An INDO Study of the Isomerization of Aziridinone

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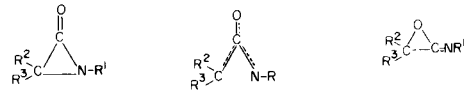
The only pathway postulated in the literature for the isomerization of aziridinone (Ia) to iminooxirane (IIIa) involves a planar, open-chain, dipolar intermediate (IIa); however, INDO calculations suggest a possible alternative pathway in which an in-plane bending of the oxygen atom towards the alkyl carbon atom occurs rather than a stretching of the alkyl-nitrogen bond. INDO calculations also suggest that the unknown compound IIIa has the same degree of stability as Ia.

Derivatives of aziridinone (Ia) exhibit a broad range of thermodynamic and kinetic stability (1). Sterically hindered 1,3-dialkylaziridinones such as (Ib) have the greatest stability, whereas 1,3-diaryl-(Ic) and triaryl-aziridinones (Id) have been neither detected nor isolated (2). The wide variation in the behavior of these aziridinones has been attributed to the intervention of a planar



(I) (II) (III)

a: R^1 R^2 R^3 H
b: R^1 R^2 *t*-alkyl; R^3 H
c: R^1 R^2 C_6H_5; R^3 H
d: R^1 R^2 R^3 = C_6H_5
e: R^1 R^2 1-adamantyl; R^3 H

or quasi-planar dipolar, charge-delocalized intermediate (II) or transition state in which a preferential steric destabilization (IIb) or electronic stabilization (IIc, IId) in comparison with (I) was postulated to occur (1). Another undetected intermediate (III) (1,3) also has been suggested to explain some of the reactions of aziridinones, sometimes as being in equilibrium with (II) (1), as well as to rationalize other reactions such as the epoxidation of ketenimines (4). Despite the great experimental interest in the isomerization of aziridinone, no quantum mechanical study of this reaction has been reported. One calculation (5) based on bond-additivity schemes estimates the difference in energy between (IIa) and (Ia) to be +28 kcal/mole. However, this calculation involves a large term to account for coulombic attraction which was estimated on the basis of a point charge model, and explicitly assumes the separation of full positive and negative charges in (IIa). We now report an INDO (6) study of the isomerization of (Ia) to (IIIa) *via* (IIa) (7) (pathway A) as well as by alternative pathways.

The INDO (8) computations were performed on an IBM 360-44 computer using a modified version of CNINDO in which COORD (9) was incorporated.

Results

Figure 1 illustrates the computed geometries of aziridinone (Ia) and iminooxirane (IIIa), both of which are unknown. Values in parentheses are the only known experimental values for an aziridinone, *viz.*, Ie (10). Figure 2 illustrates a contour map of the INDO energy surface for the aziridinone-iminooxirane system, in which the Born-Oppenheimer energy is plotted as a function of θ (vertical), ϕ (right), and ϕ' (left), the NC_2C_3, C_3C_2O, and NC_2O bond angles, respectively. The surface was generated by interpolation and extrapolation from more than 100 points, with particular attention to points lying along the pathways discussed. The energy at selected points [fixed values of θ and ϕ, and $\phi' = 360^\circ-(\theta + \phi)$] was minimized as a function of the remaining 12 independent coordinates, and the total minimizational and computational error for the points along the pathways should be less than 6 kcal/mole.

Discussion

Figure 2 reveals that, within the limits of accuracy of the INDO surface, the structure (II) is neither a definite intermediate nor a plausible transition state in the conversion of (I) into (III), at least for the unsubstituted aziridinone, since the energy at this point is almost the highest (214 kcal/mole) on the surface investigated. By contrast, the alternative pathway (I) → (IV) → (III) (pathway B) has a maximum INDO barrier of only 105 kcal/mole, which is less than half that of pathway A (1). Pathway B involves an in-plane bending of the oxygen atom towards C_3 rather than a stretching of the N-C_3

