Ground States of Molecules. Part 35.[1] MINDO/3 Study of the Cornforth Rearrangement

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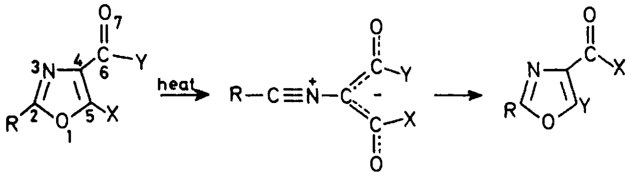
MINDO/3 calculations are reported for the Cornforth rearrangement of 5-methoxyoxazole-4-carboxamide and of the 2-vinyl derivative to the corresponding methyl 5-amino-oxazole-4-carboxylates. The reaction involves an unusual intermediate for which no satisfactory classical structure can be written. The results account well for the experimental evidence concerning such reactions.

OXAZOLES with carbonyl substituents in the 4-position can undergo the rearrangement (1) ⟶ (2) on heating, a reaction first observed by Cornforth [2,3] and so termed the Cornforth rearrangement.[4] The reaction was originally observed in the case of 2-substituted 5-alkoxyoxazole-4-carbonyl chlorides [X = OR, Y = Cl in (1) and (2)], but numerous other examples are now known,[2,3,5] with various groups R, X, and Y.



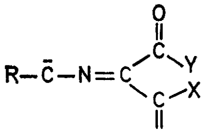
(1) (3) (2)

a; R = Ph, Y = NR^{1}R^2, X = OMe

An obvious mechanism for the reaction involves fission to the zwitterion (3), which can then recyclize by attachment of the triply bonded carbon atom to either oxygen atom. This mechanism has been supported by isotopic tracer studies.[6] A carbonyl-stabilized nitrile ylide intermediate [analogous to (3)] has been postulated for the thermal extrusion of CO_2 from 4-carbonyl-substituted oxazol-5-ones.[7] Cyclization of this species affords oxazole derivatives.

We have recently reported [8,9] a detailed kinetic study of the reaction in the case of a variety of 2-phenyl-5-methoxyoxazole-4-carboxamides (1a). These rearrange on heating to the corresponding amino-esters (2a). When substituents were introduced into the 2-phenyl group or into a phenyl group attached to the amide nitrogen atom, the rates followed the Hammett relation and the signs of the corresponding ρ values were consistent with the formation of the zwitterion (3a) in the rate-determining step. However, the magnitudes of ρ were small and the rates of the reactions were relatively insensitive to changes in the polarity of the reaction medium. The transition state must therefore be much less polar than the formulation (3) would suggest. Therefore either the intermediate must be relatively non-polar or the transition state must occur early in the reaction converting (1a) into it. The latter possibility seems unlikely since the conversion of (1a) into (2a) would be expected to be endothermic.

Thus the nature of the intermediate presents an interesting problem. In our previous communication [8] we suggested, though without much conviction, that it might be better represented by the carbenoid structure



(4)

(4) than by (3). We have now carried out MINDO/3 [10] calculations which seem to provide a definite answer.

In order to minimize the amount of computation required, we first studied the conversion of 4-carbamoyl-5-methoxyoxazole (5) into the amino-ester (7). The length (r_1) of the breaking C–O bond in (5) was taken as the reaction co-ordinate, the energy being minimized [10] with respect to *all* other geometrical variables for successive increments (0.15 Å) in r_1. Since the reaction

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[1] Part 34, *J. Amer. Chem. Soc.*, in the press.

[2] J. W. Cornforth in 'The Chemistry of Penicillin,' Princeton University Press, Princeton, New Jersey, 1949, p. 700.

[3] For a review of oxazole chemistry, see M. J. S. Dewar and I. J. Turchi, *Chem. Rev.*, 1975, **75**, 389.

[4] M. J. S. Dewar, 'The Electronic Theory of Organic Chemistry,' Oxford University Press, 1949.

[5] M. J. S. Dewar and I. J. Turchi, *J. Org. Chem.*, 1975, **40**, 1521.

[6] C. G. Stuckwisch and D. D. Powers, *J. Org. Chem.*, 1960, **25**, 1819.

[7] W. Steglich and G. Höfle, *Chem. Ber.*, 1971, **104**, 1408.

[8] M. J. S. Dewar, P. A. Spanniger, and I. J. Turchi, *J.C.S. Chem. Comm.*, 1973, 925.

