# **10.** *A Kinetic Study of the Hydrolysis of Certain Alkyl Acetates and Corresponding Lactones.*

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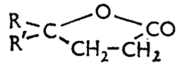
Arrhenius parameters for the alkaline hydrolysis of the esters
RR′MeC·OAc
where R and R′ are H, Me, or Ph are compared with those for correspondingly substituted γ-lactones. Marked differences found for highly substituted compounds are explained as steric effects. No similar comparison can be made for acid-catalysed hydrolyses because most of the γ-lactones are not hydrolysed appreciably. Optically active γ-phenyl-γ-valerolactone is readily racemised in weakly acidic media, a weak absorption band with a maximum at 520 mμ slowly developing. These phenomena are discussed.

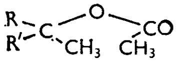
THE considerable attention that has been given to the effect of alkyl substitution on the rates of hydrolysis of esters has been directed primarily towards variations in the acid residue.[1] Taft tried to differentiate between inductive, steric, and resonance effects by using a variety of correlations [2] and suggested that in the alkaline hydrolysis of certain acetates ROAc the rates are largely independent of steric influences, variations being governed by the electronegativity of the group R.

However, for esters substituted in the β-position of the acid residue, Newman concluded that polar effects are insignificant compared with steric effects.[3] In contrast, Sarel, Tsai, and Newman [4] considered that both polar and steric effects significantly modify the rates of alkaline hydrolysis of esters when the alkyl group is changed from primary to secondary or tertiary.

Stevens and Tarbell [5] made some general observations on the marked differences in rates of base-catalysed hydrolysis of certain esters and γ-lactones, but did not differentiate between energy and entropy factors.

We have attempted to distinguish between possible contributions from polar and steric factors by comparing Arrhenius parameters for the alkaline hydrolysis of various γ-substituted γ-lactones (I) and the corresponding esters (II). If polar effects predominate, then there should be little difference in the trends for these two classes, but if steric effects are important a considerable difference is to be expected.

(I) 

 (II)

The results in 43% aqueous acetone are summarised in Figs. 1—3, giving bimolecular rate constants at 20° and the Arrhenius parameters log $A$ and $E$, respectively, plotted against the nature of the groups R and R′ as ordinates.

The effect of increasing substitution on the rate is qualitatively similar for lactones and esters. However, the trends in log $A$ and $E$ for the last two members of the series are reversed, and it is this contrast with which we will primarily be concerned.

*Kinetic Form of Alkaline Hydrolysis.*—A second-order rate law was obeyed, as required for mechanism $B_{AC}2$. In accord with this was the complete retention of activity when (—)-γ-phenyl-γ-valerolactone was re-formed after alkaline hydrolysis.

It seemed possible that some of the differences (Figs. 1—3) could arise because of a change in reaction from hydrolysis to elimination. However, the ultraviolet and infrared

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[1] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953.

[2] Taft in " Steric Effects in Organic Chemistry," ed. Newman, John Wiley and Sons, Inc., New York, 1956, p. 556.

[3] Newman, see ref. 2, p. 201.

[4] Sarel, Tsai, and Newman, *J. Amer. Chem. Soc.*, 1956, **78**, 5387.

[5] Stevens and Tarbell, *J. Org. Chem.*, 1954, **19**, 1996.

spectra of the products obtained by hydrolysis of the phenyl-substituted compounds showed that olefins had been formed, if at all, in negligible amounts.

*Intermediates.*—Bender[6] established that an intermediate of life-time sufficiently great to permit proton migration is formed during alkaline hydrolysis of a series of benzoates, including t-butyl benzoate. The only reasonable structure for this intermediate is one in which the trigonally hybridised carbonyl-carbon atom has become tetrahedral, and extrapolation from the benzoates to the esters and lactones now discussed seems reasonable. Since the rate of $^{18}$O exchange was somewhat less than the rate of hydrolysis, and since proton exchange in the complex should be rapid, the energy barriers enclosing the complex must be small, relative to the overall barrier to reaction, and the transition states for the loss of this complex probably resemble the complex more closely than they resemble the reactants or products.

