanism, although higher levels of theory predict a concerted mechanism.

Introduction

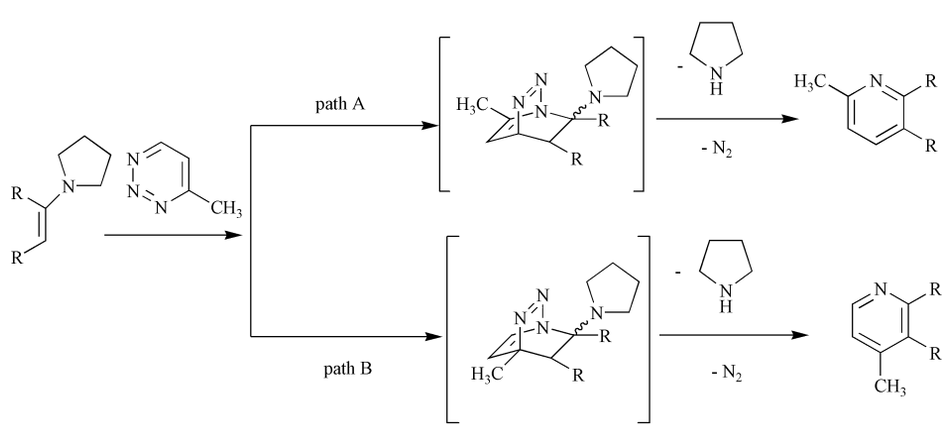
1,2,3-Triazines are heteroaromatic systems that can react as dienes in inverse-demand Diels–Alder cycloadditions with electron-rich dienophiles.[1] Thus, several reactions have been reported[2–5] between 1,2,3-triazine (or its 4- or 5-methyl derivatives) and electron-rich dienophiles to afford pyridines and pyridazines (Scheme 1). This approach has been successfully employed to prepare alkaloid derivatives.[6,7]



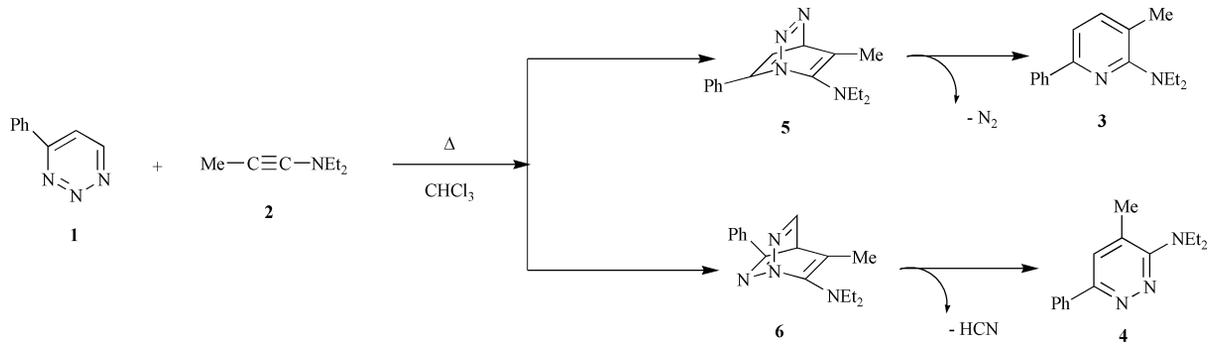
Scheme 1

The mechanism proposed for this reaction involves a Diels–Alder cycloaddition between the 1,2,3-triazine and the dienophile. These reactions do, however, suffer from regioselectivity problems. When monosubstituted triazines are employed, it is possible to obtain two possible substituted pyridines. Moreover, 1,2,3-triazines may act as 1-azadienes to afford pyridine derivatives and as 1,2-diazadienes to give pyridazine derivatives. Some authors have shown also mechanistic problems. Okatani *et al.*[3] investigated the solvent and temperature effects on the regioselectivity of the cycloaddition of 4-methyl-1,2,3-triazine and several enamines (Scheme 2). Using dry $CHCl_3$ as the solvent they obtained only 2,3,6-trisubstituted pyridines (path A). In contrast, when high boiling solvents were employed, cycloaddition of 4-methyl-1,2,3-triazines with cyclooctanone pyrrolidine enamine took place by both path A and path B, producing the cycloadducts from two possible dienes (*i.e.* with N-3/C-6 and N-1/C-4 atoms, respectively).

