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THEORETICAL STUDY OF THE GAS-PHASE THERMAL ISOMERIZATION OF ISOXAZOLES. PART I. ISOXAZOLE

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An MNDO study was made of the gas-phase thermal isomerization of isoxazole to explore theoretically the proposed reaction mechanism. The results showed that isoxazole isomerizes through an azirine, as an intermediate, to oxazole via a nitrile ylide or to ketenimine, with similar activation energies, and that the first step is rate limiting, in agreement with the experimental results. These results also show that isomerization to a nitrile is possible, but in this case the energy barrier is greater than the corresponding isomerization to oxazole. The MNDO study also supports a concerted process for the rate-limiting step, as reported earlier on the basis of experimental studies.

INTRODUCTION

We have been interested in the flash vacuum thermol ysis (FVT) of some pyrazole[1–3] and isoxazole derivatives[4–6] as a technique for carrying out kinetic measurements,[7] which previously led us to postulate reaction mechanisms supported not only on the basis of the products obtained but also on the basis of activation parameters derived from those measurements.

Theoretical studies of the proposed mechanisms and correlation of experimental results with theoretical calculations have allowed us to predict the behaviour of an isoxazole according to the position and kind of substituents on the heterocyclic ring. Our first attempts were based on the models suggested by Epiotis[8] for 1,3-sigmatropic shifts[9,10] and we have recently published a theoretical study[11] using the MNDO method.[12]

We have found that most of the isoxazoles (I) that we have studied isomerize into the corresponding oxazole (III) or nitrile (IV). We have also demonstrated the intermediacy of the 2-H azirine (II) isomer in these reactions[4,5] (Scheme 1); in addition we have suggested that the step I → II is the slow one.

On the other hand, we have suggested that 5-aminoisoxazole derivatives undergo a 1,3-sigmatropic shift and 5-methylisoxazole derivatives undergo either a 1,3-sigmatropic shift or rearrange via a diradical (Scheme 1).[5,9] In the FVT of 4-acetylisoxazole[10] we have suggested a diradical pathway based on the log A value, which is much greater than those observed for the previously reported isoxazole derivatives and also because the —COMe group at position 4 of the isoxazole ring increases the stability of the diradical intermediate.

Further, we postulated a general reactivity pattern for isoxazole derivatives (Scheme 1). In this paper we report a theoretical study of these reactions, which was undertaken to confirm or reject the proposed reaction mechanism.

PROCEDURE

All calculations were performed on a Tandy 3000 or Epson Equity III+ personal computer, using the MNDO semi-empirical molecular orbital procedure described by Dewar and Thiel,[12] and force calculations were carried out on an IBM 3031 computer. Calculations were carried out with complete geometry optimization with no geometrical constraints and using the standard gradient method.

Full geometry optimization was performed for all compounds (**1–8**) and true minima were confirmed through vibrational analysis. Hypersurfaces were calculated by assigning fixed values to the appropriate coordinates and optimizing all the others. Saddle-points were located by one-dimensional reaction paths or two-dimensional grid searches, and the resulting approximate transition-state geometries were refined by gradient norm minimization until diagonalization of the Hessian matrix yielded only one negative eigenvalue.

Since RHF procedures give energies for biradicals that are far too positive, the results were obtained both with the normal (RHF) version and with two open-shell versions, using either the 'half-electron' approximation[13]