FIG. 1. *Variations in second-order rate constants (k) for the alkaline hydrolysis of esters (E) and γ-lactones (L) in 43% (w/w) aqueous acetone at 20°. The ordinate gives the groups R and R′ for the esters and corresponding lactones. HHH refers to methyl acetate.*

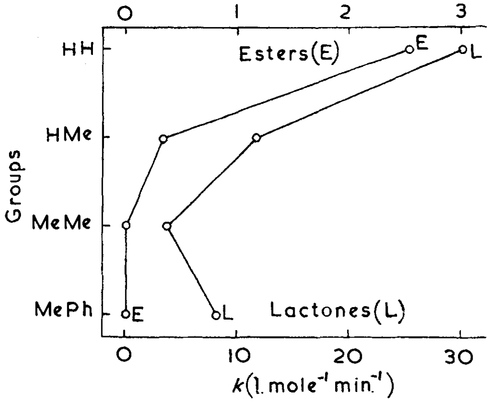
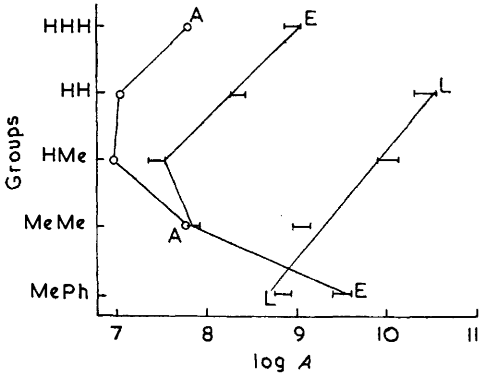


FIG. 2. *Variations in* log *A for the alkaline hydrolysis of esters (E) and γ-lactones (L), and for the esterification of certain β-substituted carboxylic acids (A).*[10]



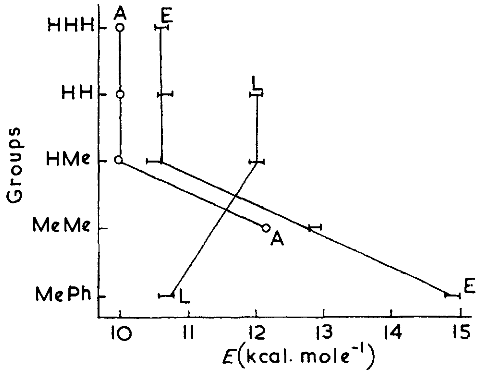


FIG. 3. *Variations in activation energy for the alkaline hydrolysis of esters (E) and γ-lactones (L), and for the esterification of β-substituted carboxylic acids (A).*[10]

The results can be discussed in terms of two alternative transition states: that in which the bond between hydroxyl-oxygen and carbonyl-carbon atom has not completely formed, and that in which the bond between alkoxyl-oxygen and carbonyl-carbon atom has begun to break. Since the intermediate has never been detected by direct physical means, we infer that its concentration must be small at all times and that stationary-state kinetics may therefore be used.

[6] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626.

This gives the following expression for the overall rate of hydrolysis:

$$\text{Rate} = \frac{k_1k_2}{k_{-1} + k_2}[\text{OH}^-][\text{Ester}]$$

where $k_1$, $k_{-1}$, and $k_2$ are the rate constants for the individual steps:

$$\text{ROAc} + \text{OH}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Complex}$$

$$\text{Complex} \xrightarrow{k_2} \text{Products}$$

Hence the overall rate constant, $k'$, found experimentally is given by:

$$k' = k_1k_2/(k_{-1} + k_2)$$

If we set $k_{-1} = xk_2$, this may be written $k' = k_1/(x + 1)$. Making the postulate that the rates of proton exchange in all the intermediate complexes considered here are nearly equal, one can conclude that $x$ is approximately constant, since the ratio of $^{18}$O exchange to hydrolysis, reported by Bender, is remarkably similar for all esters,[6] and hence to a first approximation the rate constants can be discussed in terms of the transition state for the formation of the intermediate complex.

The following is based upon this approximation.

*Effect of Substituents.*—Trends in the Arrhenius parameters for the hydrolysis of esters and corresponding lactones on substitution are similar for esters of primary and secondary alcohols, but change abruptly for esters of tertiary alcohols, in contrast to the lactones (Figs. 1—3).