Ohsawa and coworkers[4] studied this reaction in greater detail. In the reaction between 4-phenyl-1,2,3-triazine (**1**) and *N*,*N*-diethylprop-1-ynylamine (**2**) they obtained an equimolar mixture of **3** and **4** (Scheme 3). These compounds were supposed to be produced *via* the Diels–Alder adducts **5** and **6**, respectively (Scheme 3). Molecular orbital calculations indicated that the highest coefficients of the LUMO were at the N-2 and C-5 positions of **1**, whereas C-4 and N-1 were electron deficient. Thus, formation of **5** seemed to involve a non-concerted ionic mechanism and that of **6** an orbital-controlled reaction path. The steric repulsion between the phenyl and



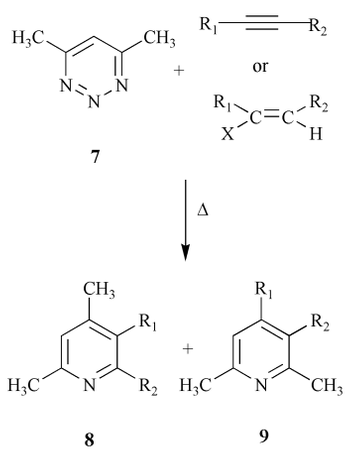
Scheme 2



Scheme 3

diethylamino groups in the TS leading to adduct **5** made formation of this compound sufficiently disadvantageous that adducts **6** became relatively significant.

In the same paper they described the reactions of 4,6-dimethyl-1,2,3-triazine as diene. Although 2,4-dimethylpyridines **8**, the expected Diels–Alder products, were obtained, products **9** were also unexpectedly obtained (Scheme 4). For



Scheme 4

example, when **7** was heated with ketene diethyl acetal the 2,6-dimethylpyridine derivative was the major product. Formation of both 2,4- and 2,6-dimethylpyridine derivatives can be explained by involvement of the azacyclobutadiene (azete) intermediate **10** (Scheme 5); the formation of this compound *cannot* be explained by a Diels–Alder-type cycloaddition between **7** and the dienophile. Thus, the intermediary formation of an azacyclobutadiene by loss of nitrogen from **7**, followed by the addition of dienophile either by route (A) or (B) (Scheme 5), produces 2,4- or 2,6-dimethylpyridines, respectively.

Very little is known about the properties of monocyclic azabutadienes.[8–11] The calculated resonance energies of cyclobutadiene (−18 kcal mol^{-1})[12] and azacyclobutadiene (azete) (−15.5 kcal mol^{-1})[13–15] show both the antiaromatic character of these compounds and the stabilizing effect of the nitrogen atom.[16,17] In view of the negative resonance energies it is not surprising that attempts to prepare monocyclic azacyclobutadienes have thus far been unsuccessful. Even pyrolysis or photolysis of trisubstituted 1,2,3-triazines[9,16,17] afforded only acetylenes and nitriles. According to the push–pull principle, the introduction of amino groups should provide sufficient stabilisation for monocyclic azacyclobutadienes to exist. The azetes **11**[9] and **12**[18,19] (Fig. 1) have been obtained, in admixture

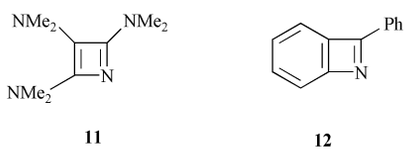
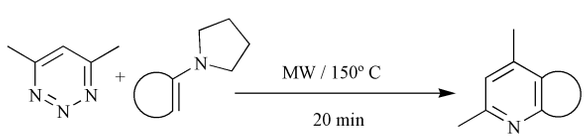