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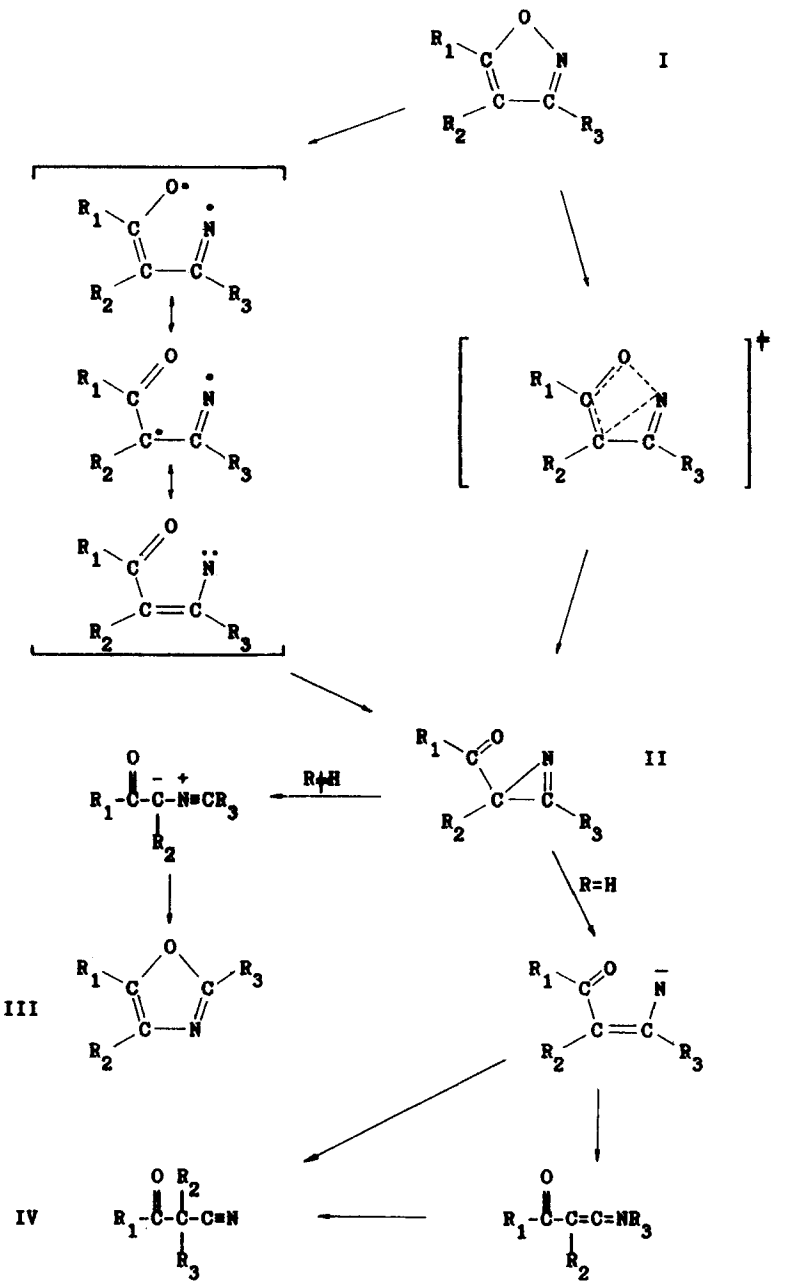
with 3×3 CI[14] (MNDO-HE-CI) or the UHF formalism (UMNDO).

Probe calculations were made using both MNDO-HE-CI and UMNDO procedures. The latter afforded the best results and therefore was used for the open-shell calculations.

RESULTS AND DISCUSSION

In order to begin the study, we made a calculation to optimize the isoxazole molecular geometry and to estimate its ΔH_f using approximate initial values.[16] The results agree fairly well with those reported by Dewar and Ford.[17]



Scheme I

All experimental studies on isoxazole or their derivatives suggest the scission of the N—O bond, closure to a three-membered ring (azirine) and/or opening to a linear structure. To study these possibilities we carried out an RHF calculation to find the potential energy surface (PES) in relation to these variables, that is, the N—O bond length (scission) and the C_4—C_3—N angle (closure or opening). As an intermediate diradical in the step isoxazole (**1**) → azirine (**2**) (see Scheme 1) also seemed possible, as proposed previously, the same calculations were carried out using the open-shell version (UMNDO). The computed PES is plotted in Figure 1.

Figure 2 shows the optimized geometries of the chemical species described in Figure 1 and also in Figures 3–8.

In Figure 1 the equilibrium points of the isoxazole (**1**), azirine (**2**) and ketenimine (**3**) can be clearly seen. The energetically more favourable reaction path involves first a stretching and breaking of the N—O bond, thus forming an intermediate placed in the upper valley of the surface with an activation energy (*AE*) of about 65·5 kcal mol^{-1} (1 kcal = 4·184 kJ). It can also be seen that the most suitable path is closure to the azirine **2** and not ring opening to the ketenimine **3** with a greater $\Delta H^{\neq}$.

