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Theoretical Study of the Solvent Effects on the Mechanisms of Addition of Dimethyl Acetylenedicarboxylate to 1-Methyl-2-Vinylpyrrole

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Abstract: The molecular mechanisms for the addition of dimethyl acetylenedicarboxylate to 1-methyl-2-vinylpyrrole have been investigated using PM3 semiempirical procedure and *ab initio* method at HF/3-21G basis set level both *in vacuo* and $CHCl_3$ solvent. Two competitive mechanisms can exist *in vacuo*: an asynchronous concerted and a stepwise mechanism. The solvent reaction field was found to have a noticeable effect on the reaction pathways and, in $CHCl_3$ solvent, the two steps mechanism is preferred, suggesting that the solvent is capable of modulating the two possible molecular mechanisms.
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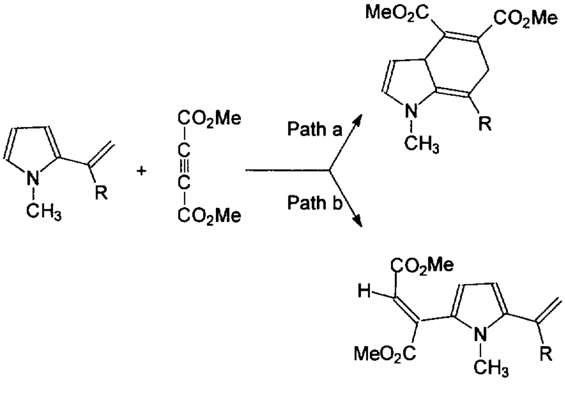
1. Introduction

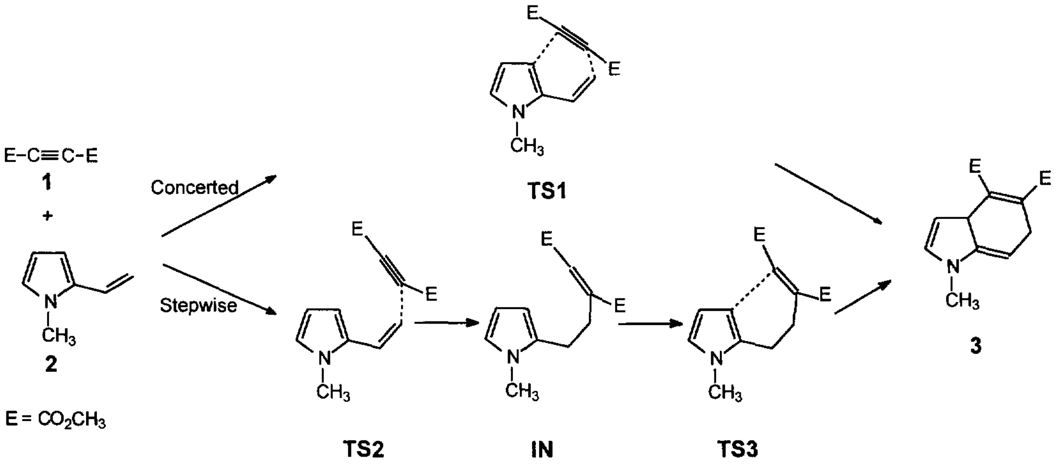
Synthetic applications of the addition reactions of the 1-methyl-2-(1-substituted vinyl)pyrroles with dimethyl acetylenedicarboxylate to yield dihydroindoledicarboxylic esters as a new route to synthezise indole systems have been well documented by Jones et al.[1-3] For these reactions, two alternative pathways have been proposed by these authors involving a Diels-Alder cycloaddition (Scheme 1, path a) and a Michael type addition of the acetylenic diester on the C-5 position of the pyrrole ring (Scheme 1, path b).



Scheme 1. The reaction of dimethyl acetylenedicarboxylate with 1-methyl-2-(1-substituted vinyl)pyrroles.