[9] M. J. S. Dewar and I. J. Turchi, *J. Amer. Chem. Soc.*, 1974, **96**, 6148.

[10] R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Amer. Chem. Soc.*, 1975, **97**, 1285, 1294, 1302.

proved, as expected, to involve a stable intermediate (6), we studied the conversion of (7) into (6) in a similar manner, using the length (r_2) of the breaking bond as the reaction co-ordinate. The forward and backward reaction paths were similar, suggesting[11] that r_1 and r_2 are satisfactory reaction co-ordinates. The corresponding minimum energy reaction path (MERP) is shown in Figure 1 as a plot of calculated heats of formation (ΔH_f) *versus* r_1 or r_2.

It will be seen that the transition state for the overall reaction corresponds to that for the first step, *i.e.* (5) ⟶ (6). The transition states were located approximately from the plots of ΔH_f *versus* r_1 and r_2 and then refined by minimizing the scalar gradient of the energy by a procedure[12] analogous to that of Komornicki and McIver.[13]

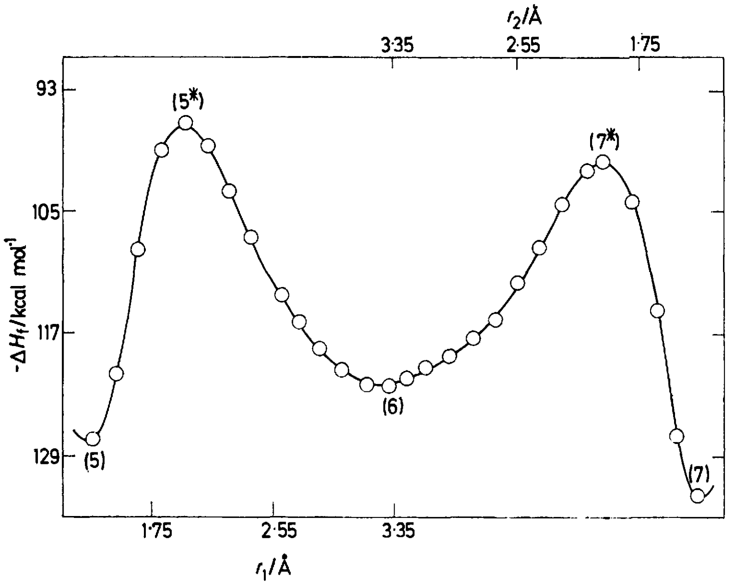

FIGURE 1 Plot of energy (kcal mol^{-1}) *vs.* reaction co-ordinate (r_1 and r_2 in Å) for the interconversion of (5) and (7)

Figure 2 shows the calculated geometries, heats of formation, dipole moments, and distributions of formal charge in (5), (6), and (7), and the transition states for conversion of (5) into (6) [(5*)] and of (6) to (7) [(7*)].

First we consider the distribution of formal charge in (6). This corresponds neither to the zwitterionic structure (3) nor to the carbenoid structure (4). Thus the nitrogen atom becomes more positive by only 0.51 unit on passing from (5) or (7) to (6), while the change in the net charge of the ring oxygen atom is even smaller (−0.18 unit), and that of the amide carbonyl oxygen is almost nil. On the other hand the carbon atom in the 2-position of the ring becomes more negative by almost 0.5 unit. The distribution of formal charge is therefore closer to that in the dimethyleneammonium ylide (8) than that of the nitrile ylide (3) [or (3a)].

The geometry of this species also supports our conclusion. The HC(2)N(3) bond angle (132°) is not much greater than that (120°) expected for (8). The C(2)–N(3) bond (1.187 Å) is longer (0.03 Å) than the normal CN triple bond, and the N(3)–C(4) bond (1.31 Å) is only slightly longer (0.02 Å) than a CN double bond. The C(4)–C(6) (1.504 Å) and C(4)–C(5) (1.486 Å) bonds are both *longer* (0.05 and 0.04 Å, respectively) than the CC single bond of αβ-unsaturated carbonyl compounds (1.45 Å), whereas they should be *shorter* in (3). Furthermore, the C=O bond distances in (8) are calculated to be the same as a normal carbonyl bond distance (1.220 Å), again implying little delocalization of the carbonyl groups.