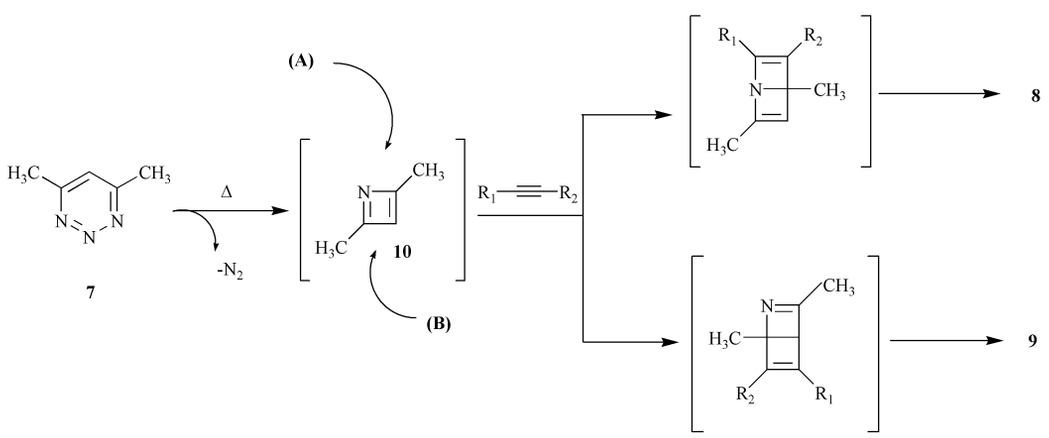
Fig. 1

with other products, by flash pyrolysis of the corresponding triazines. These compounds are stable only at very low temperature.

In connection with our studies on the application of microwave activation in organic reactions,[20–25] we recently reported[26] the cycloaddition of 4,6-dimethyl-1,2,3-triazine with enamines or their precursors under microwave irradiation in solvent-free conditions (Scheme 6). This methodology constitutes a



Scheme 6



Scheme 5

dramatic improvement in comparison with classical methods and allows fused pyridine systems to be obtained in good yields.

Although no regioselectivity problems have been observed, two mechanisms are still possible to explain the observed result. In order to elucidate the mechanism of this process, we decided to study the reaction between 2,4-dimethyl-1,2,3-triazine and cyclopentanone pyrrolidine enamine using computational methods. As mentioned above, several authors have proposed different mechanistic models to explain their experimental results, but a computational study has not been reported to date. In this context, we describe here the first computational study of this reaction using high-level computational methods. We performed our study not only in the gas phase but also in solution.

Experimental

All the results presented in this work were obtained with *ab initio* MO and DFT theories using the Gaussian 94[27] and Gaussian 98[28] programs with the standard 3-21G* and 6-31G* basis sets. Geometry optimisations of stationary points (minimum and transition structure search) were carried out at the Hartree–Fock (HF) level. In larger systems the electron correlation was expected to be critical in order to evaluate the reaction profile properly and, in these cases, we used Density Functional Theory[29] (DFT). We carried out these calculations by means of the hybrid functional developed by Becke and also Lee, Yang and Parr, which is customarily denoted as B3LYP.[30–32] Zero-point vibrational energies (ZPVE) were scaled by 0.89[33] when computed at the HF level. Stationary points were characterised by frequency calculations.[34] All reactants, intermediates and products have positive Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration. Several reaction paths were checked by intrinsic reaction coordinate (IRC) calculations.[35,36] Solvent effects were estimated by means of the Onsager model.[37,38] All the calculations reported in this work were carried out in the gas phase and with three different solvents. These solvents are: piperidine (ε = 5.8), chloroform (ε = 4.81) and *o*-dichlorobenzene (ODCB) (ε = 9.93).

Results and discussion

In this work we studied computationally the possible mechanism of the reaction between 4,6-dimethyl-1,2,3-triazines and cyclopentanone pyrrolidine enamine. In our previous experimental work,[26] we described the cycloaddition of 4,6-dimethyl-1,2,3-triazines with pyrrolidine enamines under microwave irradiation. The reactions take place under microwave irradiation in solvent-free conditions at atmospheric pressure within 20 minutes to afford the corresponding heterocyclic products in 21–71% yield. In all cases we obtained only 2,4-dimethylpyridine derivatives (Scheme 6) and we have not detected any isomeric 2,6-dimethylpyridines. In view of these results two mechanisms are possible: the Diels–Alder reaction, considering the concerted and stepwise paths, and the formation of pyridine *via* the azete intermediate. By studying the reaction mechanism in the gas phase and taking into account solvent effects, we could elucidate why the 2,6-dimethylpyridine is not obtained under our reaction conditions.

