Ketone Neighbouring-group Effects in Ester Hydrolyses

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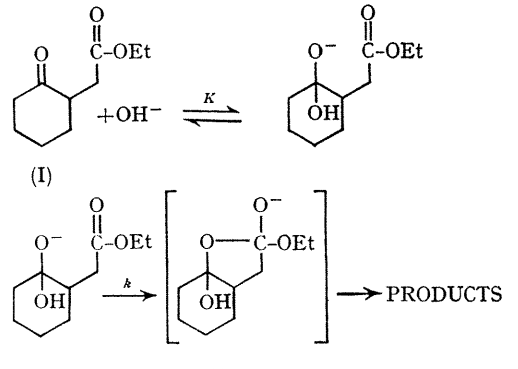
Summary The carbonyl group accelerates the hydrolysis of γ-keto-esters and results in abnormally low activation energies.

ALTHOUGH intramolecular catalysis of ester hydrolysis has been extensively studied, the effects of the keto-group on such hydrolyses have received little attention.[1-4] We report the effect of the neighbouring keto-group on the alkaline hydrolysis of ethyl 2-oxocyclohexylacetate (I) and ethyl 2-oxocyclopentylacetate (II).† Second-order rate constants for hydrolysis in 80% ethanol (v/v) show that (I) is 60 times more reactive than ethyl cyclohexylacetate and (II) 199 times more reactive than ethyl cyclopentylacetate at 25·0°. These rate enhancements indicate participation by the neighbouring γ-keto-group.

The hydrolyses were found to be quite insensitive to temperature effects. This is reflected in the unusually small enthalpies of activation, especially those for the reactions in 10% EtOH (see Table). Normally, values of ΔH^* of 12—15 kcal./mole are observed for ester hydrolyses; whereas, in the case of (II) a value of zero, within experimental error, is noted. These low activation energies suggest a rapid prior equilibrium step in the reaction. One possible equilibrium is the rapid reversible hydration of the ketone carbonyl (or addition of hydroxide) as shown in the Figure. If the rate determining step is the intramolecular attack of the alkoxide carbonyl-adduct at the carboxyl carbon atom, the observed second-order rate constant is the product of the intramolecular rate constant, k, and the equilibrium constant, K, for the hydration, *i.e.*, $k_{obs} = kK$. The small enthalpies of activation are explicable then, if the hydration process is exothermic; and, from the data available,[5] it appears that the reversible hydration of carbonyl compounds is, in fact, exothermic.

TABLE. *Enthalpies of activation and effect of solvent*

Ester	Solvent % EtOH	10^3k_{obs} (l.mole^{-1} sec.$^{-1}$)		ΔH^* (kcal./mole)
		15·1°	25·0°	
(I)	80	23·8	49·6	10·9
	10	145	196	4·5
(II)	80	190	215	1·4
	10	257	251	0



FIGURE

It is relevant to note that similarly small enthalpies of activation (*ca.* 1—5 kcal./mole) have been determined for semicarbazone formation.[6] The mechanism of this reaction bears close resemblance to that proposed for hydrolysis of γ-keto-esters. In the former case, the prior equilibrium is the rapid reversible addition of semicarbazide to

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† Hydrolysis products were identified as the corresponding carboxylic acids.

the carbonyl compound after which rate determining dehydration occurs.

Although our data does not preclude other possibilities (*e.g.*, the kinetically indistinguishable reversible formation of an enolate ion) the above mechanism is analogous to those postulated for methyl 2-benzoyl-6-methylbenzoate[2,3] and methyl 2-formylbenzoate.[4]

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