The carbonyl carbon atoms in (8) are out of the plane formed by C(2), N(3), and C(4) by 8°. Our calculations show that the structure having the HC(1)N(5)C(4) moiety linear and N(3), C(4), C(5), and C(6) coplanar is less stable than the corresponding completely optimized structure by 2.5 kcal mol^{-1}.

Although the formal charges and geometry of the intermediate correspond better to (8) than to any alternative classical structure, clearly no one structure represents its properties adequately and it cannot even be represented as a hybrid of such structures. It is indeed a rather curious ' non-classical ' species.

The calculated distributions of formal charge in the transition states (5*) and (7*) clearly do not correspond to those in the related oxazoles, being somewhat closer to those in the intermediate (6). Since (6) itself is predicted to be little more polar than (5) or (7), it is not surprising that the rates of rearrangement of the analogous amide (1a) are so insensitive to changes in solvent polarity. Thus (1a; R^1 = Me, R^2 = Ph) rearranged only twice as fast in dimethyl sulphoxide (ε 46.6) as in chlorobenzene (ε 5.6). On the other hand the

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[11] *Cf.* M. J. S. Dewar and S. Kirschner, *J. Amer. Chem. Soc.*, 1971, **93**, 4292.

[12] R. H. Bartels, M. J. S. Dewar, and P. K. Weiner, in preparation.

[13] A. Komornicki and J. McIver, *J. Amer. Chem. Soc.*, 1973, **95**, 4512.

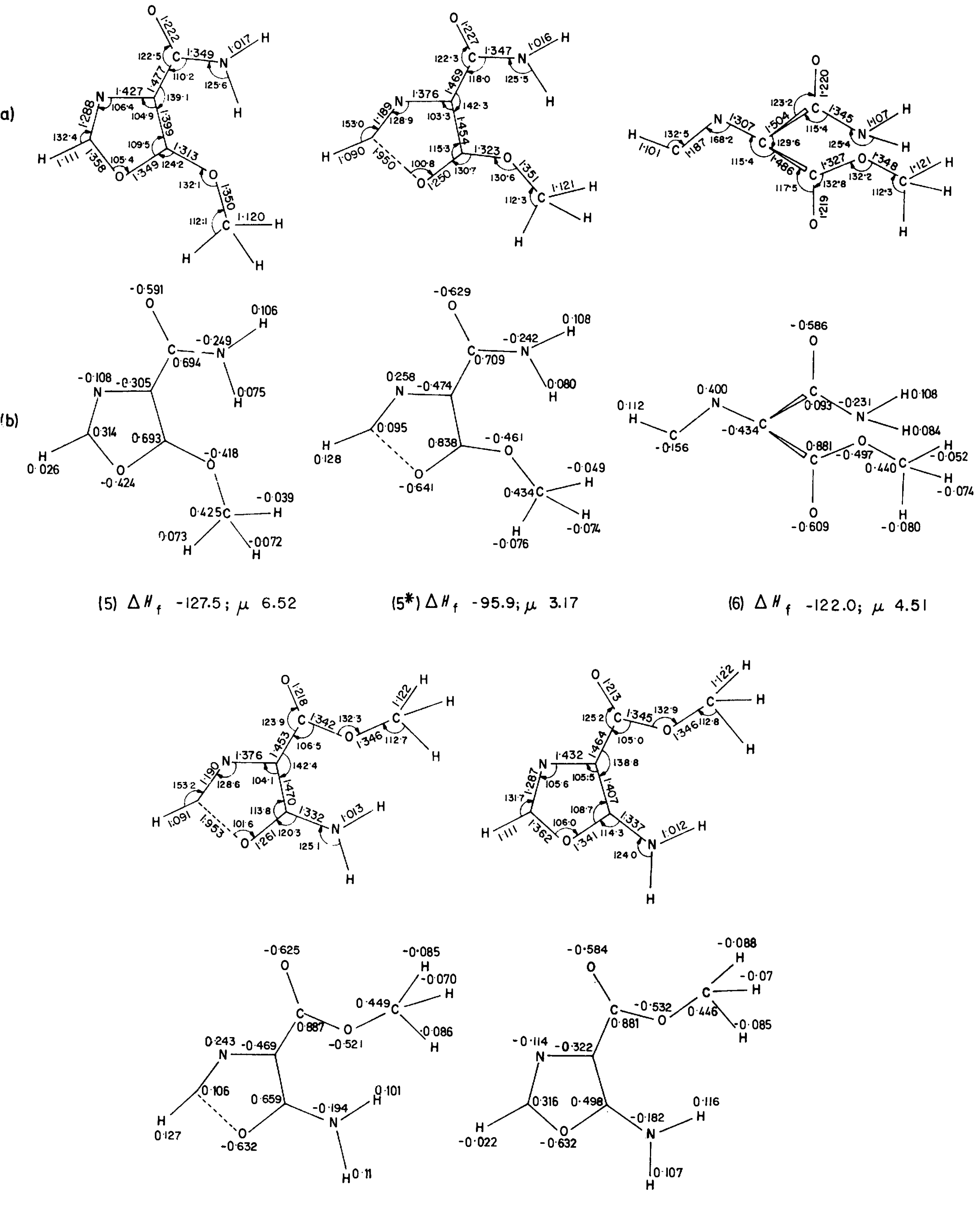
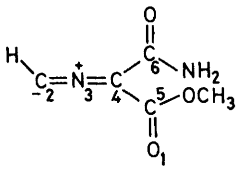