Table 1 Activation energies (ΔEa_1 and ΔEa_2, kcal mol^{-1}) and energies of reaction (ΔE_{rxn}, kcal mol^{-1}) of the reaction depicted in Fig. 2 in the gas phase

	ΔEa_1	ΔEa_2	ΔE_{rxn}
HF/3-21G* + ZPVE[a]	114.99	6.44	19.27
HF/6-31G* + ZPVE[a]	116.88	14.42	2.19
B3LYP/6-31G* + ZPVE[a]	95.63	1.32	18.91

[a] The ZPVE corrections, computed at all the levels, are included.

Mechanism *via* azete intermediate

Formation of pyridine *via* an azete intermediate implies the thermal decomposition of a Dewar triazine as the first step. However, although Regitz and coworkers[10] proposed that the thermal decomposition of Dewar triazines produces only nitriles and acetylenes, Ohsawa and coworkers[4] proposed the formation of this azete intermediate by thermal decomposition of the triazine. In order to clarify if this mechanism is operative in our reaction, we studied computationally the reaction profile for the formation of the azete intermediate by thermal decomposition of 4,6-dimethyl-1,2,3-triazine and its subsequent reaction with cyclopentanone pyrrolidine enamine. We selected this enamine in order to minimize the computational cost. The reaction profile, with all its stationary points located at several levels of theory, is depicted in Fig. 2 and the corresponding energies of activation and reaction are shown in Table 1. IRC calculations confirmed that TS0 connects reactants to INT0 and that TS1 connects INT0 with products. Some geometrical parameters are given in Tables 2, 3 and 4.

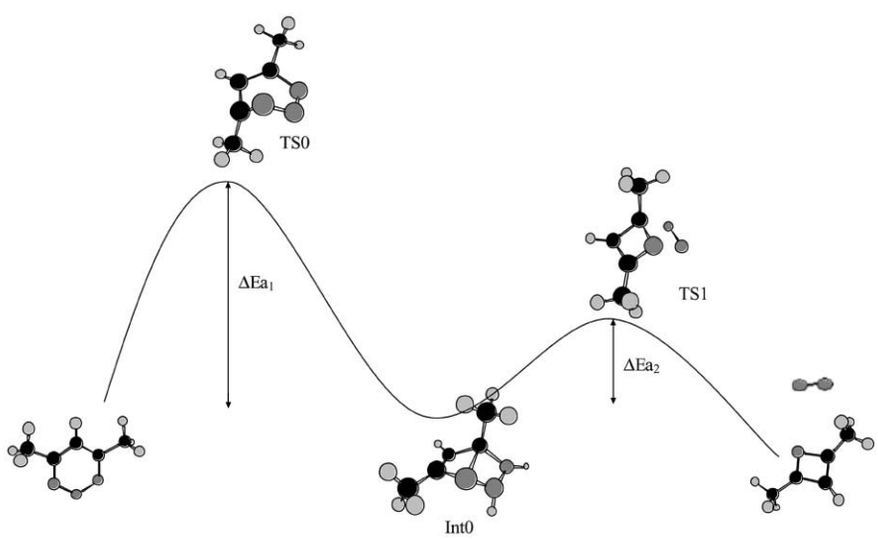


Fig. 2 Reaction profile found for the formation of azete intermediate *via* thermal decomposition of the 4,6-dimethyl-1,2,3-triazine and its reaction with cyclopentanone pyrrolidine enamine at the B3LYP/6-31G* level. Some selected geometrical parameters are shown in Tables 2, 3, and 4.

Table 2 Some geometrical parameters of TS0. Distances are given in Å, angles and dihedral angles in degrees

	d N_1–C_4	*a* N_2–N_1–C_6	*ω* N_1–N_2–N_3–C_4	*ω* N_3–N_2–N_1–C_6
HF/6-31G*	2.110	108.227	−11.057	77.764
B3LYP/6-31G*	2.227	110.259	−12.663	33.764

Table 3 Some geometrical parameters of INT0. Distances are given in Å, angles and dihedral angles in degrees

	d N_1–C_4	*a* N_2–N_1–C_6	*ω* N_1–N_2–N_3–C_4	*ω* N_3–N_2–N_1–C_6
HF/6-31G*	1.490	110.779	−2.577	86.807
B3LYP/6-31G*	1.539	109.259	−2.982	86.485

