Pergamon

Tetrahedron Vol. 51, No. 32, pp. 8739-8748, 1995
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0040-4020/95 $9.50+0.00

0040-4020(95)00490-4

Theoretical Study of the Reaction of Dimethyl Acetylenedicarboxylate with 1-Methyl-2-(1-substituted vinyl)pyrroles

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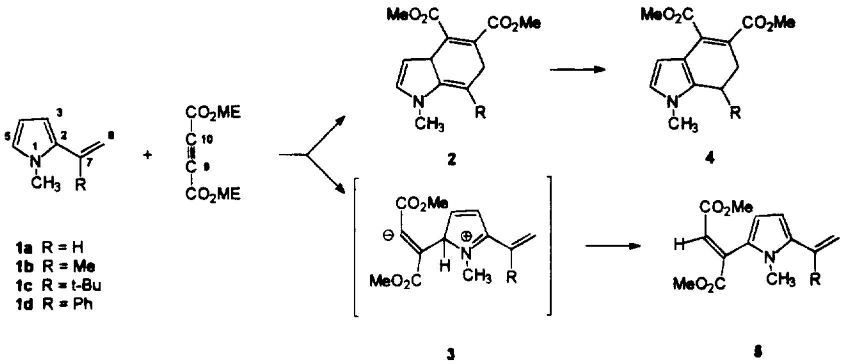
Abstract: A theoretical study of the transition structure for the electrophilic attack step of the 1-methyl-2-vinylpyrrole to dimethyl acetylenedicarboxylate is reported with analytical gradients at AM1 and PM3 semi-empirical levels and *ab initio* at 3-21G level. The geometry, electronic structure, and vector components are qualitatively computer level and model independent.
The competition of the Michael addition reactions and Diels-Alder reactions of 1-methyl-2-(1-substituted vinyl)pyrroles with dimethyl acetylenedicarboxylate has been studied at the PM3 semi-empirical level.

Introduction

In previous work[1,2] we have described synthetic applications of the Diels-Alder reaction of 2-vinylpyrroles with dimethyl acetylenedicarboxylate (DMAD) to yield dihydroindoledicarboxylic esters **1** → **4**. We also reported that, in several instances, an alternate reaction pathway involving the Michael addition of the acetylenic diester to the pyrrole ring **1** → **5** was followed.[1,3] We noted that the different pathways were dependent upon the steric and electronic effects of substituents at the 1-position of the pyrrole ring and/or on the vinyl group (Table 1).[1]



Scheme 1

Table 1. Reaction of 1-methyl-2-(1-substituted vinyl)pyrroles with dimethyl acetylenedicarboxylate in $CHCl_3$ at 20°C[1]

Vinylpyrrole	Reaction Time (hours)	% Yield of Michael Adduct **5**	% Yield of Diels-Alder Adduct **2**
1a	4	29	21
1b	3	39	0
1c	20	44	0
1d	7	62	38

In this paper we report a theoretical study of the transition structure for electrophilic attack at the α-position of a pyrrole ring by DMAD, which has not been reported before. The transition structures for the Diels-Alder reaction of DMAD with 1-methyl-2-(1-substituted vinyl)pyrroles has also been studied in order to rationalise the experimental results.

Computational Methods

Semi-empirical calculations, AM1[4] and PM3[5], were carried out using the MOPAC93[6] programme and *ab initio* calculations have been performed with GAUSSIAN92[7] at 3-21G basis set level.[8]

The calculations of the ground structures and transition states of the Michael and Diels-Alder reactions for the vinylpyrroles **1a-1d** with DMAD were performed using the PM3 and the full geometry optimisation was carried out at RHF level. The molecular geometries of the transition structures, at semi-empirical level, were optimised using the TS routine.[9] Stationary points on the energy hypersurfaces were located by minimising the gradients of energy to 0.5. The nature of each of these stationary points was established by calculating analytically and diagonalizing this matrix of second derivatives of energy to determine the unique imaginary frequency (0.0 for a local minimum and 1.0 for a transition state).

All calculations were performed on a IBM POWER PC-250 workstation at the Department de Quimica Orgànica, Universitat de Valencia.

Results and Discussion

(a) Study of the transition structure for the electrophilic attack of the 1-methyl-2-vinylpyrrole to DMAD.

The transition structure (Figure 1) for the electrophilic attack of DMAD on 1-methyl-2-vinylpyrrole was fully characterised. Tables 2 - 4 present the most characteristic data for the geometries and the transition vectors[9] of the saddle point obtained by semi-empirical (AM1 and PM3) and *ab initio* (at 3-21G basis set level) calculations. Figure 2 illustrates the reaction profile obtained by the two semi-empirical methods showing that the activation energies calculated by the two procedures are very similar.