The course of the reaction mechanism via these alternative paths is dependent on the size and type of the substituent at the 1-position of the pyrrole ring as well as the absence of a substituent (R) at the 1-position of the vinyl substituent.[1-3] In a previous PM3 theoretical study[4] in gas phase we presented the facility of the different substituted-vinylpyrroles and dimethyl acetylenedicarboxylate to act as dienes and dienophile in a Diels-Alder reaction or as nucleophiles and electrophile in a Michael reaction, respectively. These calculations point out that the corresponding transition structures (TSs) associated with the rate limiting step of both competitive molecular mechanisms for Diels-Alder and Michael reactions yield similar activation energies. However, the experimental results were obtained in $CHCl_3$ solution and our calculations corresponded to gas phase or *in vacuo* conditions.

For chemical reactions where changes in polarity between the reactants and TS take place, solvent effects can vary the reaction rate and mechanism.[5] On the other hand, some classes of reactions can be immune to solvent effects if they have isopolar TSs appearing in the reaction pathways. However, these facts are strikingly challenged by experimental observations that simple Diels-Alder reactions show rate accelerations by factors of 10^2-10^4 in aqueous solution over hydrocarbon solvent.[6] Some efforts in our laboratory have been devoted to the theoretical treatment of solvent effects in chemical reactivity studies[7] in order to determine the reaction mechanisms and how the solute-solvent interactions can affect the different barrier heights and the relative energies of reactants, possible intermediates and products on potential energy surface (PES). The computational approach for the theoretical treatment of solvent effects is based on continuum models[8] where the solute is embedded in a cavity while the solvent, treated as a continuous medium having the same dielectric constant as the bulk liquid, is incorporated in the solute Hamiltonian as a perturbation. In this reaction field approach, the bulk medium is polarized by the solute molecules. The electronic distribution of the solute polarizes the continuum which generates an electric field inside the cavity which in turn affects the solute's geometry and electronic structure.

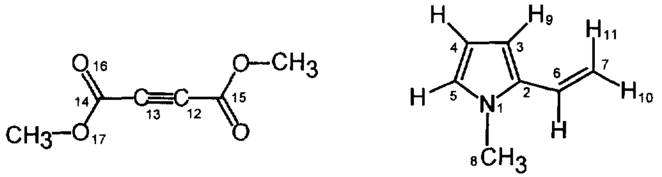


Scheme 2. Schematic representation of the concerted and stepwise mechanisms of the addition of dimethyl acetylenedicarboxylate **1** to 1-methyl-2-vinylpyrrole **2**.

Within the above context, and as a part of a research program devoted to the study of the solvent effects on the molecular mechanisms of different chemical reactions, in this paper we carry out an extensive exploration of the PES *in vacuo* and in $CHCl_3$ solvent for the reaction pathways associated with the addition of dimethyl acetylenedicarboxylate **1** to 1-methyl-2-vinylpyrrole **2**, corresponding to competitive Diels-Alder and Michael reactions yielding the same product **3** (Scheme 2). The paper is organized as follows: the methods, model and computing procedures are briefly described in section 2. In section 3, the results for the different reactive pathways are presented and discussed. Finally, our main conclusions are summarized in section 4.

2. Methods, Model and Computing Procedures

PM3[9] semiempirical calculations were carried out using the MOPAC93 program[10] while the *ab initio* method at HF/3-21G basis set level has been performed with GAUSSIAN 94 series of programs.[11] The large size of the system prevents its study at higher level of theory. Nevertheless, deciding the level necessary for an accurate description of a reactive PES is still a demanding task. Recently, Borden and Davidson[12] discussed the importance of the selection of the computational method necessary to obtain an accurate description of chemical reactions, including the Diels-Alder addition. The PESs have been calculated in detail to ensure that all relevant stationary points have been located and properly characterized. Stationary points on PES were characterized by frequency calculations. The exact characterization of the TSs was achieved using a simple algorithm developed by us.[13] The optimization was carried out using an eigenvalue following routine[14] and the Berny analytical gradient optimization method.[15] Finally, the nature of each stationary point was established by calculating analytically and diagonalizing the matrix of the energy second derivatives to determine the number of imaginary frequencies, zero for local minimum and one for a TS. The transition vector (TV) ,[16] i.e., the eigenvector associated to the unique negative eigenvalue of the force constant matrix has been characterized. The Intrinsic Reaction Coordinate (IRC) pathways from the TSs to the two lower energy structures have been traced using the second order Gonzalez and Schlegel integration method,[17] in order to verify that each saddle point links the two putative minima. Atoms numbering for the selected models **1**, dimethyl acetylenedicarboxylate, and **2**, 1-methyl-2-vinylpyrrole, are depicted in Figure 1.