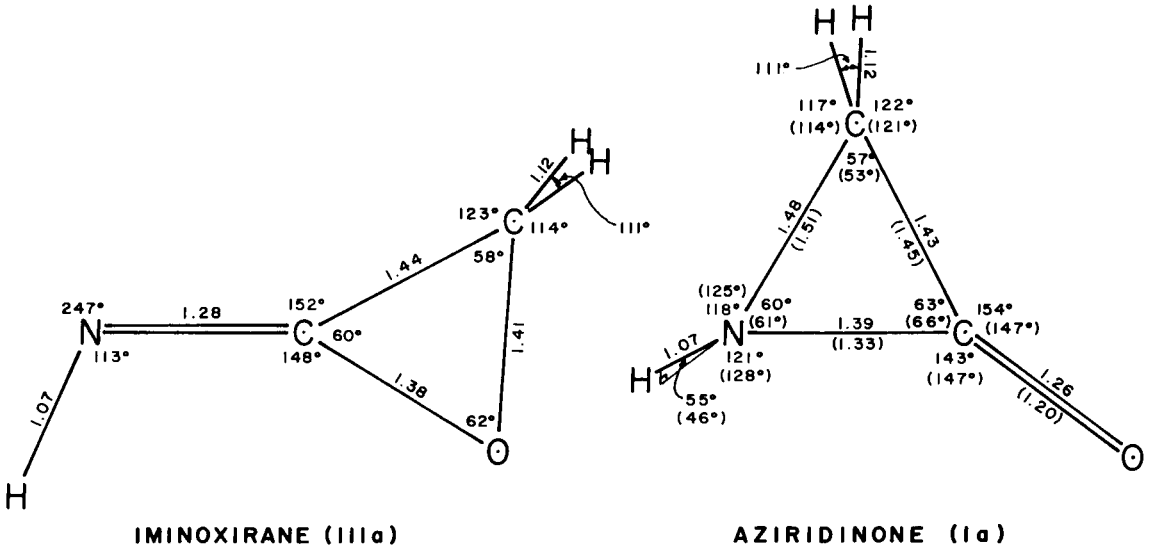


Figure 1. Geometries of aziridinone (Ia) and iminooxirane (IIIa) calculated by the INDO method. Values in parentheses are X-ray diffraction data on Ie.