Several features relating to the formation of the transition state for the electrophilic attack on the vinylpyrrole by DMAD are critical to the course of the reaction: (i) The transition vector yields very concisely the essentials of the chemical process under study.[10] The formation of a new bond between C5 and C9 requires a simultaneous change in hybridisation of C5 from sp^2 to sp^3 and of C9 from sp to sp^2. (ii) The presence of the carboxyl group on C9 is necessary for the Michael addition reaction; the reaction of **1a** with methyl propiolate does not lead to a Michael adduct.[1] It appears that the carboxyl group can delocalise the charge generated in the formation of the zwitterion **3**, as seen by the similar higher electron density on C12 and C11, thereby stabilising the TS. (iii) The preferred conformation of TS is determined by a maximum overlap between the highest occupied (HOMO of **1a**) and the lowest unoccupied (LUMO of DMAD) molecular orbitals.[11] (iv) The comparative analysis of the semi-empirical and *ab initio* results obtained for this TS confirms the geometrical invariance of structure and the capability of the semi-empirical approaches. (v) The activation energy, calculated using the PM3 method, for the electrophilic attack of DMAD on the vinylpyrrole **1a** (34.59 kcal) is of the same order as that needed for the Diels-Alder reaction (34.46 kcal). These results are compatible with the observed formation of both Michael and the Diels-Alder adducts in *ca.* 1:1 ratio.[2]

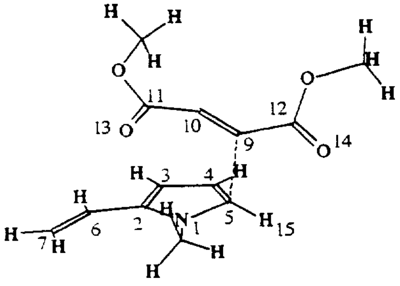


Figure 1. 3-21G Transition structure for the electrophilic attack of DMAD on 1-methyl-2-vinylpyrrole.

Table 2. Selected geometric parameters for the transition structure for the electrophilic attack of DMAD on 1-methyl-2-vinylpyrrole, calculated using AM1, PM3 and 3-21G.

	AM1	PM3	3-21G
Distance (Å)			
C4-C5	1.463	1.459	1.426
C5-C9	1.806	1.747	1.894
C9-C10	1.240	1.245	1.250
Bond Angles (°)			
C5-C9-C10	118.54	118.56	120.1
C5-C9-C12	103.33	105.68	103.0
H15-C5-C4	122.25	119.10	125.1
C9-C5-C4	102.80	105.80	97.3
Dihedral Angle (°)			
H15-C5-C4-N1	133.54	128.28	143.9
N1-C5-C9-C10	-19.53	-20.37	-20.6
C7-C6-C2-C3	16.4	-0.10	46.7

Table 3. Net atomic charges for the transition structure for the Michael addition of DMAD with 1-methyl-2-vinylpyrrole

	AM1	PM3
N1	-0.10	0.34
C9	0.02	0.05
C10	-0.37	-0.48
C11	0.42	0.52
C12	0.37	0.43

Table 4. Imaginary frequency (cm^{-1}), eigenvalue, force constants (F in a.u.) and the corresponding eigenvector (C) associated with the unique negative eigenvalue for the transition state for the Michael addition of DMAD with 1-methyl-2-vinylpyrrole, using AM1, PM3 and 3-21G level calculations.

	AM1		PM3		3-21G	
Imaginary Frequency	628.28i		493.01i		520.58i	
Eigenvalue	-0.08000		-0.05068		-0.05215	
Variables	C	F	C	F	C	F
C4-C5	-0.122	0.831	-0.119	0.778	-0.129	0.720
C5-C9	0.872	0.024	0.881	0.026	0.778	0.064
C9-C10	-0.098	1.009	-0.102	0.969	-0.137	0.875
C5-C9-C10	-0.173	0.397	-0.158	0.325	-0.162	0.817
C5-C9-C12	-0.198	0.334	-0.206	0.265	-0.132	0.533
H15-C5-C4	0.133	0.184	0.134	0.191	0.114	0.231
H15-C5-C4-N1	0.238	0.153	0.255	0.132	0.335	0.12

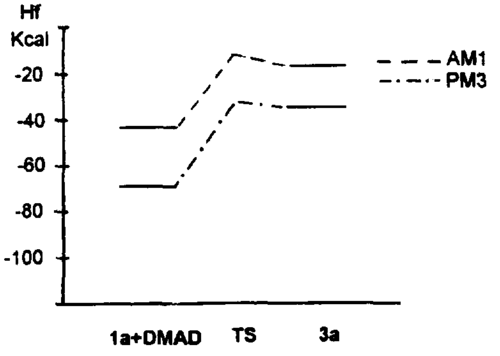


Figure 2. Reaction profile for the electrophilic attack of DMAD on 1-methyl-2-vinylpyrrole.