1 **2**

Figure 1. Atoms numbering for the structures **1** and **2**.

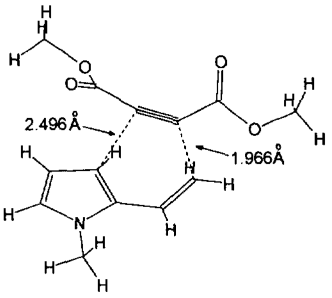
Electrostatic interactions with the surrounding solvent can be expected to constitute a decisive factor when ionic and polar species are concerned in the reaction mechanism. The differential stabilization of one reaction path with respect to the other could indeed change the relative order obtained in gas-phase calculation.[7] The solvent effects have been considered by means of continuum models. In these procedures the solvent is assimilated to a continuous medium characterized by the dielectric constant (ε) which surrounds a molecular-shaped cavity in which the solute is placed. We have used the dielectric constant at 298 K, ε=4.80, for the $CHCl_3$. Recently, Tomasi and Persico[8] have presented an overview of methods based on continuous distributions of the solvent. In particular, several applications of this method have been proved to be quite successful in reproducing the general features of a number of Diels-Alder and related reactions.[18-20] We have included electrostatic solvent interaction in our study of the reaction mechanisms, thereby attempting to identify the influence of the solvent on the reaction pathways.

The geometry optimization for the stationary structures on PES including solvent effects has been carried out at PM3 semiempirical level using the Conductor-like Screening Model (COSMO) option[21] included in the MOPAC93 package program.[10] This COSMO model, proposed by Klamt and Schüürmann,[21] calculates the electrostatic solvation energy by representing the solute charge distribution as a set of point charges and dipoles in the neglect differential diatomic overlap formalism. Bulk solvent effects at *ab initio* level have been taken into account by means of the cavity model developed by Tomasi et al.[22] The cavity chosen for the calculations was the solvent-excluded surface obtained by overlapping spheres. As usual, the radii of the initial spheres are 20% larger than the van der Waals radii (R_O=1.68Å, R_C=1.96Å, R_N=1.80Å, and R_H=1.44Å).

3. Results and Discussion.

3.1. PES in vacuo.

In a study of a chemical reaction it is important to realize that the finding of one TS does not exclude the possibility of alternative reaction paths having other TSs. In order to discriminate between alternative reaction channels, an extensive exploration of the PES by means of PM3 and *ab initio* HF/3-21G methods of the addition reaction of **1** to **2** has rendered three TSs: **TS1** (concerted mechanism) and **TS2** and **TS3** (stepwise mechanism), see Scheme 2. The **TS1** and **TS2** can be assigned to Diels-Alder and the first step of Michael additions, respectively. Figures 2 and 3 show the **TS1**, **TS2**, **TS3** and intermediate, **IN**, while Tables 1 and 2 gather the results of the geometries and the TV for the **TS1**, **TS2** and **TS3** obtained with PM3 and HF/3-21G calculations.



TS1

Figure 2. **TS1** geometry obtained with the HF/3-21G calculations.

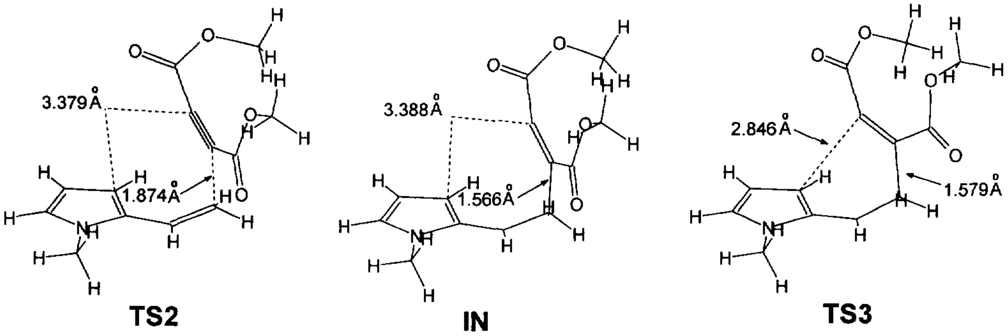


Figure 3.TS2, IN and **TS3** geometries obtained with the HF/3-21G calculations.