FIGURE 2 (a) Calculated geometries (bond lengths in Å; bond angles in degrees) for (5)—(7) and the transition states (5*) and (7*); (b) calculated formal charges, heats of formation (ΔH_f/kcal mol^{-1}), and dipole moments (μ/D) for (5)—(7) and the transition states (5*) and (7*) rate of rearrangement in benzyl alcohol (ε 13.4) was double that in nitrobenzene (ε 34.8). This difference can be attributed to specific solvation by hydrogen bonding to the oxygen atom of the oxazole ring, which becomes significantly more negative on passing to the intermediate.



(8)

The charge distributions in (5), (5*), and (6) also exemplify in a striking way one of the main differences between SCF MO theory and earlier treatments, *i.e.* the tendency of SCF MO charges to alternate.† Consider for example C(2). In (5), C(2) is adjacent to two atoms with large negative charges so the charge at C(2) is correspondingly large and positive. In (5*), however, the charge on nitrogen is now large and positive. C(2) is consequently adjacent to two atoms with large and opposite charges. Moreover, whereas the magnitude of the charge on oxygen is greater than that on nitrogen, the CO distance is also greater than the CN distance. The effects therefore almost cancel so C(2) is almost neutral. Finally, in (6), C(2) is adjacent only to the positively charged nitrogen; the charge on C(2) is now large and negative.

These considerations must be taken into account in any attempts to interpret substituent effects in terms of SCF MO charge distributions. Thus a negative charge at a carbon atom is commonly taken as an indication of a tendency towards electron release. This is not so in the case of C(2) in (6). The negative charge on C(2) is due to an increase in effective electronegativity, as a result of the presence of an adjacent atom with a large positive charge. The negative charge at C(2) merely reflects, and compensates for, the corresponding increase in electronegativity. If a phenyl group is attached to C(2), the negative charge of C(2) will then lead to no corresponding electron release. On the contrary, the positively charged nitrogen atom β to the ring will exert an electron-attracting ($+E$ [15]) electromeric effect.

Similar complications occur in calculating field effects since the charges at the various atoms in a molecule can have large values of opposite signs. The field effect must be calculated by summing the individual potentials due to the individual atomic charges.

Consider for example the effects of substituents in a phenyl group attached at the 2-position of (5) on the rate of rearrangement, *i.e.* on the relative energies of (5) and (5*).

On passing from (5) to (5*), the atom adjacent to phenyl [*i.e.* C(2)] becomes more negative by 0.219 unit. This, however, does *not* lead to a π-inductive electron release, for reasons indicated above. Any change in the effective electric potential of the *meta*- and *para*-positions in the benzene ring will depend on the electromeric and field effects and the latter will in turn depend on the changes in charge at *all* positions in (5) on passing to (5*).

The latter changes might be expected to be small since the ring nitrogen becomes much more positive on passing from (5) to (5*) (by 0.366 unit) but at the same time this nitrogen atom is more remote than C(2) from the *meta*- and *para*-positions in the phenyl group. There will also be a contribution from the ring oxygen atom, which is more remote again but which becomes much more negative (by 0.217 unit) on passing from (5) to (5*).

