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A THEORETICAL STUDY OF REGIOSELECTIVITY AND SYNCHRONICITY OF 1,3 DIPOLAR CYCLOADDITION REACTIONS

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Abstract-In the present paper we report a MNDO theoretical study of the 1,3 dipolar cycloaddition reaction between substituted cyclic azomethine ylides and the dipolarophile chloroacrylonitrile. The minimum energy potential surface calculated for the reaction explaines the regioselectivity observed experimentally.
An asynchronous mechanism is proposed for the reaction.

A considerable amount of theoretical calculation has been reported in the last decade concerning the nature of cycloaddition reactions. The main subject of controversy has been the synchronicity of the reaction. While there is a group that proposes a concerted one-step mechanism others propose a two-step one involving a biradical or zwitterion as intermediate.[1]

Among the experimental facts mentioned in the controversy are the stereospecificity, the activation entropy, the activation energy, the solvent effect, the periselectivity, the regioselectivity and the reactivity of the dipolarophiles.[2,3]

Numerous theoretical calculations have been carried out in this field. Poppinger,[4] by means of "ab initio" calculations reaches a slightly asynchronous transition state for the reaction of fulminic acid with acetylene, while Dewar with the MNDO method finds a highly asynchronous transition state.[5]

Schaefer reinvestigated this reaction. The two basis set used (4-31G and 9s5p/4s2p) yielded very similar and relatively symmetric transition-state geometries. A difference of 10 between the force constants for the two new bonds being formed in the transition state suggests a lack of symmetry in this respect.[6]

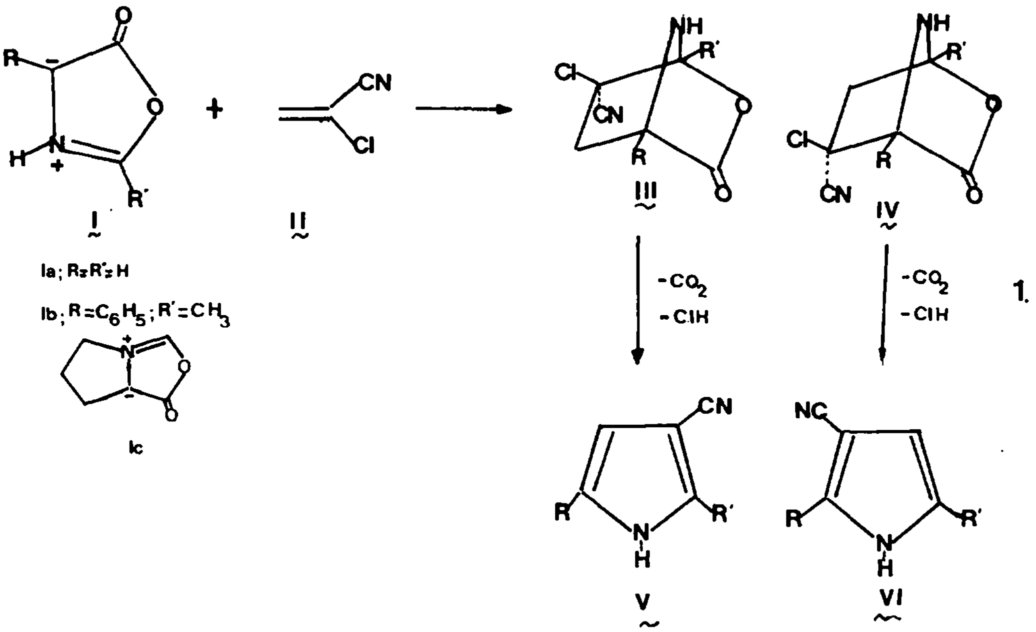
On the other hand, Leroy et. al.[7] have carried out "ab initio" studies on a wide variety of 1,3-dipoles and dipolarophiles. These studies attribute to the 1,3 cycloadditions a not very large variable asynchronism.

More recently Bertran et al.[8] have reported a MINDO/3 study of the potential surface for the 1,3-dipolar cycloadditions of carbonyl and azomethine ylides with ethylene and substituted ethylenes. The effect of the introduction of different substituents on the dipolarophile, the influence of the solvent polarity on the reaction rate and the stereospecificity observed are explained in terms of a two-step mechanism.