The **TS1** for the concerted mechanism corresponds to an asynchronous Diels-Alder cycloaddition. The values for C7-C12 and C3-C13 bond lengths are 2.057 and 2.214 Å (PM3) and 1.966 and 2.496 Å (HF/3-21G), respectively. This asynchronicity is due to the loss of aromaticity of the pyrrole ring and a considerable steric π-π repulsion between the carboxylate group of **1** and the aromatic pyrrole ring in the **TS1**. The *ab initio* result yields greater asynchronicity than PM3 data. Similar results have been found in the literature for related systems.[23-26] The components of the TV of the **TS1** are mainly associated with C7-C12 and C3-C13 bond lengths. The diagonal force constants are positive and the negative eigenvalue arises from the cross terms in the Hessian matrix.

The values for C7-C12 and C3-C13 bond lengths for the **TS2** are 1.730 and 3.280 Å (PM3) and 1.874 and 3.379 Å (HF/3-21G), respectively. The dominant component of the TV is associated to the C7-C12 bond length. Also the diagonal force constants are positive and the negative eigenvalue arises from the cross terms in the Hessian matrix, being the force constant value for the C7-C12 bond making very low. A similar TS has

Table 1. Selected geometrical parameters (**G**), imaginary frequency (cm^{-1}), eigenvalue, force constants in a.u. (**F**) and the corresponding eigenvector (**C**) associated with the unique negative eigenvalue for **TS1** and **TS2** obtained with PM3 and HF/3-21G calculations *in vacuo*.

	PM3						HF/3-21G					
	TS1			TS2			TS1			TS2		
Imaginary Frequency	720.70i			530.83i			537.04i			449.82i		
Eigenvalue	-0.113970			-0.061676			-0.06625			-0.06022		
Variables:	C	G	F	C	G	F	C	G	F	C	G	F
C2-C6	-0.12	1.402	1.60	-0.09	1.403	1.25	-0.12	1.381	1.50	-0.10	1.398	0.95
C6-C7	0.15	1.378	0.84	0.16	1.406	0.60	0.16	1.386	0.70	0.15	1.386	0.55
C7-C12	-0.64	2.057	0.15	-0.88	1.730	0.14	-0.76	1.966	0.15	-0.78	1.874	0.17
C3-C13	-0.54	2.214	0.14	-0.09	3.280	0.06	-0.41	2.496	0.16	-0.10	3.379	0.06
C15-C12-C7	0.26	98.7	0.18	0.21	107.2	0.28	0.16	109.1	0.48	0.17	103.9	0.52
C14-C13-C3	0.27	97.9	0.15	0.11	86.4	0.05	0.21	88.5	0.13	0.35	109.5	0.04
H9-C3-C2-N1	0.17	-156.4	0.08	-0.01	176.4	0.06	0.12	-169.9	0.09	-0.03	180.2	0.08
H10-C7-C6-C2	0.03	175.0	0.10	0.17	-159.1	0.15	0.08	177.1	0.14	0.19	-167.5	0.15
H11-C7-C6-C2	-0.23	-33.2	0.10	-0.19	-26.9	0.14	-0.28	-35.6	0.15	-0.16	-19.6	0.14

Table 2. Selected geometrical parameters (G), imaginary frequency (cm^{-1}), eigenvalue, force constants in a.u. (F) and the corresponding eigenvector (C) associated with the unique negative eigenvalue for **TS3** obtained with PM3 and HF/3-21G calculations *in vacuo*.