We have calculated the net change in potential at the *meta*- and *para*-positions and find it becomes slightly more positive. Since the ring nitrogen atom becomes more positive on passing from (5) to (5*), there should be a contributing $+E$ effect due to this change. One would therefore expect there to be a net increase in electron release from the 2-phenyl group into the oxazole system during conversion of (5) into (5*). The observed ρ^+ value for substituents in the phenyl group (-1.16) is consistent with this.

Consider now the effect of substituents in a phenyl group attached to the amide nitrogen atom in (5) (1a; $R^1 = H$, $R^2 = C_6H_4X$). On passing from (5) to (5*), the formal charges on the amide nitrogen atom remain virtually unchanged; any $-E$ effects on the adjacent phenyl group should remain essentially constant. Moreover the charges on the amide carbon and oxygen atoms also change very little and the net negative charge on the whole amide group changes only by 0.02 unit. Any effects of substituents in the phenyl group must therefore depend on electrostatic interactions with more distant atoms, in particular the ring carbon atom [C(4)] adjacent to the amide group, which becomes much more positive (by 0.169 unit) on passing from (5) to (5*). Since C(4) is quite far from the phenyl group attached to the amide nitrogen, the effect of this interaction should be small. The corresponding Hammett ρ value is indeed small and positive ($+0.34$).[9]

According to our calculations, the conversion of (5) into (7) is exothermic by 5.6 kcal mol^{-1}. This is in agreement with the apparent [9] irreversibility of such rearrangements. On the other hand, the intermediate (6) is predicted to lie only 5.5 kcal mol^{-1} above (5) in energy and to be separated from (5) and (7) by quite high barriers (26.1 and 21.9 kcal mol^{-1}, respectively). On this basis it seems difficult to explain our failure [9] to trap the intermediate, even though the present calculations suggest that it does not have a simple nitrile ylide structure. It seems in fact likely that MINDO/3

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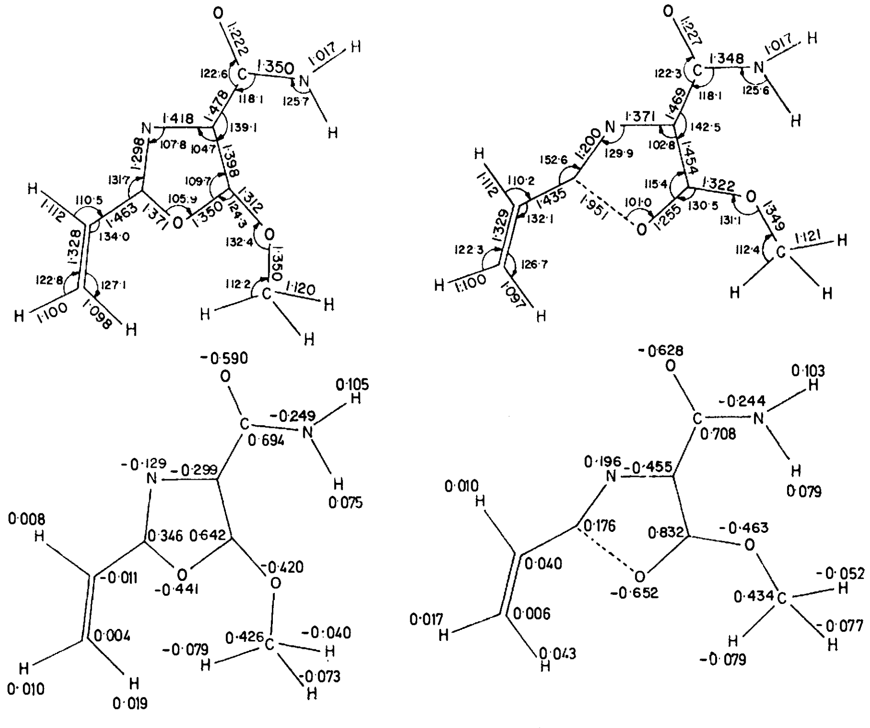
† This effect is well known: see *e.g.* ref. 14; however, the reasons for it, while obvious, do not seem to have been pointed out in print. We have therefore included a brief discussion in an Appendix to this paper.

[14] W. J. Hehre and J. A. Pople, *J. Amer. Chem. Soc.*, 1970, **92**, 2191.