(b) Comparative study of the Michael and Diels-Alder reactions of DMAD with the vinylpyrroles

Using PM3 calculations, the optimal geometries of the four vinylpyrroles and of the corresponding TS of the Diels-Alder reaction were acceptable, but the activation energies calculated for the cycloaddition reactions of the three substituted vinylpyrroles **1b-1d**, when compared with the value obtained for 1-methyl-2-vinylpyrrole **1a**, did not correlate in all respects with the observed experimental results (Table 5). However, the activation energies calculated for the formation of the TS for the Michael reaction of the four vinylpyrroles were shown to be very similar; this is a consequence of the substituents on the vinyl group exerting little steric influence on the reaction as they are further from the reactive C-5 site on the pyrrole ring (Figure 4).

Table 5. PM3 energy (kcal mol^{-1}) for the reaction of DMAD with 1-methyl-2-(1-substituted vinyl)pyrroles.

	Diels-Alder reaction			Michael reaction	
Pyrrole	Ground State Energy	Transition State Energy	Activation Energy (Ea)	Transition State Energy	Activation Energy (Ea)
1a	-67.77	-33.31	34.46	-33.18	34.59
1b	-75.97	-42.23	33.74	-41.37	34.60
1c	-88.15	-50.86	37.29	-54.75	33.40
1d	-40.01	-7.78	32.23	-5.77	34.23

In order to explain the observed experimental results and because the energies obtained for the transition structures, as calculated by semi-empirical methods, are very similar, it was necessary to examine the geometries for the different structures. However, in the first instance, we determined the ground state geometries of the vinylpyrroles (Figure 3). For 1-methyl-2-vinylpyrrole **1a**, the vinyl group is coplanar with the pyrrole ring. This geometry has maximum delocalisation between the π-systems of the pyrrole ring and of the vinyl group and it differs from those of the 1-methyl-2(substituted vinyl)pyrroles **1b** and **1c**, where the vinyl groups are twisted (57.0° and 61.6°, respectively). The non-coplanar conformations of the vinyl groups and the pyrrole ring result from repulsive interactions between the 1-methyl group and the substituents in the vinyl group, particularly for **1c**. In contrast, the vinyl group and the pyrrole ring of **1d** are coplanar, as the phenyl group adopts a perpendicular conformation to the plane of the vinyl group. Consequently, although the phenyl group may exert an electronic effect upon the reaction, it does not interact sterically with the 1-methyl group.

Comparison of the transition structures for the Diels-Alder reaction shows that the geometries for the four systems are very similar (Figure 4 and Table 6). All the geometries show an asynchronous TS with bond distances of *ca.* 2.02Å between the C-8 of the vinyl group and the C-9 of the DMAD, and bond distances of *ca.* 2.25 Å between the C-3 of the pyrrole ring and C-10 of the DMAD. For maximum interaction, the reactive dienic system should be coplanar, which requires the 1-methyl group and the substituent on the vinyl group to be in the same plane, resulting in steric interactions when these substituents are bulky.

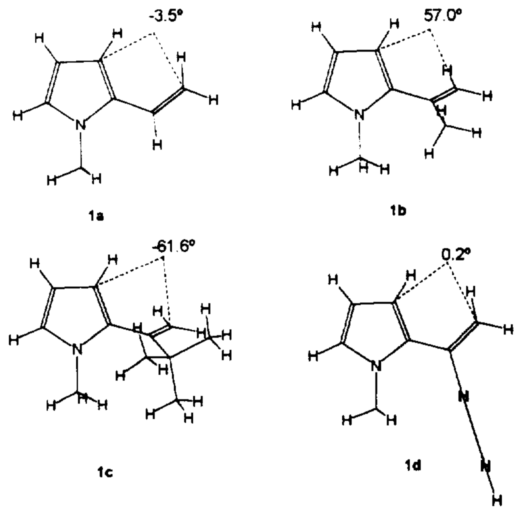


Figure 3. Geometry of the ground states of 1-methyl-2-(1-substituted vinyl)pyrroles