	PM3			HF/3-21G		
Imaginary Frequency		93.37i			52.47i	
Eigenvalue		-0.009331			-0.006100	
Variables:	**C**	**G**	**F**	**C**	**G**	**F**
C3-C13	-0.89	2.847	0.07	-0.76	2.848	0.12
H9-C3-C2-N1	0.13	-178.9	0.06	0.20	-177.3	0.08
H10-C7-C6-C2	-0.16	-167.3	0.17	-0.18	-166.8	0.21
H11-C7-C6-C2	-0.18	-43.6	0.16	-0.21	-41.6	0.20
C12-C7-C6-C2	-0.19	74.5	4.68	-0.21	76.4	4.84
C15-C12-C7-C6	0.17	115.9	0.08	0.28	107.2	0.09
O16-C14-C13-C3	0.03	86.0	0.08	0.27	63.9	0.15
O17-C14-C13-C3	0.05	-88.9	0.09	0.26	-108.8	0.20

been reported in a preceding paper by us (see Figure 1 in ref. 4) for the electrophilic attack of dimethyl acetylenedicarboxylate to C5 atom of the 1-methyl-2-vinylpyrrole. The second step, corresponding to the transformation from the intermediate **IN** to **3**, presents a minuscule barrier: 0.5 and 0.9 kcal/mol for PM3 and *ab initio* methods, respectively; the corresponding **TS3** is located on a flat quadratic zone of the PES (negative eigenvalue 50i cm^{-1}) and its structure is very similar to **IN**. The hypersurface is very flat in the area of **TS2**, **IN** and **TS3** (Figure 5a). Thus, a small variation of energy leads to a significant variation of the geometry, and this fact can explain the unsatisfactory agreement between semiempirical and *ab initio* TS geometries. Clearly, at these levels of theory the intermediate **IN** collapses to the product with little or no activation. The rate limiting step for addition process is the first step corresponding to the formation of the intermediate.

The concerted pathway for the addition process is energetically favourable (Figure 5a). The difference of barrier heights between **TS2** and **TS1** are 0.4 and 3.8 kcal/mol for PM3 and HF/3-21G calculations, respectively. Recently, Jursic[25] has carried out an AM1 semiempirical study of the reactivity of thiophenes as dienes in Diels-Alder reactions, showing that when strong dienophiles such as tetracyanoethene are used, the possibility of a two step mechanism appears on calculated PES for the cycloaddition but their associated energy is approximately 5 kcal/mol larger than the corresponding to the concerted mechanism, in agreement with our present calculations.

Until now, the study was performed solely at RHF level and in order to estimate the biradical character associated with the stepwise mechanism, the inclusion of UHF is mandatory. It would be necessary to use a procedure able to deal reliably with biradicals. It is well known that RHF procedure predicts energies for biradical-like species much too positive while UHF treatment favour biradical structures. Furthemore, the semiempirical methods tend to overestimate the stability of biradicals.[27] To study the possible biradical character of the nonconcerted addition mechanism, it is therefore necessary to use an appropriate open shell treatment. Following the method proposed by Pople et al.,[28] the energy difference between RHF and UHF total energies has been calculated. The RHF wavefunction has an instability and the UHF singlet energy can fall below the RHF quantity and this value is a measure of the biradical character of a given system. We have estimated the biradical character of the nonconcerted **TS2** in order to compare it with the concerted **TS1**.

Calculations without any symmetry restrictions at UHF/3-21G level have been carried out. E(RHF)-E(UHF) difference for **TS2** is 10.5 kcal/mol, showing a significant biradical character of the involved species. The biradical character of these stationary points was ensured by analyzing the spin density matrices and the $<S^2>$ value is 1.4. The total energy for **TS1** obtained at UHF level is identical with the RHF one while the **TS2** has lower energies than **TS1**; the pathway via **TS2** is energetically favoured with respect to the one step process via **TS1**. However, for **IN**, the E(RHF)-E(UHF) difference and the $<S^2>$ value are 0.0, showing that the RHF wave function is an appropriate solution and the zwitterionic character of this intermediate. These results show that, in gas phase, both alternative reaction pathways are accessible.

