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Nature of the Intermediate in the Cornforth Rearrangement

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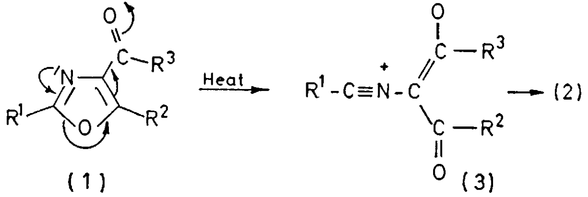
Summary The thermal rearrangement of 4-carbonyl substituted oxazoles gave a negative value for the reaction constant ρ, and correlated with enhanced σ values (σ^+); a small rate increase was observed upon running the reaction in solvents of increasing dielectric constant.

THE thermal rearrangement of 4-carbonyl substituted oxazoles was first observed by Cornforth.[1] The general reaction is given in equation (1). One special case of interest is the rearrangement of hydroxymethyleneoxazolones (**1**; $R^2 = OH$, $R^3 = H$) to oxazole-4-carboxylic acids.[2,5]


(1) (2) (1)

The mechanism proposed[1,3,4] for these reactions involves opening of the oxazole ring (**1**) to form an acyclic intermediate which recloses to (**2**). The intermediate was written as a stabilized nitrogen ylide (**3**).

We have examined the kinetics of the thermal rearrangement of various oxazoles (**1**) in the hope of gaining further insight into the nature of the intermediate. Compounds of the type [**1**; $R^1 = Ar$, $R^2 = OMe$, $R^3 = N(Me)Ph$]‡ were synthesized by known literature procedures,[1] and the kinetics of their rearrangement to (**2**) [$R^1 = Ar$, $R^2 = N(Me)Ph$, $R^3 = OMe$] were studied by n.m.r. spectroscopy at 95·3 ± 0·1°. The reaction was followed to two half-lives of starting material and was found to be of first order throughout and irreversible.


(1) (3)

The first order rate constants ($10^5\,k/s^{-1}$) in four solvents of varying polarity (D = dielectric constant at 25°C) were as follows: dimethyl sulphoxide (DMSO) (D = 46·6) 9·04 ± 0·12; nitrobenzene (D = 34·8) 6·59 ± 0·07; *o*-dichlorobenzene (D = 9·93) 6·30 ± 0·07; chlorobenzene (D = 5·62) 5·92 ± 0·04.

The rate clearly changes little with the polarity of the solvent, that in DMSO being less than double that in chlorobenzene. This indicates that the transition state must be only slightly more polar than the reactant.

The rearrangements of a number of oxazoles [**1**; R^1 = substituted Ph; $R^2 = OMe$; $R^3 = N(Me)Ph$] were studied in nitrobenzene. The rate constants ($10^5 k/s^{-1}$) for various substituents were as follows: *p*-OMe, 34·8 ± 0·5; *p*-Me, 13·4 ± 0·2; *p*-Bu^t, 13·4 ± 0·2; H, 6·59 ± 0·07; *p*-F, 4·12 ± 0·03; *p*-Br, 2·54 ± 0·03; *m*-Br, 1·63 ± 0·03; *p*-CF$_3$, 1·07 ±0·01. A plot of log k against σ was not linear, the points for the electron-releasing substituents (MeO-, Me-, Bu^t-)

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‡ Satisfactory analyses were obtained on new compounds.

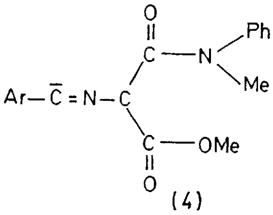
lying above a line drawn through the rest. On the other hand a plot of log *k* against σ^+ showed only random scatter from a straight line [equation (2)] (k_0 = rate constant for phenyl). This suggests that electron deficiency develops

$$\log k - \log k_0 = -(1{\cdot}16 \pm 0{\cdot}11)\rho\sigma^+ \qquad (2)$$

at the 2-position in the oxazole ring on passing from (**1**) to the transition state.

This would, of course, be consistent with the formation of the zwitterionic species (**3**) as an intermediate. In this case, however, one would expect the transition state to be highly polar, a conclusion at variance with the observed solvent effect. The transition state for forming (**3**) could be relatively nonpolar only if it occurred very early along the reaction path. This could be so only if the formation of (**3**) from (**1**) were exothermic which seems very unlikely. Moreover, the low value of ρ ($-1{\cdot}16$) in equation (2) implies that no large positive charge can develop adjacent to the 2-phenyl group on forming the transition state.

These results suggest that a better classical representation of the intermediate might be provided by the carbenoid structure (**4**),



(4)

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

[2] H. T. Clarke, J. R. Johnson, and R. Robinson, 'The Chemistry of Penicillin,' Princeton University Press, Princeton, New Jersey, 1949, p. 694.

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

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

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