Table 4 Some geometrical parameters of TS1. Distances are given in Å, angles and dihedral angles in degrees

	d N_1–N_2	*d* N_3–N_4	*a* N_2–N_1–C_6
HF/6-31G*	1.844	1.695	109.014
B3LYP/6-31G*	1.845	1.639	108.802

Table 5 Activation energies (ΔEa_1 and ΔEa_2, kcal mol^{-1}) and energies of reaction (ΔE_{rxn}, kcal mol^{-1}) of the reaction depicted in Fig. 2 in different solvents

Solvent	Theoretical level	ΔEa_1	ΔEa_2	ΔE_{rxn}
Piperidine $\varepsilon = 5.8$	HF/3-21G* + ZPVE[a]	116.56	7.52	51.83
	HF/6-31G* + ZPVE[a]	118.69	14.71	4.83
	B3LYP/6-31G* + ZPVE[a]	96.71	1.39	20.51
Chloroform $\varepsilon = 4.81$	HF/3-21G* + ZPVE[a]	116.46	7.44	51.69
	HF/6-31G* + ZPVE[a]	118.57	14.69	4.67
	B3LYP/6-31G* + ZPVE[a]	96.64	1.39	20.40
ODCB $\varepsilon = 9.93$	HF/3-21G* + ZPVE[a]	116.78	7.69	52.21
	HF/6-31G* + ZPVE[a]	118.97	14.75	5.26
	B3LYP/6-31G* + ZPVE[a]	96.87	1.40	20.75

[a] The ZPVE corrections, computed at all the levels, are included.

Table 6 Activation energies (ΔEa_1 and ΔEa_2, kcal mol^{-1}) and energies of reaction (ΔE_{rxn}, kcal mol^{-1}) of the reaction depicted in Fig. 3 in the gas phase

	ΔEa_1	ΔEa_2	ΔE_{rxn}
HF/3-21G*[a]	34.47	41.92	4.60
HF/6-31G*[a]	46.08	43.08	25.60

[a] The ZPVE corrections, computed at all the levels, are included.

Table 7 Activation energies (ΔEa_1 and ΔEa_2, kcal mol^{-1}) and energies of reaction (ΔE_{rxn}, kcal mol^{-1}) of the reaction depicted in Fig. 3 in different solvents

Solvent	Theoretical level	ΔEa_1	ΔEa_2	ΔE_{rxn}
Piperidine $\varepsilon = 5.8$	HF/3-21G* + ZPVE[a]	36.51	37.19	7.46
	HF/6-31G* + ZPVE[a]	46.85	42.94	23.30
Chloroform $\varepsilon = 4.81$	HF/3-21G* + ZPVE[a]	38.62	37.47	9.52
	HF/6-31G* + ZPVE[a]	47.10	42.97	23.42
ODCB $\varepsilon = 9.93$	HF/3-21G* + ZPVE[a]	36.81	36.60	7.86
	HF/6-31G* + ZPVE[a]	47.11	43.00	23.81

[a] The ZPVE corrections, computed at all the levels, are included.

As demonstrated by the results in Table 1, isomerization of triazine to a Dewar triazine is very energy demanding (≅100 kcal mol^{-1}). The energy of TS0 is so high because of the loss of aromaticity in the triazine. In contrast, the second activation energy is very low and this energy is associated with the loss of nitrogen.

From a structural viewpoint, it can be seen that TS0 and INT0 adopt a butterfly geometry, with the angle N_2–N_1–C_6 being near to 109°.

The next step was to study the solvent effect on this reaction profile and to compare these results with those observed in the gas phase (Table 5). We reoptimized the stationary points using the Onsager model, as implemented in Gaussian 98, with three different solvents. Chloroform and ODCB (*o*-dichlorobenzene) were selected because all of the previously described reactions were performed in these solvents. In contrast, we decided to use piperidine as a solvent for the calculations due to its similarity to pyrrolidine, so we can reproduce more accurately our experimental conditions, because pyrrolidine present as starting material or produced in the reaction can act as a solvent. According to our results (Table 5), the activation energies in the presence of solvent do not vary significantly with respect to those obtained in the gas phase. Indeed, the stabilisations of all the stationary points are in the same order. These data reveal that the activation energies do not vary significantly from one solvent to another. In addition, the geometrical and energetic features are very similar to those obtained in the gas phase. Due to the high activation energy of the first step we conclude that this mechanism does not take place in our reaction.