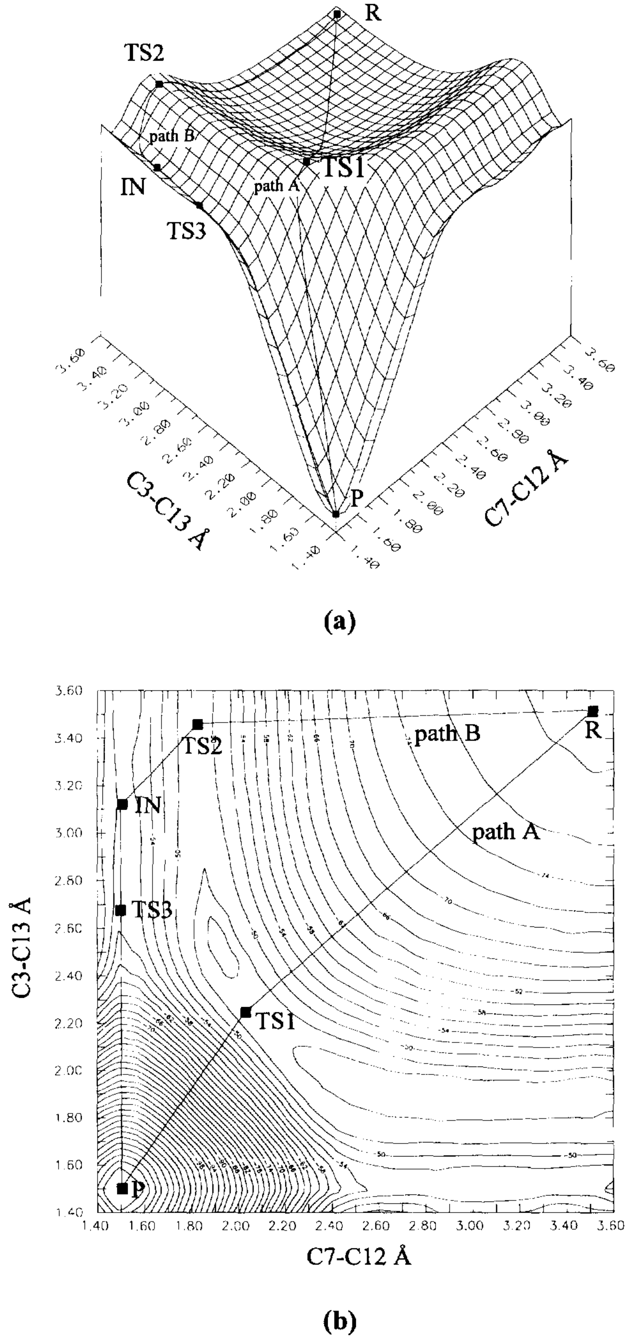
One step further implies understanding the electronic charges undergone by the different fragments, dimethyl acetylenedicarboxylate and 1-methyl-2-vinylpyrrole, along the competitive pathways. For this purpose, we have performed a natural population analysis. The results obtained with the HF/3-21G method show that the quantity of charge transfer at **TS1**, **TS2**, **IN** and **TS3** are 0.28, 0.43, 0.78 and 0.72 a.u., respectively; while the dipole moments obtained at HF/3-21G level for **TS1**, **TS2**, **IN**, **TS3** and product **3** are 4.88, 6.76, 10.91, 9.75 and 2.70 Debye, respectively. These results show that a large charge separation is involved along the stepwise mechanism; therefore, the reaction rate and nature of molecular mechanism should be influenced by the polarity of solvent.

3.2 Solvent Effects Calculations.

Solvent effects on Diels-Alder cycloaddition are well known[29-31] and have received considerable attention especially in the last few years because these studies can clarify the role of the solvent on Diels-Alder mechanism[32-34] or related pericyclic reactions.[35,36] The next step in our investigation was to study the solvent effects on the basic features of the molecular mechanisms for the addition of the dimethyl acetylenedicarboxylate to 1-methyl-2-vinylpyrrole. A pictorial representation of the PES in $CHCl_3$, as a function of the forming C3-C13 and C7-C12 bonds, including the position of the stationary points, is depicted in Figure 4. Table 3 shows the selected geometrical parameters of the **TS1**, **TS2**, **IN** and **TS3** stationary points *in vacuo* and with inclusion of the solvent effect. An analysis of the results indicates that there are no large modifications in the geometry for these points, in accordance with the hypothesis of Tomasi et al.[37] that in

Table 3. Selected geometrical parameters of the **TS1**, **TS2**, **IN** and **TS3** stationary points obtained with PM3 calculations *in vacuo* and in $CHCl_3$.