Nevertheless when a molecule has the energy necessary to break the N—O bond, it directs only to the relative minima of the potential energy surface corresponding to the azirine **2**, which requires no additional energy. In accordance with this, the more likely reaction pathway showing a reliable energetics may be that shown in Fig. 1 which suggests a concerted mechanism in agreement with the experimental results.[10] The hypersurfaces performed using both

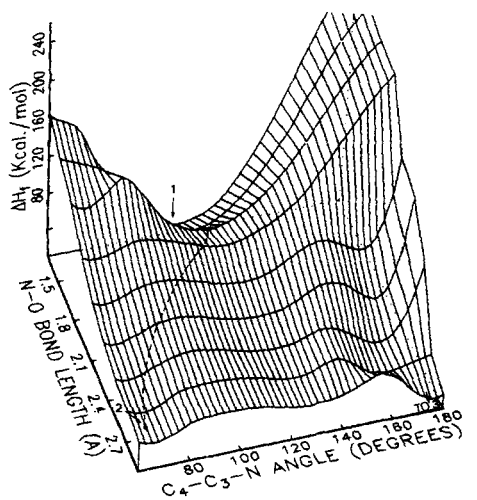
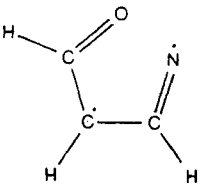


Figure 1. Potential energy surface calculated by using UMNDO for the isomerization of isoxazole (**1**) to the azirine **2** or ketenimine **3**

open- and closed-shell calculations show that the PES do not change significantly in shape, but the energies of the transition state (TS) and the presumed intermediate markedly change and therefore the UMNDO calculated *AE* is more reliable and nearer to the experimental values of about 41 kcal mol^{-1}.[5]

In order to compare these results, in Figure 3 we have plotted the enthalpy profile of the reaction against the N—O bond length. When the system overcomes the TS its goes unfailingly to the azirine isomer **2** and not necessarily through the diradical intermediate, which according to our results is a singlet 1,3-diradical (**8**).



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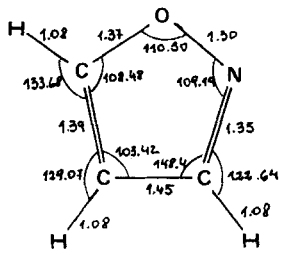
Although the formation of the corresponding ketenimine **3** is unfavourable, this product may afford the experimentally observed nitrile **4** through a 1,3-hydrogen shift; therefore, we carried out a theoretical study to compare the results with the proposed mechanism going through the azirine **2**. The results are shown in Figure 4. The *AE* from this step is about 87·7 kcal mol^{-1} compared with a value of 81·6 kcal mol^{-1} using UMNDO, indicating that this step would involve a much higher energy barrier than the path isoxazole (**1**) → azirine (**2**) → nitrile (**4**).

The last reaction step (**2** → **4**) was studied through a 1,2-hydrogen shift from position 2 of the azirine ring. For geometrical reasons, when the hydrogen atom is placed near C-3 of the azirine ring, it inserts itself in the C-2—C-3 bond, breaking it and giving the isonitrile **7**.

Although the isonitrile–nitrile isomerization is a well known, fast reaction which requires only a low energy,[18,19] we may assume the intermediacy of the isonitrile **7**. The *AE* calculated for the step azirine (**2**) → isonitrile (**7**) is 80·2 kcal mol^{-1} (79·4 kcal mol^{-1} using UMNDO), which implies a barrier much greater than the step isoxazole (**1**) → azirine (**2**), this being hypothetically the rate-limiting step. In order to examine this process further we carried out a calculation using two-dimensional grids vs the N—C-3 and C-3—H bond lengths in the azirine (**2**) ring.

The results of these RHF–MNDO calculations are given in Figure 5, where it can be seen that the energetically more favourable reaction path goes through a relative energy minimum to give the nitrile **4** isomer with an *AE* of about 54·6 kcal mol^{-1} (37·9 kcal mol^{-1} using UMNDO). This is a value smaller than that for the corresponding azirine (**2**) → isonitrile (**7**) step. The



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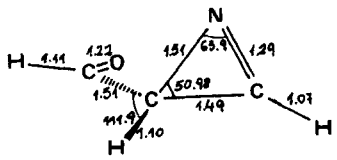

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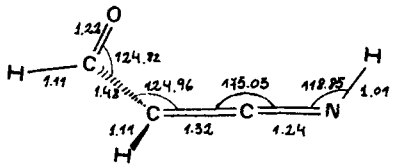