Mechanism *via* inverse-demand Diels–Alder cycloaddition

We subsequently studied the reaction profile for an inverse-demand Diels–Alder cycloaddition at the HF level and we found that the reaction is predicted to be stepwise at the HF/6-31G* level. The reaction profile for this process and some geometrical features of stationary points TS0b, INT0b and TS1b are depicted in Fig. 3. The corresponding energies of activation and reaction are shown in Table 6.

Harsh conditions (150 °C) were required for the reaction, which is consistent with the large calculated activation energy of about 40 kcal mol^{-1}. We located a polar zwitterionic intermediate INT0b. The positive charge is stabilised by delocalisation on the pyrrolidine nitrogen and the negative charge is delocalised between the triazine nitrogens. This intermediate was only 1–2 kcal mol^{-1} below TS0b. IRC calculations indicate that all the stationary points are connected.

Once again, the introduction of the solvent did not change the reaction profile. Thus, HF(L1A1)/6-31G* calculations also predict a stepwise mechanism. The activation energies are in the same order as those obtained in the gas phase (Table 7).

In all cases the product must evolve to the pyridine ring system by loss of nitrogen and pyrrolidine.

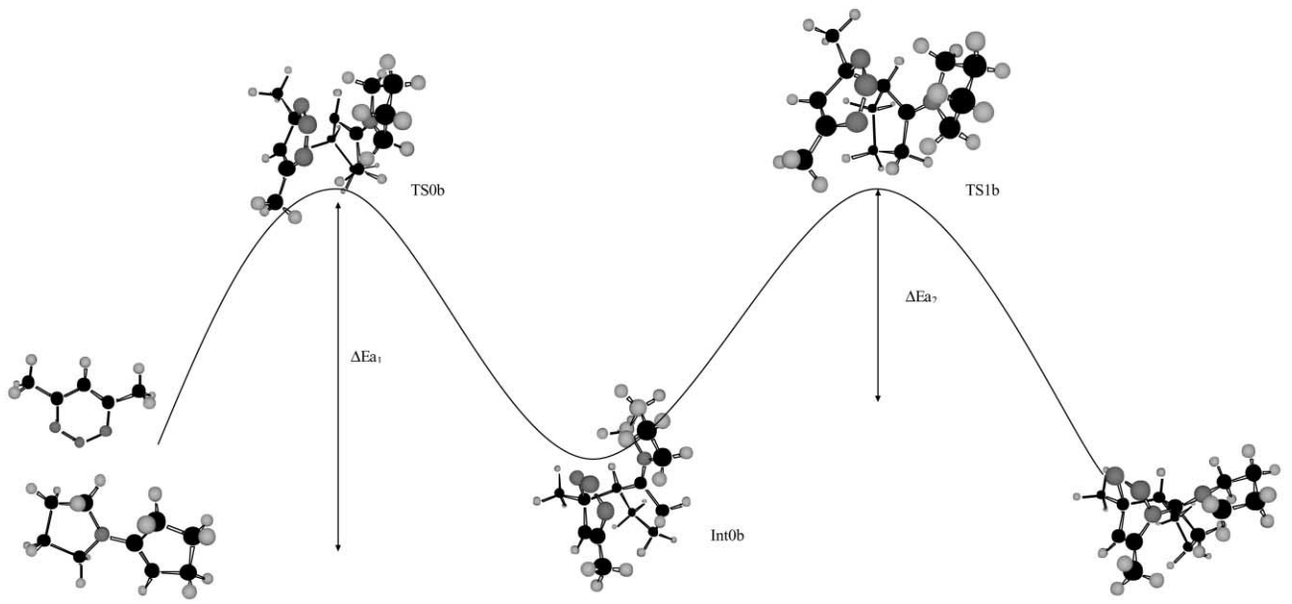


Fig. 3 Reaction profile found for the Diels–Alder reaction between 4,6-dimethyl-1,2,3-triazine and cyclopentanone pyrrolidine enamine at HF/6-31G* level.