		C6-C7	C2-C6	C2-C3	C3-C13	C12-C13	C7-C12
TS1	in vacuo	1.378	1.402	1.421	2.214	1.241	2.057
	$ClCH_3$	1.381	1.402	1.424	2.267	1.242	2.024
TS2	in vacuo	1.406	1.404	1.418	3.280	1.247	1.729
	$ClCH_3$	1.396	1.406	1.422	3.472	1.239	1.833
IN	in vacuo	1.439	1.387	1.429	3.577	1.268	1.578
	$ClCH_3$	1.476	1.356	1.458	3.135	1.291	1.515
TS3	in vacuo	1.471	1.344	1.431	2.848	1.313	1.579
	$ClCH_3$	1.474	1.356	1.458	2.673	1.299	1.518



(a)

(b)

Figure 4. Potential energy surface of the addition reaction of dimethyl acetylenedicarboxylate **1** with 1-methyl-2-vinylpyrrole **2** (PM3/$CHCl_3$ results): tridimensional (a) and bidimensional (b) representations. The reactants (**R**), different TSs, intermediate (**IN**) and product (**P**) are located in the surfaces.

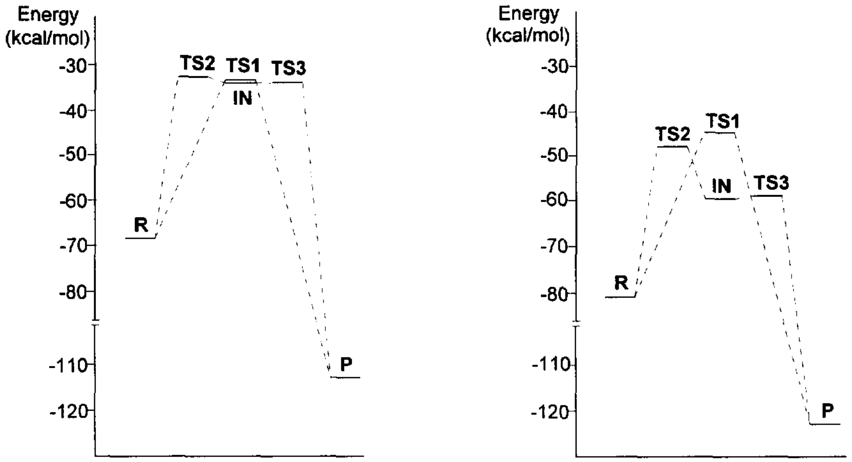
Table 4. PM3 heats of formation (kcal/mol) and HF/3-21G total energies (a.u.) of the stationary points of the concerted and stepwise mechanisms for the addition of **2** to **1** in vacuo and in $CHCl_3$. ΔE corresponds to the energy difference (kcal/mol) between the in $CHCl_3$ and *in vacuo* values.

	PM3			HF/3-21G		
	in vacuo	$ClCH_3$	ΔE	*in vacuo*	$ClCH_3$	ΔE
1	-108.17	-118.63	-10.46	-527.130127	-527.143901	-8.64
2	40.54	36.90	-3.64	-322.917801	-322.923472	-3.56
TS1	-33.30	-45.25	-12.31	-849.994379	-850.016605	-13.95
TS2	-32.94	-47.82	-14.88	-849.987701	-850.016437	-18.03
INT	-33.78	-62.19	-28.41	-849.999617	-850.040090	-25.40
TS3	-33.12	-61.74	-28.62	-849.997772	-850.036014	-24.00
3	-112.45	-123.48	-11.03	-850.114306	-850.132443	-11.38

the case of minima, the approximation of frozen geometries can often be considered as adequate. Although this can be more questionable in the case of TSs, only small modifications for the geometry of TSs in solution are detected. Similar results have been found by Ruiz-López et al.[20] in the study of the solvent effects on chemical reactivity for related systems. For this reason, HF/3-21G solvent effect calculations have been carried out on the gas phase geometries.