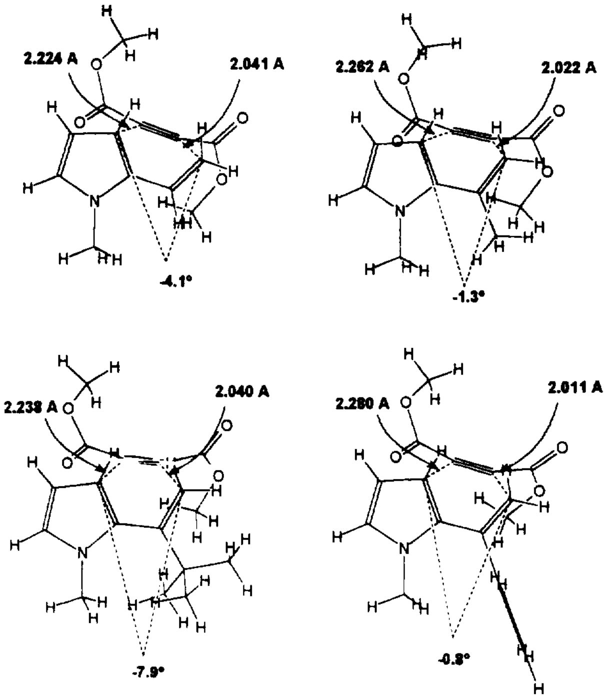


Figure 4. Diels-Alder transition structures

The steric effect is particularly critical in the case of the vinylpyrroles **1b** and **1c**. In **1c**, for example, a severe interaction is reflected in the higher activation energy for the Diels-Alder reaction and also in the twisted dienic system (*ca.* 8°). In contrast, where the steric interaction is negligible, as for example in the case of the vinylpyrrole **1d** where the conformation of the phenyl ring in the TS and in the ground state are identical, the activation energy for the Diels-Alder reaction is very similar to that for **1a** with the consequence that the reactivity of **1d** with DMAD corresponds closely to that of **1a** (Table 1).

Table 6. Imaginary frequency (cm^{-1}) associated with the unique negative eigenvalue for the transition structure for the Diels-Alder reaction of DMAD with the vinylpyrroles.

Pyrrole	Frequency	Eigenvalue	C7-C10	C3-C9
1a	-722.6240	-0.11217	0.649	0.527
1b	-692.7944	-0.10772	0.669	0.516
1c	-704.9004	-0.11351	0.660	0.537
1d	-692.4893	-0.11351	0.698	0.501

Table 7. Imaginary frequency (cm^{-1}) associated with the unique eigenvalue for the transition structure for the Michael reaction of DMAD with the vinylpyrroles.

Pyrrole	Frequency	Eigenvalue	C5-C9
1a	-493.0153	-0.05968	0.882
1b	-496.4116	-0.06267	0.898
1c	-505.3684	-0.06749	0.891
1d	-508.9270	-0.06615	0.899

When the transition structures for electrophilic attack of DMAD on the 1-methyl-2-(substituted vinyl)pyrroles (Figure 5 and Table 7) were examined, it was found that the geometries are very similar. The bond distance between C-5 and C-9 for the four transition structures is *ca.* 1.75 Å, and DMAD adopts the same disposition with respect to the pyrrole ring (*ca* 20° dihedral angle to N-1-C-5) in each case. Additionally, in each transition state, the 2-vinyl groups are twisted with respect to the pyrrole ring to almost the same extent as in the ground state. Thus, for vinylpyrroles **1a** and **1b**, the dihedral angle between the pyrrole ring and the vinyl group transition structures is only slightly smaller than that in the ground state. These differences can be rationalised in terms of stabilisation of the transition state by delocalisation of the positive charge from the pyrrole ring into the 2-vinyl group. As a consequence, the activation energy for the Michael reactions involving **1a** and **1b** are very similar and the same chemical reactivity towards DMAD is observed with the two compounds. In contrast with the Michael reaction, the activation energy for the formation of the TS of the Diels-Alder reaction for **1b** must be larger than that for **1a** and, as a consequence, although 1-methyl-2-vinylpyrrole reacts to give both

Diels-Alder and Michael adducts, 1-methyl-2-propen-2-ylpyrrole fails to produce the Diels-Alder adduct as a result of the steric interaction between the two methyl groups. Conversely, it was noted that the vinyl group is twisted out of the plane of the pyrrole ring to a slightly greater extent in the TS for the electrophilic attack of DMAD on **1c** and **1d**, than it is in the ground states of **1c** and **1d**. This difference in conformation results from repulsive interaction between DMAD and the substituents present on the vinyl group and, as a consequence, the activation energy for the formation of the Michael addition TS is greater and the rate of reaction is slower.