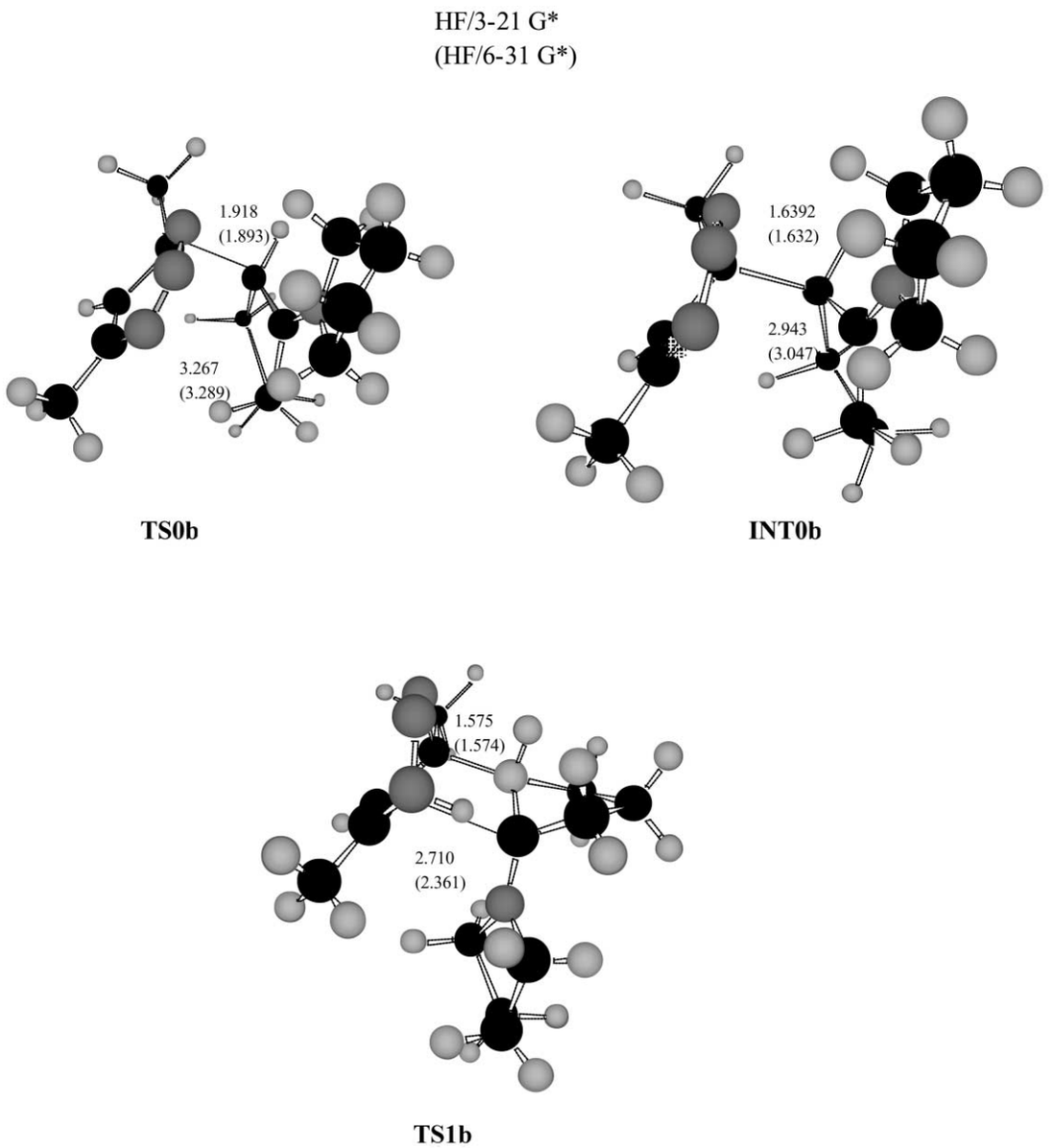


Fig. 4 Stationary points found in the Diels–Alder reaction between 4,6-dimethyl-1,2,3-triazine and cyclopentanone pyrrolidine enamine at the HF/6-31G* level. Bond distances are given in Å.