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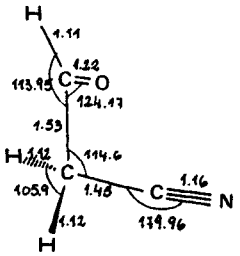

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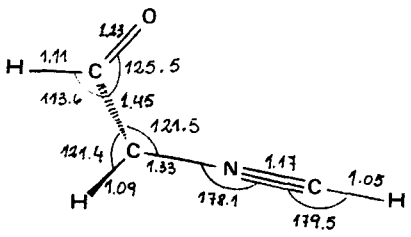

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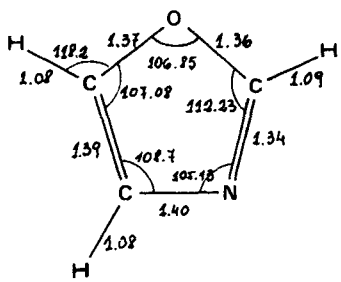

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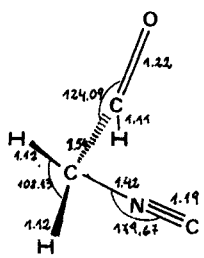

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Figure 2. Optimized geometries from isoxazole (**1**) and its isomers (**2**–**7**) cited in text

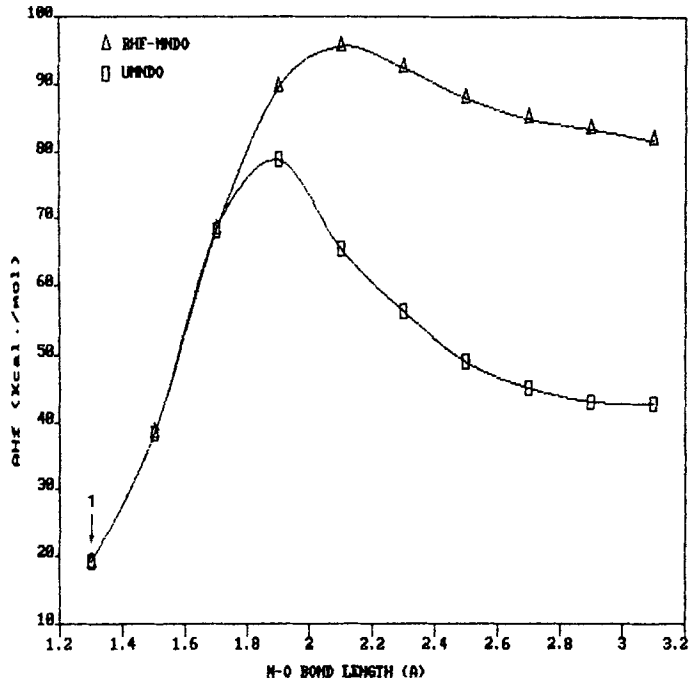

Figure 3. Enthalpy profile of the N—O bond scission using both (▵) RHF—MNDO and (□) UMNDO methods

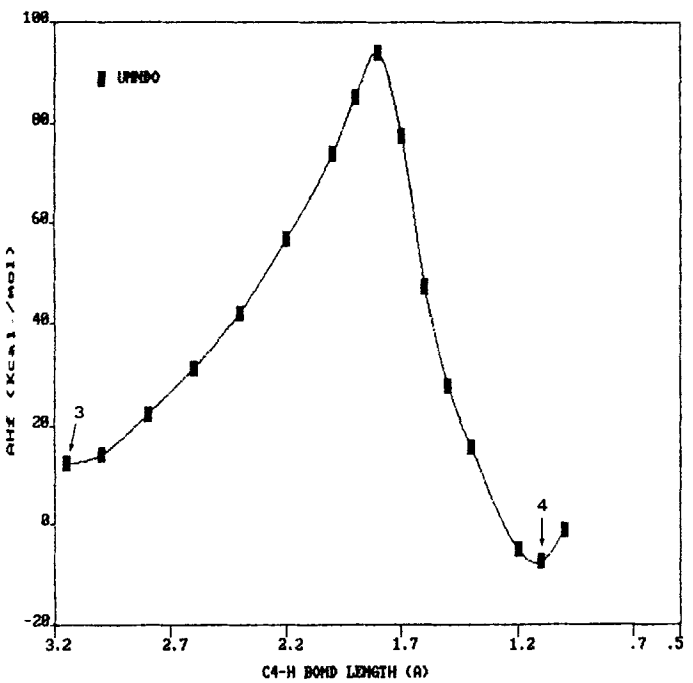

Figure 4. Enthalpy profile for the ketenimine (**3**)–nitrile (**4**) isomerization