These changes could be due to polar, resonance, or steric interactions. Even in the phenyl-substituted compounds it is hard to see how any resonance effect could play a significant rôle. It has, however, been suggested that polar effects should be important.[2] Such effects should be comparable for esters and $\gamma$-lactones, so the differences must be caused by some other, over-riding phenomenon. For various reasons, it seems to us that polar effects will be unimportant for this class of esters. (i) Substitution in the $\alpha$-position of the alkyl group is equivalent to $\beta$-substitution in the acid residue, and the latter is thought to have only a small polar effect.[3] (ii) Electron-release to carbonyl-carbon and -oxygen atoms would alter the energy term, leaving the pre-exponential factor unchanged: this is the reverse of what is found for esters of primary and secondary alcohols. (iii) The effect of a methyl should be opposite to that of a phenyl group: in fact, when methyl is replaced by phenyl the trend ascribed to methyl is enhanced. (iv) The rate of alkaline hydrolysis of diphenylmethyl acetate [7] is practically unchanged when phenyl is replaced by *p*-methoxyphenyl.[8] These considerations lend weight to the suggestion that the significant step involves formation rather than decomposition of the intermediate complex.

It is therefore concluded that the trends reported above are primarily due to steric interactions in the transition state.

*Entropy of Activation.*—The small, steady decrease in $\log_{10} A$ for all the lactones and for esters of primary and secondary alcohols is probably due to steric and ponderal effects [9] (cf. Fig. 2); it does not seem to be related to changes in the energy of activation since these changes are negligibly small except for esters of tertiary alcohols.

A study of scale models shows that for esters of tertiary alcohols, but not others, the only strain-free conformation is one in which the molecule is coiled so that one side of the plane of the carbonyl group is quite open, the methyl groups being pressed close to the carbonyl-carbon atom on the other side. Thus approach of hydroxide ion on one side is

[7] Israel, unpublished results quoted in ref. 8.

[8] Bunton and Hardwick, *J.*, 1957, 3043.

[9] Ingold, *Quart. Rev.*, 1957, **11**, 1.

probably completely prevented whereas a very wide angle of approach is available on the other. This situation does not arise for any of the lactones, and we postulate that the sudden change in the trends for esters of tertiary alcohols is due to coiling.

*Energy of Activation.*—As the C–OH bond begins to form, the carbonyl-carbon atom must change its hybridisation from $sp^2$ to $sp^3$ and hence the carbonyl-oxygen atom must be forced against the coiled chain in esters of tertiary alcohols. This should lead to a major increase in the energy of activation (cf. Fig. 3). At the same time, the intermediate complex will be destabilised because of crowding, but this should be less marked than the effect on the transition state. If that is so, then the transition state may resemble the intermediate complex less in the crowded esters: this would then lead to an increase in entropy of activation (cf. Fig. 2).

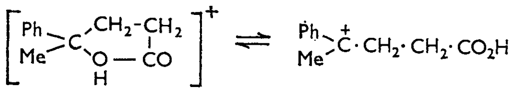
It is possible to understand the trends shown in the Figures in terms of a change in mechanism from one involving a stable addition complex to a direct $S_N2$ displacement. However, Bender[6] found appreciable oxygen exchange during the hydrolysis of esters of tertiary alcohols so this simple explanation is untenable.

*Comparison with Other Data.*—There is a striking resemblance between the results presented in Figs. 1—3 for esters of primary, secondary, and tertiary alcohols and those for esterification of acids substituted on the β-carbon atom.[10] These results, summarised in Figs. 2 and 3, strongly support the earlier suggestion that the substitutions effected here resemble substitutions on β-carbon in the acid. We suggest that the reasoning given above to explain the present results applies equally to the data of Newman's school.[10]

Emphasis has been on the different trends in the Arrhenius parameters with increasing substitution for esters and γ-lactones. The fact that γ-lactones are hydrolysed by alkali more readily than corresponding esters has been discussed by Huisgen and Ott,[11] who consider an important factor to be that γ-lactones are constrained into a *cis*-configuration with respect to the carbonyl group, whereas open esters normally have a *trans*-configuration. Our results show that, for γ-lactones, the high rate is a result of a more favourable entropy of activation. This is thought to be, in part, because esters have far more motional freedom to lose on going to the transition state than have the corresponding actones.

*Acid-catalysed Hydrolysis.*—Since acids catalyse the lactonisation of γ-hydroxy-acids the comparison made for alkaline hydrolyses could not be extended to cover acid-catalysed hydrolyses.

The acid-catalysed racemisation of γ-phenyl-γ-valerolactone is most simply understood in terms of the transient formation of a planar carbonium ion after protonation:



It was at first though that a very weak band at 520 mμ developing slowly in acid solutions of this lactone might have been due to this carbonium ion. However, in the light of subsequent work on the spectra of monoarylcarbonium ions in concentrated sulphuric acid,[12] this conclusion seems most improbable since the comparable ion $PhMe_2C^+$ was found[12] to have an intense band with a maximum at 390 mμ.

