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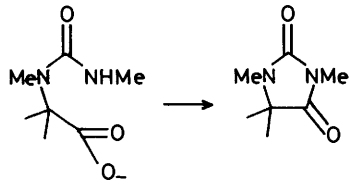
Change of Rate Determining Step Induced by the gem-Dimethyl Effect

Iva B. Blagoeva and Denis T. Tashev
Institute of Organic Chemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria
Anthony J. Kirby
University Chemical Laboratory, Cambridge CB2 1EW

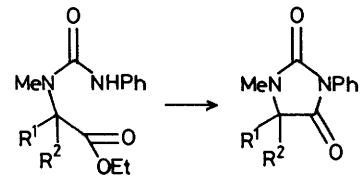
The base-catalysed cyclisation to the hydantoin of 2,2,3-trimethyl-5-phenylhydantoate (**2**; $R^1 = R^2 =$ Me) is slower than that of the 2,3-dimethyl compound, even though the acceleration expected from the gem-dimethyl effect is observed for the acid-catalysed reaction.

We have used the introduction of a pair of methyl groups to drive the remarkable cyclisation of 2,2,3,5-tetramethyl hydantoate* (**1**), which involves general acid catalysed attack on the CO_2^- group by the ureido anion.[1] This is an example of the gem-dialkyl or Thorpe–Ingold effect,[2] known to favour cyclisation processes both kinetically and thermodynamically.[2c]



(**1**)

We report a striking exception to this rule. Figure 1 shows pH-rate profiles for the cyclisation of three hydantoate esters (**2**; $R^1 = R^2 =$ H; $R^1 =$ H, $R^2 =$ Me; $R^1 = R^2 =$ Me), with one or two methyl groups at the 2-position. In the acid-catalysed region below pH 2 the introduction of one and two methyl groups increases k_{H^+} by factors of 30 and 1 100. But the picture is quite different for the base-catalysed reaction. k_{OH} For (**2**; $R^1 =$ H, $R^2 =$ Me) is only 13 times faster than for (**2**; $R^1 = R^2 =$ H), and the introduction of the second methyl group actually slows the reaction: k_{OH} for the gem-dimethyl compound is six times smaller than for (**2**; $R^1 =$ H, $R^2 =$ Me).



(**2**) (**3**)

Since the thermodynamic gem-dimethyl effect on cyclisation should be the same for both acid and base-catalysed reactions, this is evidence for a specific retardation of the base-catalysed reaction of (**2**; $R^1 = R^2 =$ Me). The mechanism of the base-catalysed cyclisation of *N*-phenylhydantoate esters is generally agreed[3–5] to involve rate determining spontaneous breakdown of the tetrahedral intermediate T^- (Scheme). In contrast to the reaction at low pH, no buffer catalysis is observed for the base-

* 2-(1,3-Dimethylureido)-2-methylpropionate.

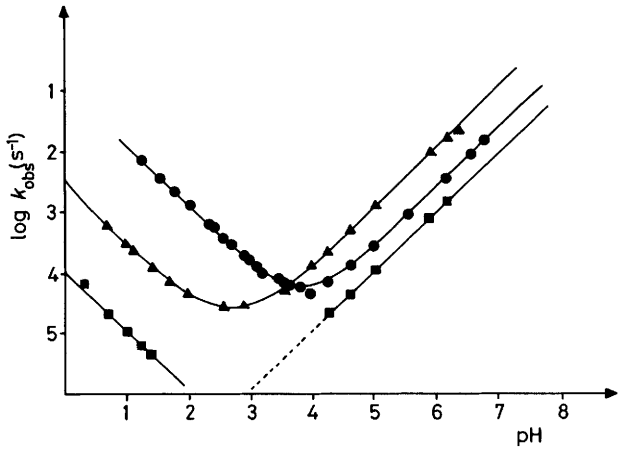


Figure 1. pH-rate profiles for the cyclisation of (**2**; $R^1 = R^2 =$ H) (squares), (**2**; $R^1 =$ H, $R^2 =$ Me) (triangles) and (**2**; $R^1 = R^2 =$ Me) (circles), at 25 °C and ionic strength 1.0M.