equilibrium position of the nitrile **4** cannot be seen explicitly because when the C-3—H bond length is smaller than 1.5 Å the C-2—C-3 bond in the ring is formally *broken*, consequently the energy rises drastically. For a better view of what is happening on the hypersurface we should have plotted the C-2—C-3 bond length also, but this is physically impossible.

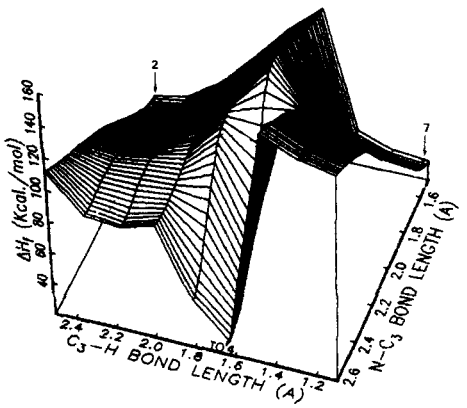

Figure 5. Potential energy surface calculated by using the RHF–MNDO for the isomerization of the azirine **2** into the nitrile **4** or isonitrile **7**

We also carried out an MNDO calculation of the step azirine (**2**) → oxazole (**6**). Although the oxazole isomer is not present as a product when position 3 of the isoxazole ring is not substituted (such as in this case), we think that these *AE* values are important for comparison with the nitrile isomerization. According to our postulate,[5] the first value must be smaller in these isoxazole derivatives. However, the situation should change in the 3-substituted isoxazole derivatives. These calculations were made through the C-1 [1,3]-sigmatropic shift rather than the N [1,3]-sigmatropic shift to restore the isoxazole **1**. The results show that the C-2—C-3 bond scission of the azirine ring takes place first giving the nitrile ylide **5**,[20] which in a second step undergoes cyclization to oxazole (**6**). This point reveals a stepwise rather than concerted mechanism for this isomerization, in agreement with the results obtained by Dewar and Turchi[21] using MINDO/3.

Figures 6 and 7 show these calculations for the steps

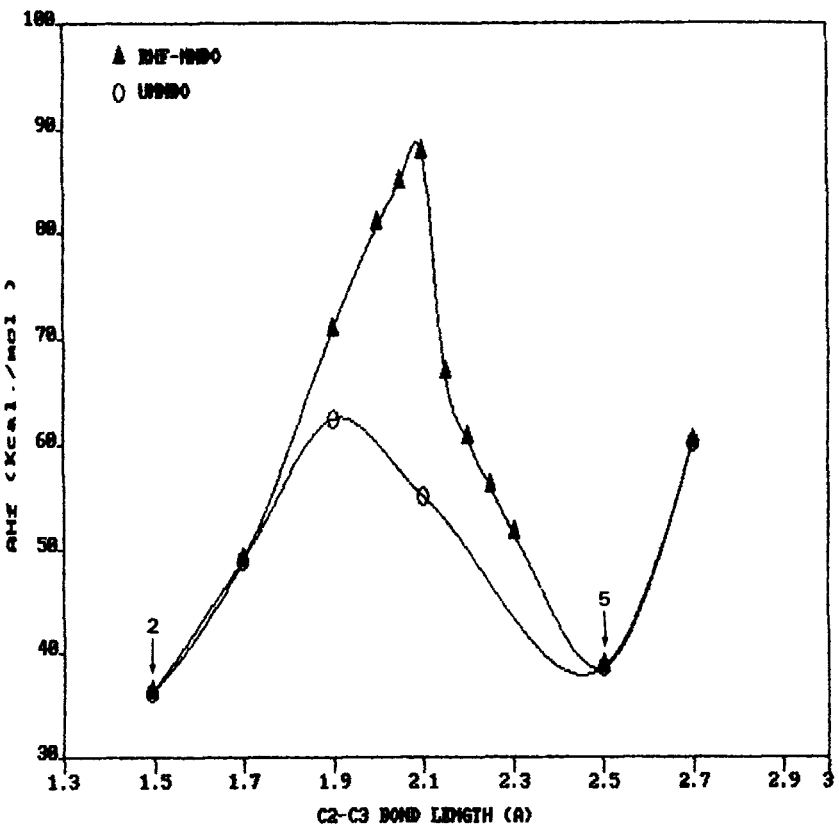

Figure 6. Enthalpy profile for the azirine (**2**)–nitrile ylide (**5**) step. ▲, RHF–MNDO, ○, UMNDO