A similar controversy exists for the Diels-Alder reaction. While the ab-initio studies support a symmetrical structure for the transition state, MINDO/3 and MNDO predict the existence of a very unsymmetrical transition state corresponding to the cyclization of an intermediate biradicaloid. Considerable indirect support for the MNDO mechanism is given by the good agreement between theoretical and experimental entropies of activation and secondary isotope effects.[5]

In a recent experimental study of the Diels-Alder reaction Dewar reconciles both positions stating that even though all these reactions are concerted, they take place in a single kinetic step, they are not synchronous, the changing in bonding does not take place in an equal extent in the transition state. This being the case not only for very unsymmetrical dienophiles but also for symmetrical ones.[9]

With this in mind we decided to investigate the regioselectivity and synchronicity observed in the 1,3 dipolar cycloadditions of azomethine ylides of structure I with the dipolarophile chloroacrylonitrile II (eq.1). The 1,3 cycloaddition of oxazolium 5-oxides with dipolarophiles has been utilized in the synthesis of a variety of heterocyclic systems, the reaction pathway involving a cycloaddition to an azomethine ylide I to give a N-bridged compound III-IV that loses carbon dioxide and hydrochloric acid to form a heterocycle V-VI.[10]



We investigated the potential surface corresponding to the formation of compounds III and IV for R=R'=-H; R=-C$_6$H$_5$, R'=-CH$_3$ as well as for azomethine ylides for type Ic. The theoretical results are in full agreement with the experimental data obtained for the reaction.[11]

Method of Calculation

All of the calculations were carried out by means of the semiempirical MNDO[12] method with full geometry optimization for reactants and products.

The transition states were initially estimated by means of the reaction coordinate method. In its initial location the new forming sigma bonds were chosen as independent variables, all the other geometric parameters were optimized for each set of value of the formers.

Once they were initially guessed the stationary points were refined by minimizing the norm of the energy. Each stationary point was characterized by calculating and diagonalizing the corresponding Hessian (force constant) matrix.

Results and Discussion

The geometries calculated for compounds Ia, II and IVa as well as the atom numbering used are shown in fig. 1.

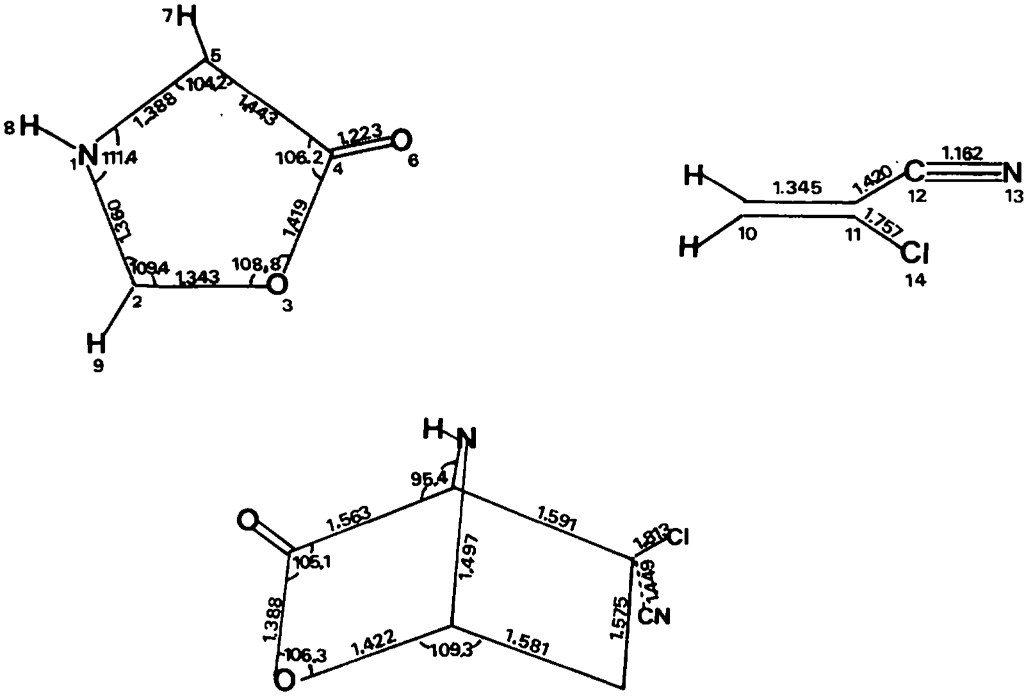
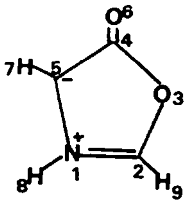