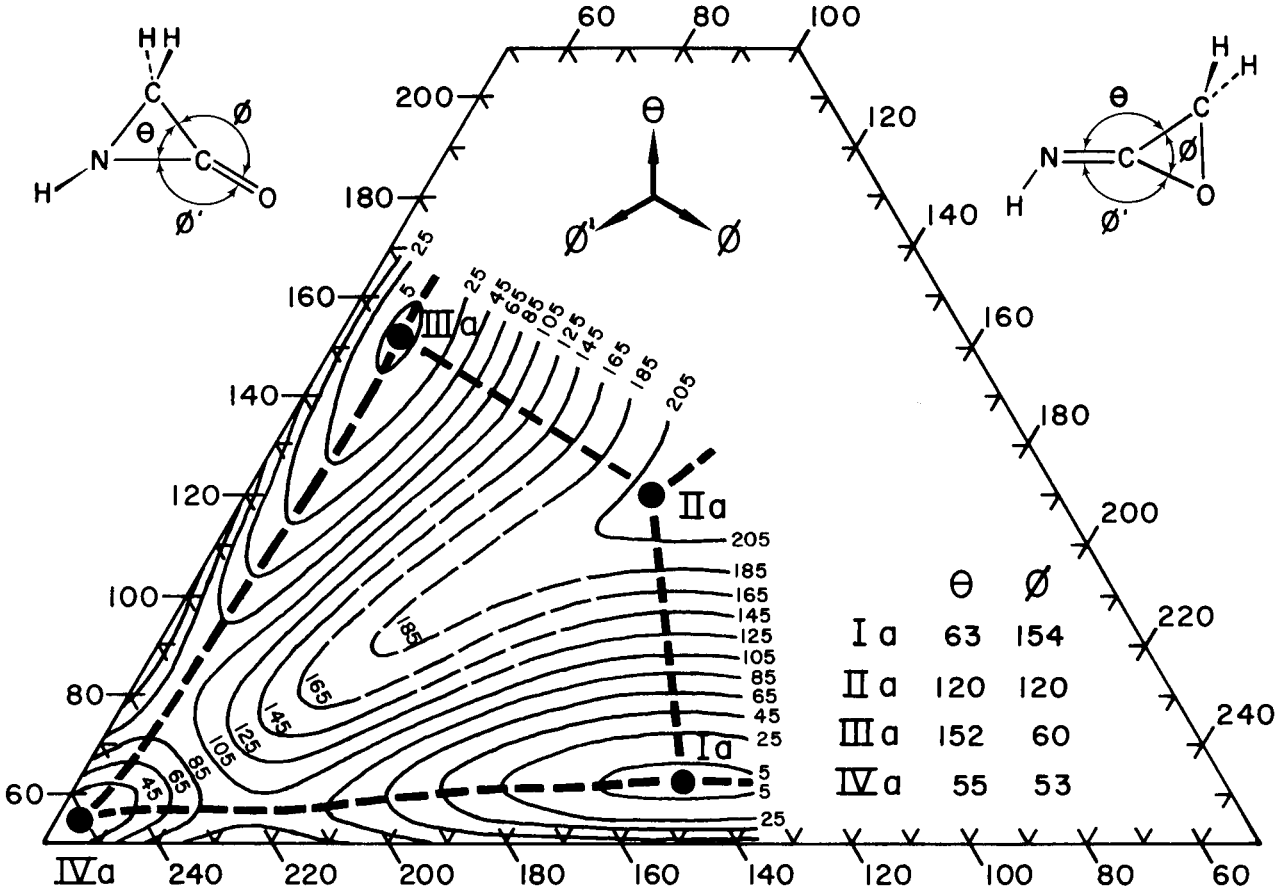


Figure 2. Contour diagram of the INDO energy surface for the isomerization of aziridinone. Contour lines are spaced 30 kcal/mole apart.