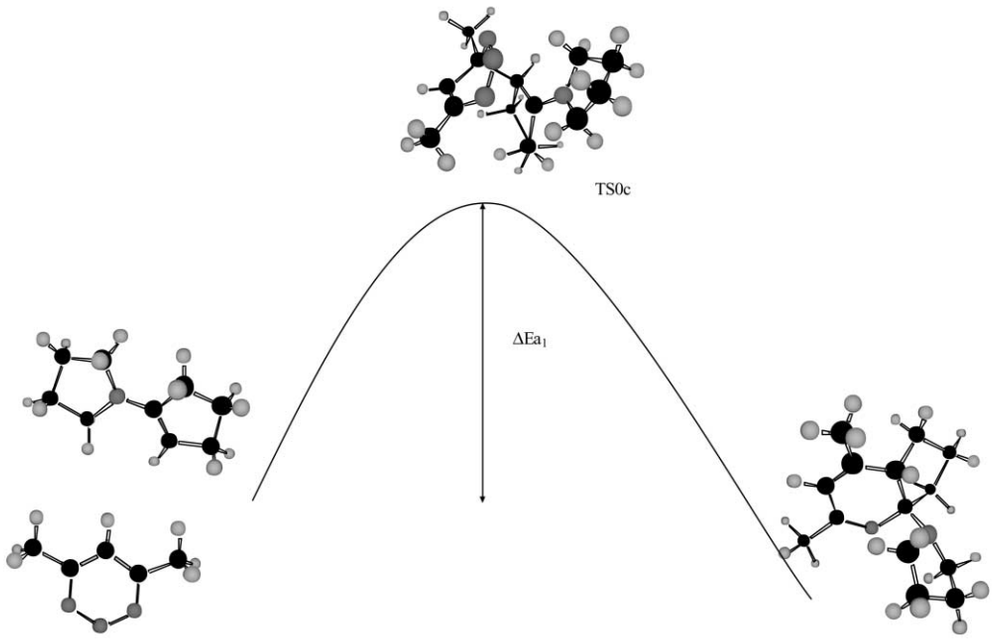


Fig. 5 Reaction profile found in the Diels–Alder reaction between 4,6-dimethyl-1,2,3-triazine and cyclopentanone pyrrolidine enamine at the B3LYP/6-31G* level.

Table 8 Activation energies ($\Delta E a_1$, kcal mol^{-1}) and energies of reaction (ΔE_{rxn}, kcal mol^{-1}) of the reaction depicted in Fig. 5

	Solvent	$\Delta E a_1$	ΔE_{rxn}
B3LYP/6-31G* + ZPVE[a]	—	30.44	−50.54
B3LYP(L1A1)/6-31G* + ZPVE[a]	Piperidine	45.94	−45.71
B3LYP(L1A1)/6-31G* + ZPVE[a]	Chloroform	45.86	−45.86
B3LYP(L1A1)/6-31G* + ZPVE[a]	ODCB	46.11	−45.36

[a] The ZPVE corrections, computed at all the levels, are included.

It is known that Hartree–Fock treatments tend to favour stepwise mechanisms to the detriment of concerted ones. A possible explanation for this lies in the well-known fact that the HF level yields dipole moments that are 10–20% too large.[39–41] B3LYP methods yield more realistic dipole moments and thus the relative stabilities of stepwise and concerted mechanisms are evaluated more accurately.

The exploration of the B3LYP/6-31G* and B3LYP(L1A1)/6-31G* energy hypersurface yields TS0c as the only saddle point connecting reactant and products (see Fig. 4). This situation is confirmed by IRC analysis. This transition state is quite asynchronous, the distance C–C (1.6423 Å) being very close to a standard C–C single bond (Fig. 5). The geometrical parameters found when the three solvents are taken into account are of the same order.

From an energetic viewpoint, the activation energies calculated in the gas phase and in solution are very similar (Table 8). This similarity is in good agreement with the experimental evidence. High temperatures are required to carry out the reaction and, perhaps, this is the reason for the low reaction yields. At the HF level we obtained an intermediate without loss of pyrrolidine and nitrogen. In this case, we obtained a different intermediate at the B3LYP/6-31G* and B3LYP-(L1A1)/6-31G* levels, which corresponds to the loss of nitrogen from the intermediate located at the HF level. Finally, this intermediate leads to the pyridine ring through the loss of pyrrolidine. The reaction is exothermic in all cases.

At present we are carrying out a computational study into the reactions of 4-methyl- and 4-phenyl-1,2,3-triazines with *N*,*N*-diethylprop-1-ynylamine in order to elucidate the process for the formation of pyridazines. We are also studying the reaction between 4,6-dimethyl-1,2,3-triazine and other dienophiles, for example ketene diethyl acetal, in order to find the mechanism leading to the formation of 2,6-dimethylpyridine.

Acknowledgements

Financial support from the Spanish DGI (project BQU2001-1095) is gratefully acknowledged.

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