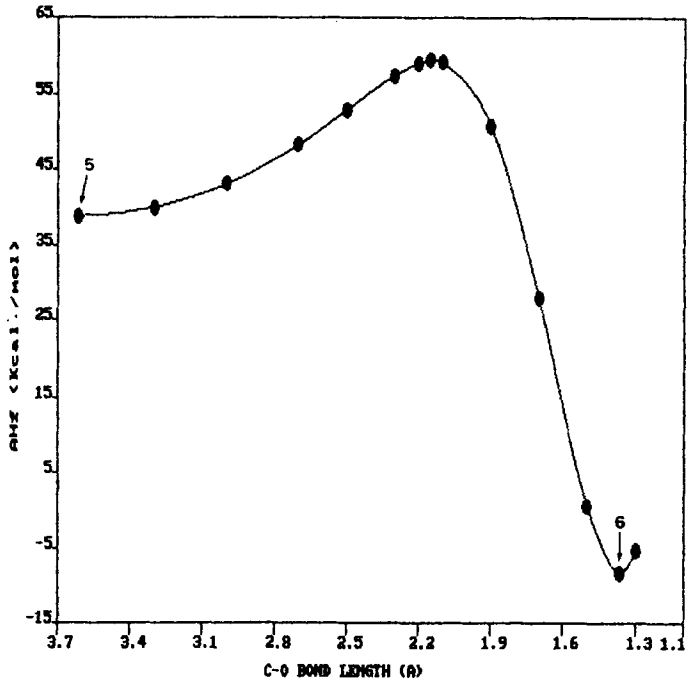

Figure 7. Enthalpy profile for the nitrile ylide (**5**)–oxazole (**6**) step

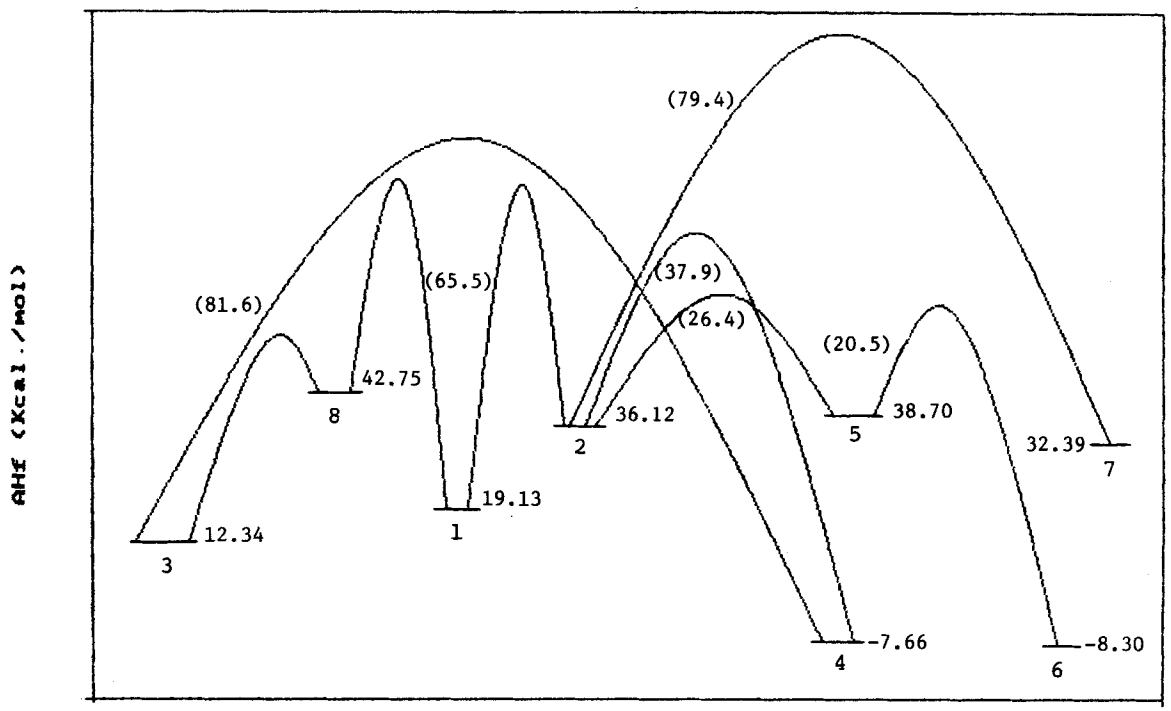

Figure 8. Summary of the results obtained by using UMNDO for the thermal isomerization of isoxazole. Values are ΔH_f and AE (in parentheses) in kcal mol^{-1}

azirine (**2**) → nitrile ylide (**5**) and nitrile ylide (**5**) → oxazole (**6**), respectively. It can be seen clearly that the rate-limiting step is the first step with an *AE* of *ca* 51·6 kcal mol^{-1} (26·4 kcal mol^{-1} using UMNDO) against 20·5 kcal mol^{-1} (UMNDO) for the step nitrile ylide (**5**) → oxazole (**6**).

These results agree fairly well with those reported by Tanaka *et al.*[22] of 24 kcal mol^{-1} for the step **2** → **6** using *ab initio* calculations at the STO-3G level and with values of *ca* 22 and 26 kcal mol^{-1} for the isomerization of some nitrile ylide → oxazole derivatives[21]. On the other hand, the geometric parameters of oxazole (**6**) (see Fig. 2) are reasonably consistent with those determined by x-ray diffraction study[23] and MINDO/3 calculation.[24] Further, the ΔH_f of **6** (see Figure 8) agrees with the value reported by Turchi and Dewar[24] of −7·63 kcal mol^{-1} using MINDO/3.

CONCLUSIONS

Figure 8 shows the enthalpy profile of the isomerization pattern of isoxazole, where the following can be clearly seen.

Nitrile **4** is formed through the azirine isomer **2** and not through the ketenimine **3**. The isomerization azirine (**2**) → nitrile (**4**) proceeds directly and not through an isonitrile isomer (**7**).

The azirine **2** isomerizes into oxazole (**6**) via the nitrile ylide **5** and not into the nitrile **4**, since the latter path has a greater *AE* in this case. Although the expected product of the thermal isomerization of isoxazole (**1**) was the nitrile **4** on the basis of experimental evidence, these results were obtained in the isomerization of 3-unsubstituted isoxazole derivatives since