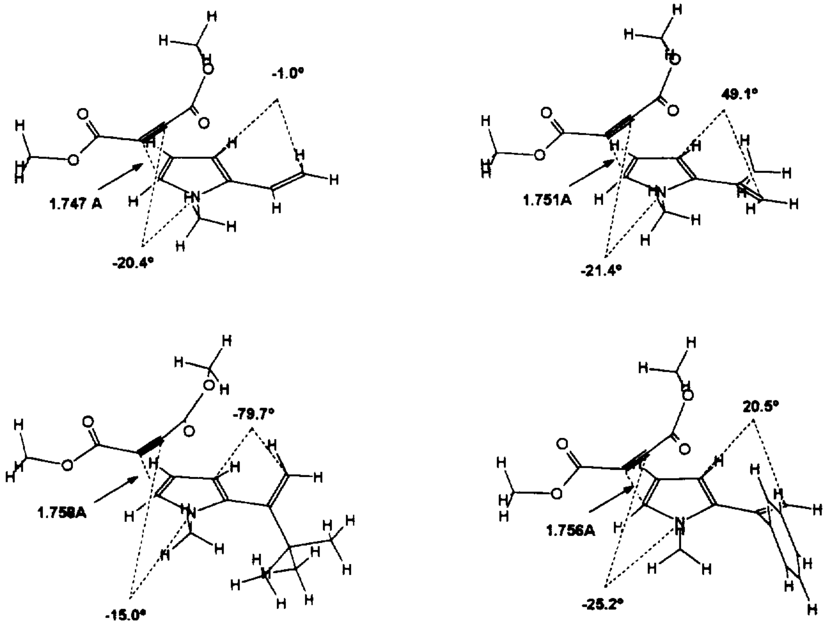


Figure 5. Transition structures for the electrophilic attack of DMAD on 1-methyl-2-(1-substituted vinyl)pyrroles

Finally, in order to establish whether the relative differences between the energies of transition states and the ground states were due to steric factors in the Diels-Alder reaction, the ground state energies were compared for the vinylpyrroles **1a**, **1b** and **1c** calculated for their coplanar conformations and for their optimal energy twisted conformations. The calculations were carried out by full geometry optimisation of the vinylpyrroles **1a**, **1b** and **1c** at 3-21 G basis set level, and the differences between minimum energy conformations and the coplanar conformations (Table 8) show the increase of the activation energy for **1b** and **1c**, relative to that for **1a** which exhibits virtually no steric hindrance in the ground state (0.11 kcal/mol). These observations indicate that steric hindrance of the coplanar conformation of the TS of the Diels-Alder reaction is a key factor in the control of the cycloaddition reactions of the vinylpyrroles with DMAD.

Table 8 3-21G Energy differences between ground state and coplanar conformations for **1a, 1b** and **1c.**

	Dihedral angle* (degrees)	Ground State (Hartree)	Coplanar State (Hartree)	ΔE (Coplanar State -Ground State) (Hartree)	(kcal)
1a	24.0	-322.917802	-322.917622	0.000180	0.11
1b	65.1	-361.736556	-361.729774	0.006782	4.26
1c	97.2	-478.193368	-478.164752	0.028616	17.96

* Dihedral angle of vinyl group

Conclusions

Our study of the structure of the transition states corresponding to electrophilic attack on 1-methyl-2-vinylpyrroles by dimethyl acetylenedicarboxylate, which leads to the formation of the Michael adduct, and the comparative study the transition states with those for the Diels-Alder reactions clearly indicate that, in the absence of a substituent at the 1-position of the vinyl group, the activation energy for the formation of the transition states for both the electrophilic attack by DMAD at the 5-position of the pyrrole ring and the cycloaddition reaction are very similar. It is also shown that substituents at the 1-position of the vinyl group have little effect upon the activation energy for the electrophilic attack by DMAD on the various pyrroles **1a** - **1d**. However, there is a significant change in the activation energy for the formation of the cycloaddition transition state with changes in the bulk of the substituent on the vinyl group as a result of the requirement of coplanarity of the diene system in the transition structures, as is evident from the conformational analysis of the vinylpyrroles **1b** and **1c**. Consequently, all geometries found for the transition structures support the earlier postulate[1] that, at 20°C, the increased bulk of the substituent on the vinyl group inhibits the cycloaddition reaction, while the effect of this group is less important for the electrophilic attack at the 5-position of the pyrrole ring. Additionally, the relatively small differences between the calculated activation energies for the two reactions also explains why the ratio of products from the two pathways change when the reaction is conducted at higher temperatures.

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(*Received in USA* 30 *December* 1994; *accepted* 13 *June* 1995)