[15] M. J. S. Dewar, 'The Molecular Orbital Theory of Organic Chemistry,' McGraw-Hill, New York, 1969.

has overestimated the relative stability of (6) by 5—10 kcal mol^{-1}, since similar errors tend to occur in other species with *sp*-hybridized centres.[10] The activation energy for conversion of (6) into (7) would then be comparable with those observed by Huisgen[16] for addition of typical dipolarophiles to reactive 1,3-dipoles. Since the entropy of activation for the unimolecular conversion of (6) into (7) must be more positive by *ca.* 30 cal mol^{-1} K^{-1} (*cf.* ref. 16) than any bimolecular dipolar addition, our failure to trap the intermediate with dipolarophiles would not then be surprising. Our other trapping experiments involved species expected to protonate the dicarbonyl moiety in the intermediate or to undergo nucleophilic addition to the $\mathrm{C{\equiv}\overset{+}{N}}$ bond. Here our calculations account immediately for the failure, because the carbon atom of the CN moiety carries a negative formal charge in (6) and because the carbonyl oxygen atoms of (6) are very little more negative than in the parent oxazole (5).



(9) ΔH_f -125.1; μ = 6.54

(9*) ΔH_f -99.1; μ 3.77

FIGURE 3 Calculated geometries (bond lengths in Å; bond angles in degrees), formal charges, heats of formation (ΔH_f/kcal mol^{-1}) and dipole moments (μ/D) for (9) and the transition state (9*)

The calculated activation energy (31.6 kcal mol^{-1}) for rearrangement of (5) is certainly consistent with our measurements[9] for various derivatives. However, it would be preferable to have a direct comparison for some compound which had been studied both experimentally and by MINDO/3. Unfortunately all our attempts to synthesize (5) have failed thus far.

Since we had previously studied the rearrangement of the 2-phenyl derivative (1a; $R^1 = R^2 = H$), finding an activation energy of 26.6 kcal mol^{-1},[17] we tried to carry out MINDO/3 calculations for it. This would also have been of interest for interpreting the effects of substituents in the 2-phenyl group. Unfortunately we were unable to get the SCF calculations for (1a; $R^1 = R^2 = H$) to converge.* We were, however, able to carry out calculations for the corresponding 2-vinyl derivative (9), which might be expected to rearrange at much the same rate as (1a; $R^1 = R^2 = H$) in view of the similar electronic effects of the phenyl and vinyl groups. The calculated activation energy (26.1 kcal mol^{-1}) was indeed in excellent agreement with that observed for the 2-phenyl derivative.

The geometries, heats of formation, dipole moment, and distribution of formal charge in (9) and in the transition state (9*) for rearrangement are shown in Figure 3. The vinyl carbon atom adjacent to the oxazole ring becomes slightly more positive on passing from (9) to (9*), in agreement with our predictions concerning the effects of substituents on the phenyl group of (1a).

One last possibility remained to be considered, *i.e.* that the intermediate in the rearrangement of (5) might

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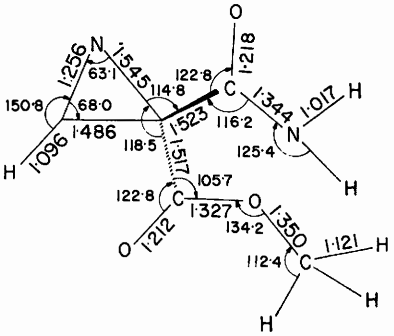
* Problems of this kind often arise in molecules where there are large formal charges, owing probably to the difficulty of picking a suitable bond order matrix. We have developed various alternative procedures, one or another of which usually solves the problem; in this case all failed.

[16] R. Huisgen, *Angew Chem. Internat. Edn.*, **1963**, **2**, 633.

[17] M. J. S. Dewar and I. J. Turchi, unpublished data.

not be (6) but the isomeric azirine (10), or that both species might be involved in the reaction.* We were, however, unable to find any low energy path from (5) to (10), the easiest route being *via* (6). Moreover (10) was predicted to lie only 6 kcal mol^{-1} below the transition state (5*) and 20 kcal mol^{-1} above (6). Since MINDO/3 still tends to overestimate the stabilization of three-membered rings,[10] it seems almost certain that (10) is higher in energy than (6) and very likely that it is also higher in energy than the transition state (5*). We do not therefore believe that such azirines can play any role in the Cornforth rearrangement.

In view of the current interest in azirines, we are reporting our calculated geometry for (**10**) (Figure 4).