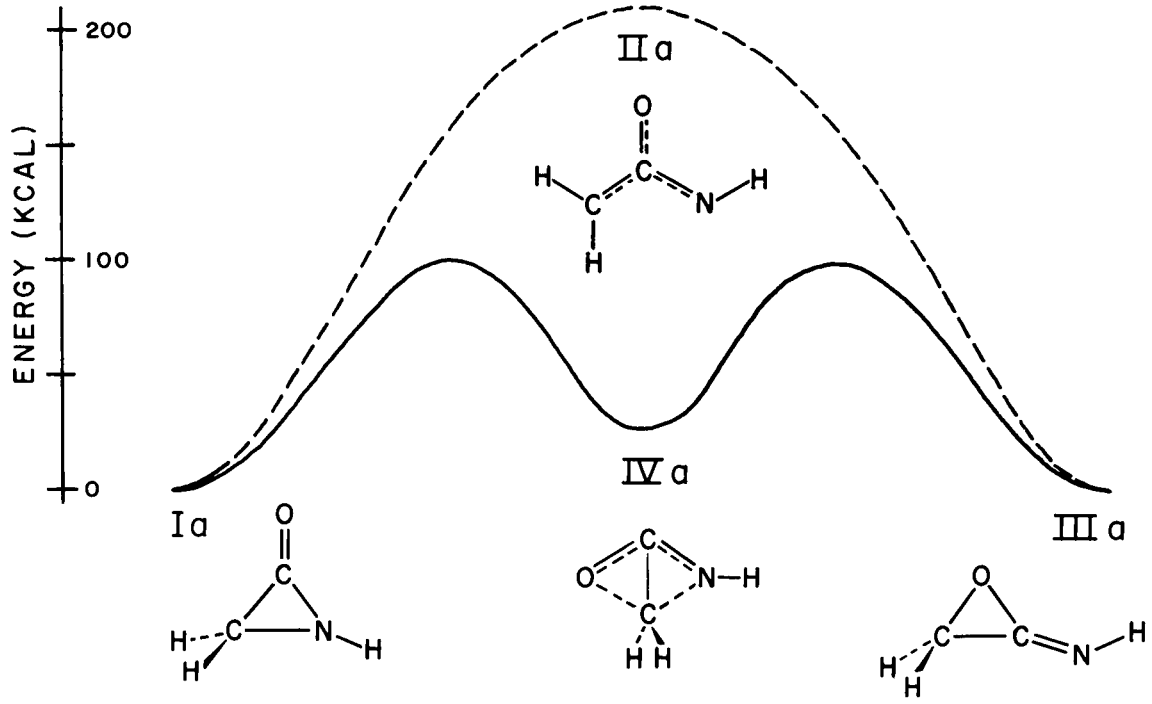


Figure 3. Alternative pathways for the isomerization of aziridinone.

bond as would happen in proceeding vertically from (I) to (II). Stabilization of (II) by delocalization is presumably insufficient to compensate for destabilization caused by bond cleavage. Apparently, the three-membered ring of (I) is preserved intact until bending allows another ring to form with minimal bond stretch (II) (Figure 3). Such a pathway is not unreasonable because, at least, small distortions caused by bending are known to be energetically more favorable than stretching.

Semi-empirical calculations of the type of INDO and CNDO/2 are known to overestimate the stability of species having a high degree of connectivity or bonding, and for this and other reasons (11, 12), the calculated instability of IIa relative to Ia has probably been exaggerated. However, the total error would have to greatly exceed 109 kcal/mole (the difference between the two pathways) in order to consider only the single pathway A for the isomerization of aziridinones as has been suggested in the literature (1). The alternative pathway B may be looked upon as an internal nucleophilic substitution on carbon, the nitrogen being the leaving group. On this basis, the two pathways are analogous to the two well-known pathways involved in nucleophilic aliphatic substitution, *viz.*, S_N1 and S_N2. The structure IVa is then a kind of distorted S_N2 transition state, although its great stability as shown in Figures 2 and 3 is most probably exaggerated on account of the high degree of connectivity.

Pathway B may shed light on the observation that ring-opening reactions of (Ib) have never yielded products derived from a neopentyl rearrangement to which such a system would easily succumb if dipolar open-chain intermediates having appreciable lifetimes were to be involved (1); yet, the dipolar intermediate (II) was considered in order to explain the differences in thermal and hydrolytic stabilities of all aziridinones. One of us (13) has previously pointed out the danger of such a sweeping generalization on the basis of the fact that thermal and hydrolytic stabilities of various aziridinones do not parallel each other, and the present paper emphasizes this caveat.

A comparison of the energies of Ia and IIIa should not be seriously affected by any errors in the INDO method on account of rings, since both compounds contain a single ring and such errors would be effectively cancelled. Hence, the low energy of IIIa (+4 kcal/mole) relative to Ia suggests that the failure of previous investigators to isolate any compound of type III is not caused by any inherent thermodynamic instability, but by a high degree of chemical reactivity.

Since compounds Ia and IIIa are unknown, one cannot assess the reliability of the bond lengths and angles

computed by us for these compound (Figure 1). However, it is interesting to note that our calculations indicate the nitrogen atom in Ia to be pyramidal rather than essentially planar as in γ-lactams (10) and formamide (14). The hydrogen atom attached to the nitrogen is lifted 55° out of the plane of the ring. X-ray diffraction data have been reported (10) for only one aziridinone (Ie), and in this compound also, the nitrogen is pyramidal, the substituent attached to the nitrogen being 46.3° out of the plane of the ring. However, the presence of bulky substituents in Ie introduces steric factors which too will affect the degree of non-planarity. Another structural feature noted in the X-ray diffraction study of Ie was that the oxygen atom and the three atoms constituting the ring are very close to being planar. We have investigated the possibility of non-planarity of the same four atoms in Ia, but the planar form has the lowest energy.

In conclusion, we wish to point out that INDO calculations suggest pathway B to be a possible mechanism for the isomerization of aziridinone that has been entirely overlooked in the literature. The question of the viability of the mechanism can only be answered by further experimental and theoretical work. We plan to investigate the validity of this pathway by higher level quantum mechanical schemes, as well as to investigate other regions of Figure 2.

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