Fig. 1

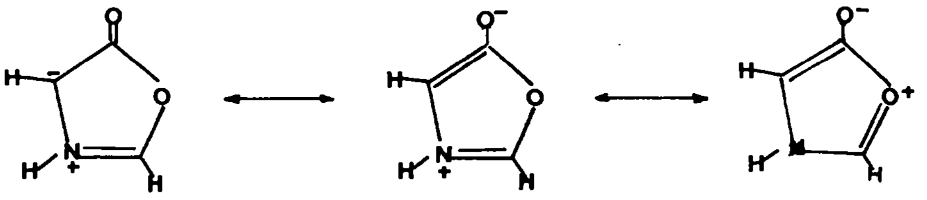
The total charge and the π charge distribution for compound Ia are shown in fig. 2.



	TOTAL CHARGES	π CHARGES
N_1	-0.0906	0.532
C_2	0.0568	-0.061
O_3	-0.1963	0.247
C_4	0.3542	0.179
C_5	-0.3052	-0.404
O_6	-0.3482	-0.485
H_7	0.1644	
H_8	0.2277	
H_9	0.16372	

Fig. 2

As we can see from the π charge distribution O_3 bears a positive charge while C_5 and O_6 are the most negative atoms of the molecule. This π charge distribution indicates that the following



are the most representative resonance structures for compound Ia. Similar charge distributions have been reported for ab initio calculations of azomethine oxides.[13]

The geometric variables calculated for compound Ia are comparable to the corresponding ones calculated with a double ζ basis set SCF method for isoxazole.[6] With respect to the N-bridged compounds IIIa and IVa, the later is calculated to be $\approx$ 2 kcal/mol lower in energy than IIIa. For both of them the cyano endo compounds are the most stable isomers.

The RMNDO potential surface calculated for reaction of Ia predicts it to occur in two steps with the successive formation of both sigma bonds via an intermediate with high biradical character. The concerted-synchronous transition states leading to compounds IIIa and IVa lie higher in energy than both of the non-synchronous ones. The minimum reaction path calculated for the reaction, the energy difference between the stationary points, and the lengths of the forming C-C bonds in each transition state are shown in Table I.

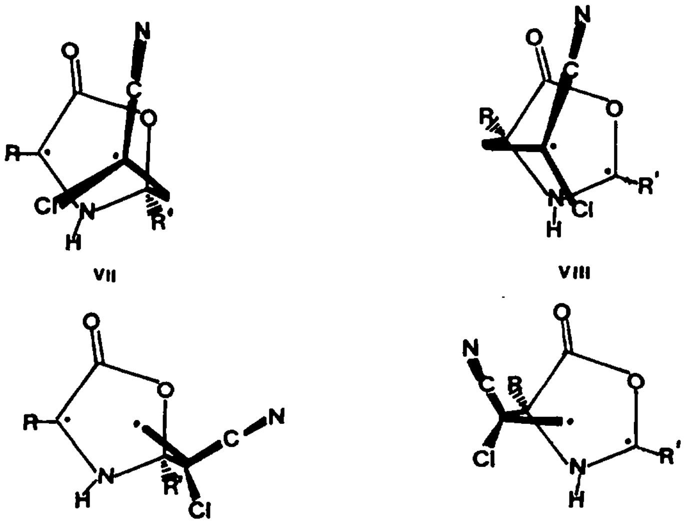
As we can see, a strong displacement of atoms 2 and 10 is produced in the first transition state. The C_5-C_{11} bond is being formed in the second transition state while the C_2-C_{10} remains unaltered. Regarding the energy of the second transition state it represents a second very small energy barrier in respect to the intermediate. Similar results have been reported for certain MINDO/3 calculations.[8]