.(10) ΔH_f -100.8 : μ 3.75

FIGURE 4 Calculated geometry (bond lengths in Å; bond angles in degrees), heat of formation (ΔH_f/kcal mol^{-1}), and dipole moment (μ/D) for methyl 2-carbamoyl-2*H*-azirine-2-carboxylate (10)

APPENDIX

The Tendency of SCF Charges to Alternate.—In the HMO method, it is assumed that the electronegativity of an atom is the same regardless of its environment, being embodied in the Hückel α parameter. In practice this cannot be the case because the atoms in a molecule are not as a rule neutral and the resulting formal charges must affect their electronegativity.

The most obvious effect arises from the charge on the atom itself, this leading to a change in electronegativity that tends to reduce the formal charge. Consider for example the allyl cation, $(CH_2\overset{\cdots}{-}CH\overset{\cdots}{-}CH_2)^+$. In the HMO approximation, each terminal carbon atom carries a half unit of positive charge while the central one is neutral. The positive charges will increase the electronegativities of the terminal atoms; as a result, they will tend to attract a greater share of the π-electrons, reducing their formal charges at the expense of the central atom which will then become positive. This effect is taken into account in the Wheland–Mann modification [18] of the HMO method and the formal charges given by it do indeed differ from the HMO ones in the expected manner.[19] In particular, the formal charge in an ion tends to become uniformly distributed over the atoms in it.

An entirely different picture emerges from SCF MO calculations, where the formal charges, even in ions, tend to alternate. Thus the terminal carbon atoms in allyl cation are now predicted to be *more* positive than they are in the HMO treatment while the central atom is now *negative*. There is indeed a general tendency for SCF charges in molecules to alternate, owing to an alternation in the contributions by electrons in π MOs.[14] This is true of both conjugated and nonconjugated molecules, the π MOs in the latter case corresponding to hyperconjugative interactions.

The reason for this effect can be seen very easily from the form of the *F*-matrix for a set of π MOs. Consider for example the diagonal *F*-matrix terms F_{ii} and F_{kk} for two adjacent atoms, these corresponding to the Hückel parameters α_i and α_k, respectively. The charge densities q_i and q_k of these two atoms contribute to F_{ii} and F_{kk} in the following way:

$$F_{ii} : \tfrac{1}{2}q_i\gamma_{ii} + q_k\gamma_{ik} \qquad \text{(i)}$$

$$F_{kk} : q_i\gamma_{ik} + \tfrac{1}{2}q_k\gamma_{kk} \qquad \text{(ii)}$$

where γ_{ii} and γ_{kk} are the repulsions between pairs of electrons in the same AO (ϕ_i or ϕ_k) and γ_{ik} is the repulsion between an electron in ϕ_i and one in ϕ_k. If atoms *i* and *k* are adjacent, as we assume them to be, γ_{ik} is in general greater than $\frac{1}{2}\gamma_{ii}$ or $\frac{1}{2}\gamma_{kk}$. Consequently a change in q_i changes F_{kk} more than it does F_{ii} and a change in q_k likewise changes F_{ii} more than it does F_{kk}. So if atom *i* becomes positive, the resulting change in electronegativity of an adjacent atom is greater than that of atom *i* itself. In the allyl cation, for example, the positive charges on the terminal carbon atoms lead to a greater increase in the electronegativity of the central atom than in the electronegativities of the terminal atoms themselves. As a result, the central atom attracts electrons away from the terminal ones and so develops a net negative charge while the positive charges in the terminal atoms increase.

The alternation of SCF charges is therefore due to the factor of one-half in equations (i) and (ii). One can see why this factor appears if one considers the physical significance of the various terms in the *F*-matrix elements.[20], †

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* This possibility was suggested to us by Professor M. J. Goldstein.

† Salem [21] has discussed the alternation of SCF charges in the alkyl ions but apparently failed to realize the importance of the factor one-half in equations (i) and (ii). The Wheland–Mann calculation corresponds to use of unity instead of one-half.

[18] G. W. Wheland and D. E. Mann, *J. Chem. Phys.*, 1949, **17**, 264.

[19] See A. Streitwieser, jun., 'Molecular Orbital Theory for Organic Chemists,' Wiley, New York, 1961, ch. 13.

[20] See ref. 15, ch. 3.

[21] L. Salem, 'Molecular Orbital Theory of Conjugated Systems,' Benjamin, New York, 1966, p. 64.