isoxazole was not yet experimentally studied. On the other hand, MNDO predicts the formation of the ketenimine **3** with an *AE* value similar to the isomerization to oxazole (**6**), despite the fact that **3** is not observed either as a product or as a reaction intermediate, as is azirine, for any isoxazole derivatives studied experimentally. These differences can be attributed not only to a failure in the MNDO method to reproduce quantitatively this reaction path, but also to a different behaviour of isoxazole (**1**) in relation to the studied 3-unsubstituted isoxazole derivatives.

In view of these results, the rate-limiting step of the overall reaction is isoxazole (**1**) → azirine (**2**), in agreement with the experimental results. Further, MNDO supports a concerted pathway for this step corresponding to the N—O bond scission in accordance with log *A* values between 9 and 11 obtained experimentally.[4,5]

Although the MNDO is well known to have difficulties in treating molecules with adjacent lone pairs of electrons and in biradicals, the results reported here afford a novel approach to the understanding of isoxazole thermal isomerization from a semi-quantitative point of view.

Finally we consider the results obtained by comparing the steps azirine (**2**) → isoxazole (**1**) and azirine (**2**) → oxazole (**6**). The former, being the reverse of the rate-limiting step, gives an *AE* of 59·5 kcal mol^{-1}, which is essentially the same as azirine (**2**) → oxazole (**6**) of 58·2 kcal mol^{-1} both using RHF, reaching 48·5 and 52·8 kcal mol^{-1}, respectively, using values obtained from open-shell calculations.

Therefore, according to MNDO calculations, the [1,3]-sigmatropic shift C → O and N → O from 1-azirine are kinetically identical. However, this conclusion is only of theoretical interest because the isomerization through nitrile ylide requires a lower energy barrier than the concerted path.

ACKNOWLEDGEMENTS

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