In Table 4, we report the PM3 calculated heats of formation and the HF/3-21G total energies of the optimized geometries of the stationary points without and with solvent effects. In Figure 5, a schematic representation of the PM3 energies of the optimized stationary points for the concerted and stepwise mechanisms either *in vacuo* (a) or in $CHCl_3$ (b) is depicted.

The inclusion of the solvent effects appears to be both qualitatively and quantitatively significant. The Table 4 shows a larger stabilization in the reactants for the dimethyl acetylenedicarboxylate **1** (*ca.* -10 and -9 kcal/mol for PM3 and HF/3-21G calculations, respectively) than for the 1-methyl-2-vinylpyrrole **2** (*ca.* -4 kcal/mol) due to the presence of two polar carboxylate groups. This stabilization is present also in **TS1**, **TS2**, **IN**, **TS3** and **3**. However, the **TS2** shows a larger stabilization with inclusion of solvent effects (*ca.* -15 and -18 kcal/mol for PM3 and HF/3-21G calculations, respectively) than **TS1** (*ca.* -12 and -14 kcal/mol for PM3 and HF/3-21G calculations, respectively). If solvent effects are included, the two step mechanism is more energetically favourable than the concerted pathway. This solvent stabilization is very large for the **IN** (*ca.* -28 and -25 kcal/mol for PM3 and HF/3-21G calculations, respectively), showing the large polar character of this intermediate. These results are related with the larger charge transfer along the reaction pathway of the stepwise mechanism, as shown by the large increment of the dipole moments for this mechanism, which is stabilized with the solvent effect inclusion. Although the **TS2** has a biradical character, due to the fact that the biradical species are very polarizable,[38] perturbations like the solvent effects can convert this biradical-like systems into stable species.[39] Thus, the main factor resulting from solvent effect inclusion is the acceleration of the stepwise mechanism with respect to the one step mechanism for the Diels-Alder reactions involving polar reactants.



(a) (b)

Figure 5. Schematic representation of the PM3 energies (heat of formation) of the optimized stationary points of the concerted and stepwise mechanisms of the addition of **1** to **2**: (a) *in vacuo* and (b) in $CHCl_3$.

4. Conclusions

In this study, we have carried out a theoretical study of the solvent effects on the reaction profiles for the addition of dimethyl acetylenedicarboxylate to 1-methyl-2-vinylpyrrole. Reaction pathways in both gas phase and $CHCl_3$ continuum solvent were calculated using the PM3 semiempirical and HF/3-21G *ab initio* methods. The specific details of the global process may change at higher levels of theory (e.g. CASSCF treatment), but despite the approximate procedure of the calculations employed here, some important features were clarified. The following conclusions can be drawn from the results reported in this study:

1) Concerted and stepwise molecular mechanisms can exist concurrently for the addition of the dimethyl acetylenedicarboxylate to 1-methyl-2-vinylpyrrole *in vacuo* and in $CHCl_3$ solvent.
2) For the stepwise mechanism, there is a well on PES corresponding to the intermediate with pronounced zwitterionic character. The formation of this intermediate is the rate limiting step.
3) The barrier heights for both concerted and stepwise mechanisms *in vacuo* and in $CHCl_3$ are similar.
4) *In vacuo*, the stepwise mechanism shows a very flat PES on the first TS and intermediate. Slight structural alterations result in a "downhill" movement of the intermediate to the product of cycloaddition.
5) The inclusion of solvent effects by means of continuum methods changes the relative order of stability of both reaction pathways; the PM3 and *ab initio* results show a preference for the two step mechanism. The magnitude of solvent effect stabilization along the competitive channels is related to the dipole moments corresponding to the stationary structures.
6) This study points out the importance of including the electrostatic solvent effects for Diels-Alder additions with high asynchronicity, where a stepwise mechanism involving polar species is possible.

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