Kinetic Evidence for a Tetrahedral Intermediate in the Isomerisation of 2-Acetylimino-3-phenacylthiazolidine

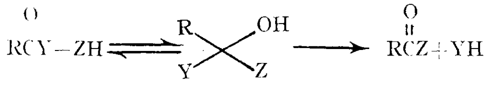
By P. J. TAYLOR

(*Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire*)

TETRAHEDRAL carbinolamines and related species (I) are now recognised as probable intermediates in many reactions of the carbonyl group.[1] Since the pioneering work of Bender on O^{18} carbonyl oxygen exchange, which suggested[2] but did not prove[3] their transient existence in ester and amide hydrolysis, evidence has accumulated for their intermediacy there[3,4] and in such reactions as Schiff's base,[5] oxime,[6] and semicarbazone[7] formation and hydrolysis, and several comprehensive reviews[1] have appeared. The crucial evidence is kinetic: a change in rate, at high or low pH, not to be explained as resulting from ionisation of the substrate. Such a break in the pH profile may be shown[1] to be consistent with a change in the rate-determining step from the formation, to the destruction, of some intermediate present under steady-state conditions. For this intermediate, structure (I; $Y = Z = OR$ or NR_2) is plausible.

In all cases so far investigated, the attacking reagent (ZH) has been an oxygen or nitrogen base. We report what we believe to be the first case in which a carbanion has been implicated.

The isomerisation of (II) to (III) through the postulated intermediate (IV) has previously been reported.[8] We have examined this reaction in water, ethanol and aqueous methanol, and find it to be first order in [OR⁻], under mildly alkaline

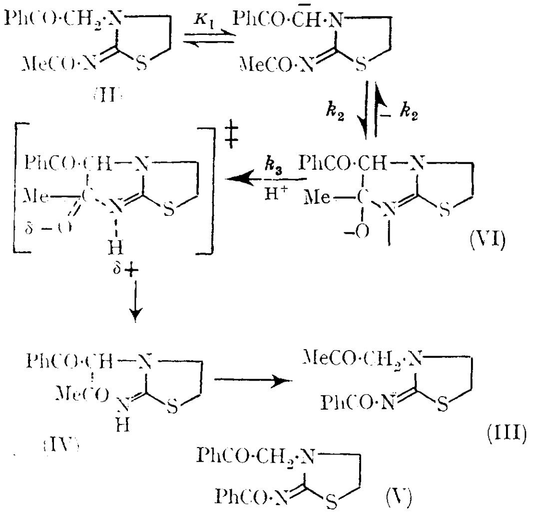


(I)

conditions. However, at higher pH in water this simple relation no longer holds. The reaction becomes progressively slower than predicted as the pH rises, and there are indications that it may approach a plateau at pH > 11. Three distinct mechanistic pathways might give rise to this phenomenon:

(i) Stoicheiometric ionisation of (II) with $pK_a \sim 10{\cdot}3$. This information is inaccessible since the isomerisation of (II) is too rapid ($t_{\frac{1}{2}} \sim 3$ min. at 25°) but the u.v. spectrum of the closely related (V), which can isomerise only to itself, shows no change up to pH 12·6, above which hydrolysis rapidly sets in. We accordingly reject this hypothesis.

(ii) A change from rate-determining formation of the tetrahedral intermediate (VI), dependent on [OH⁻], to its rate-determining cleavage, dependent on both [OH⁻] and [H⁺], as the pH rises:



The above scheme leads to the overall rate equation:

$$k_{\text{obs}} = \frac{K_1k_2k_3}{k_{-2} + k_3[\text{H}^+]} \qquad (1)$$

which clearly will lead to a rate plateau at high enough pH.

(iii) The formation of (IV) *and* its anion under steady-state conditions.† This is tantamount to placing the transition state one step beyond (IV), which, since the equilibrium heavily favours (III), is inconsistent with Hammond's postulate.[9] Detailed analysis[10] shows that, on this hypothesis, the plateau rate should be subject to a strong positive ionic strength effect; on hypothesis (ii) the effect should be small (charge separation cancelled by charge collapse). In fact, it is negligible at pH ~ 11 though considerable at lower pH (see Figure).

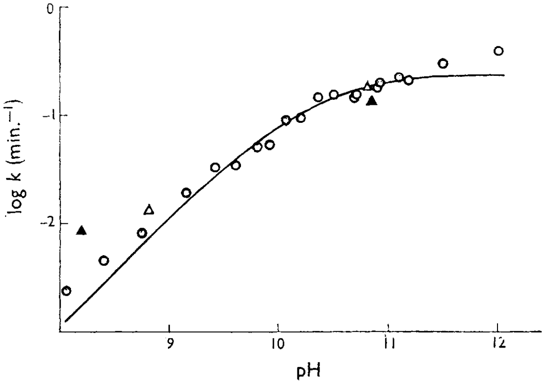


FIGURE. *Overall conversion rate* (II) → (III) *as a function of pH*: ○; *at* $I = 0{\cdot}03$; *and in the presence of*: △; M-NaCl, ▲; M-NaClO$_4$. *The line is a theoretical curve based on equation* (1), *assuming* $K_1k_2k_3 = 0{\cdot}22$ min.$^{-1}$, $k_3 = 1{\cdot}9 \times 10^{10}k_{-2}$.

Further evidence comes from E_a, which is 18·9 kcal. at pH 8·80 but 15·8 kcal. at pH 10·72. This must reflect a difference in transition state, which is inconsistent with hypotheses (i) and (iii).

We conclude that hypothesis (ii) is correct so that (VI), and therefore (IV) as originally[8] suggested, lie on the route from (II) to (III).

Equation (1) is not precisely followed (see Figure): at high pH perhaps because the uncatalysed cleavage of (VI) is a minor reaction pathway, at lower values probably because specific and general base catalysis have not been fully disentangled yet.

Nucleophilicity towards carbonyl depends almost entirely on basicity,[11] and carbanions, in general, are much less readily generated than oxygen or nitrogen bases. Very probably, this reaction is easy only because it is intramolecular; an

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† The reaction can be followed by u.v. spectroscopy but no intermediate is detectable when the traces are examined.

intermolecular mechanism of the same sort might not be so susceptible to kinetic proof, since for a rate plateau to be observed, the tetrahedral intermediate must not be too fugitive (*i.e.* $k_3[\mathrm{H}^+] \not> k_{-2}$ under all conditions). However, this example can hardly be unique.

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