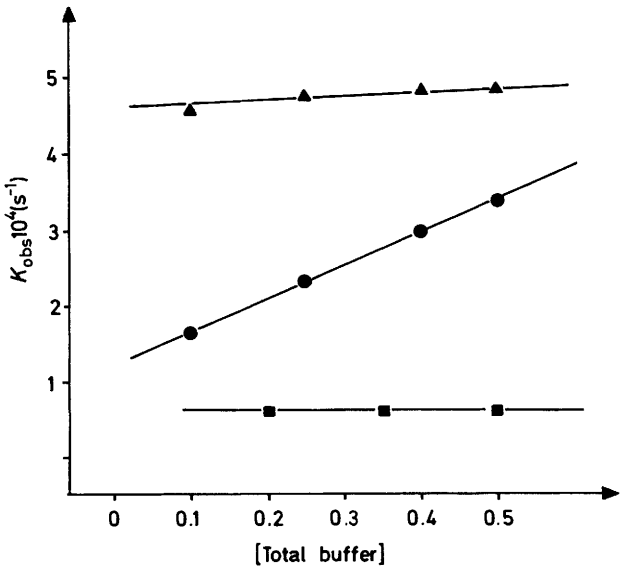
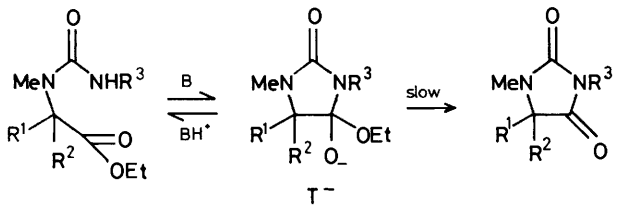


Figure 2. Buffer catalysis (50% free base acetate at 25 °C and ionic strength 1.0M) for the cyclisation of (**2**; $R^1 = R^2 =$ Me) (circles), and its absence for the reactions of (**2**; $R^1 = R^2 =$ H) (squares) and (**2**; $R^1 =$ H, $R^2 =$ Me) (triangles).

catalysed cyclisation of *N*-phenylhydantoate esters,[3] or of the hydrolysis of the hydantoins produced.[4,5] We have confirmed this result for (**2**; $R^1 = R^2 = H$); and (**2**; $R^1 = H$, $R^2 = Me$); but the cyclisation of (**2**; $R^1 = R^2 = Me$) shows strong buffer catalysis over the whole pH-range. These results are illustrated in Figure 2 for reactions in acetate buffer.

The clear conclusion is that the rate determining transition state is different for the cyclisation of (**2**; $R^1 = R^2 = Me$). The only reasonable alternative transition state (Scheme) is that for the base-catalysed formation of T^-, so we conclude that this step is rate determining for the cyclisation of (**2**; $R^1 = R^2 = Me$) [In principle, the breakdown of T^- (Scheme) should become cleanly rate determining for the cyclisation of (**2**; $R^1 = R^2 = Me$) also at sufficiently high buffer concentration, but this is not achievable under our experimental conditions.]



Evidently the loss of EtO^- from T^- is now faster than ring opening. One reason could be an accelerated elimination of EtO^- from the fully substituted T^- ($R^1 = R^2 = Me$, $R^3 = Ph$), but steric acceleration of this sort will act to some extent on both modes of decomposition of T^-. It seems certain that a major factor is a reduction in the rate of C–N cleavage, caused by the gem-dimethyl effect, working in reverse to disfavour the ring-opening. (Similar effects have been identified recently for the ring-opening reactions of dihydrouracils[6] and cyclopropanes,[7] and seem likely to be general.) However, a change of rate determining step is not in itself sufficient to explain why the base-catalysed cyclisation of (**2**; $R^1 = R^2 = Me$) is actually *slower* than that of (**2**; $R^1 = H$, $R^2 = Me$), and this problem is under active investigation.

Acknowledgements

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