TABLE I: Properties Calculated by RMNDO for Stationary Points on the Potential Surface for the Reaction of Azomethine Ylide Ia with the Dipolarophile II

Compound	ΔH_f(kcal/mol)	TS forming bond lengths (Å) C_2- C_{10}	 C_5- C_{11}
Ia	-34.57		
II	38.12		
First TS	36.14	1.90	3.70
Intermediate	29.21	1.57	3.00
Second TS	30.00	1.57	2.90
Product (IVa)	-25.28		

In dealing with asymmetric dipoles and dipolarophiles and since the mechanism is in two steps, four possible asynchronous paths exist by which cycloaddition can take place depending on which end of the asymmetric dipolarophile and of the dipole, the first sigma bond is formed.

From these four possibilities, shown in fig. 3 and leading to biradical intermediates VII, VIII, IX and X, only VII and VIII need be considered because relative to hydrogen all substituents stabilize a radical center.[3]



VII

VIII

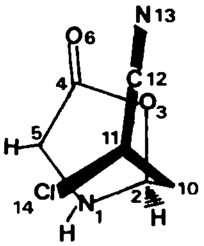
IX

X

Fig. 3

In the general eq. 1, the two possible regioisomeric products III and IV arise from the diradicals VIII and VII, respectively.

For reaction of compound Ia the biradical VIIa corresponds to a stationary point of the potential surface lying 39 kcal/mol lower in energy than structure VIIIa. The RMNDO total charge distribution for the most stable intermediate VIIa is shown in fig. 4. It can be seen that the RHF distribution attributes partial formal charges to the biradical. The true structure of it would have to be determined by inclusion of CI.



N_1	- 0.2331
C_2	0.2312
O_3	- 0.2676
C_4	0.3357
C_5	0.0777
O_6	- 0.2378
C_{10}	0.0571
C_{11}	- 0.2305
C_{12}	- 0.0238
N_{13}	- 0.1116
Cl_{14}	- 0.1398

Fig. 4

Intermediate VIIa is calculated as the most stable even though a lower charge transfer accompanies its formation (t = 0.3) in comparison with the one that corresponds to formation of intermediate VIIIa (t = 0.5).

These results indicate that the reaction of Ia with chloro acrylonitrile would lead regiospecifically to products through the N-bridgehead compound IVa.

The calculation was extended to an investigation of the potential surface of the reactions of azomethine ylides Ib and Ic. For compound Ic the calculation predicts a behavior similar to that obtained for type Ia ylide, the energy difference between the reaction paths which lead ultimately to compounds IIIc and IVc being preserved. This reaction was shown experimentally to be regiospecific[11] with formation of compound VIc. For compound Ib the calculation predicts a considerable decrease in energy between the surfaces responsible for both possible regioisomers. This reaction was shown to be regioselective experimentally with formation of compound VIb and Vb in 70 and 30 percentage yields respectively.[11]

Following frontier orbital theory and according to Sustmann's[14] classification within Fukui's frontier orbital aproximation the reaction is HOMO(HO) controlled (the interaction of the dipole HO with the dipolarophile LUMO(LU) is the greatest). In this approximation the first sigma bond should be formed at those ends of the reactants which have the greater pair of coefficients for the dominat HOMO-LUMO interaction. From inspection of the frontier orbitals the C2-C11 should have been the first sigma bond formed. At this point we could explain the preference for the C2-C10 bond formation on the basis of second order interactions probably established between the CN group of the dipolarophile and the C=O group of the dipole. Nevertheless, overlap populations between them are calculated to be null by MNDO.

We conclude that while FO theory does not lead to a satisfactory prediction of the regioselectivity of these reactions, MNDO does.

This method as well as MINDO/3 propose the cycloaddition reaction to take place in two steps. Even though this asynchronism has been attributed to the fact that semiempirical methods neglect overlap the argument has been refused by Dewar on the basis that MNDO and MINDO/3 have been parametrized to reproduce experimental results.[5]

Based on the present calculation, mainly on the low potential barrier between the intermediate and the second calculated transition state we conclude that cyclic azomethine ylides react with chloroacrylonitrile in a concerted asynchronous way.

The present calculation does also indicate the importance of the method to determine the regiospecificity of the reactions.

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