In concentrated sulphuric acid γ-phenyl-γ-valerolactone also gives a yellow solution, with a band at about 360 mμ. This we tentatively ascribe to the carbonium ion (possibly also protonated on the carbonyl group). The appearance of a pink colour in weakly acidic solutions is reminiscent of the behaviour of several other compounds, and a discussion given elsewhere may be relevant.[12] The only significant additional information that this result provides is that racemisation is faster than development of colour. Hence the

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[10] Loening, Garrett, and Newman, *J. Amer. Chem. Soc.*, 1952, **74**, 3929.

[11] Huisgen and Ott, *Tetrahedron*, 1959, **6**, 253.

[12] Grace and Symons, *J.*, 1959, 958.

planar carbonium ion may well be an essential intermediate in the formation of the coloured species.

## EXPERIMENTAL

*Materials.*—$\gamma$-Phenyl-$\gamma$-valerolactone, prepared from ethyl lævulate and bromobenzene,[13] had b. p. 89—92°/0·04 mm. The lactone was converted into $\gamma$-hydroxy-$\gamma$-phenylvaleric acid which was resolved as its brucine salt.[14] The resulting optically active acid was lactonised by azeotropic distillation with dry benzene, since it is readily racemised in acid solution.

t-Butyl acetate, prepared from t-butyl alcohol and acetyl chloride, in the presence of dimethylaniline, had b. p. 97—98°.

Phenylpropan-2-ol, prepared from acetone and phenylmagnesium bromide, had b. p. 52°/3 mm. This, with acetyl chloride and dimethylaniline in ether, gave the acetate, b. p. 58—61°/3 mm.

Other reactants and solvents were dried and purified by standard procedures.

Carbonate-free solutions of potassium hydroxide in water, aqueous acetone, and aqueous dioxan were prepared in an atmosphere of carbon dioxide-free nitrogen in a dry-box. Sticks of "AnalaR" grade potassium hydroxide were liberally washed with water to remove carbonates before being dissolved in purified water, the resulting solutions being stored in bottles coated internally with wax to prevent the formation of soluble silicates. These solutions were standardised against potassium hydrogen phthalate, with standard procedures to prevent access of atmospheric carbon dioxide. The calculated quantity of purified acetone or dioxan was added to the standardised solutions. Since acetone reacts slowly with potassium hydroxide, solutions were used immediately after preparation. Solutions of lactones were prepared in the same solvent mixtures, and reaction was initiated by rapid mixing in a two-limbed stoppered tube after temperature equilibration.

*Method.*—The reactions were followed titrimetrically by quenching aliquot parts with excesss of standardised hydrochloric acid followed by back-titration under carbon dioxide-free conditions. Hydrolysis of optically active $\gamma$-phenyl-$\gamma$-valerolactone was also followed polarimetrically, a polarimeter tube controlled within 0·05° being used. For low-temperature studies, jets of dry nitrogen were directed on the end-plates of the tube to prevent misting. For each reaction at least three temperatures were selected, and reactions were followed to more than 80% completion, the course being accurately of second-order under all conditions. In most cases the initial concentrations, $a$, of the reactants were equal, and the second-order rate constant $k$ was estimated from plots of time, $t$, against $(a - x)^{-1}$.

*Arrhenius parameters for the alkaline hydrolysis of certain esters and lactones in aqueous acetone.*

| | R | R′ | Acetone (% w/w) | $E$ (kcal./mole) | log $A$ | $k$ (l. mole$^{-1}$ min.$^{-1}$, 20°) | Ref. |
|---|---|---|---|---|---|---|---|
| Esters | H | H | 43 | 10·70 | 8·38 | | *b* |
| | H | H | 62 | 12·0 | 9·2 | | *c* |
| | H | Me | 43 | 10·53 | 7·43 | 0·3548 | *a* |
| | H | Me | 62 | 12·20 | 8·5 | | *c* |
| | Me | Me | 43 | 12·9 | 7·85 | 0·0171 | *a* |
| | Me | Me | 62 | 14·3 | 8·7 | | *c* |
| | Me | Ph | 43 | 14·92 | 9·5 | 0·0233 | *a* |
| | Me | Ph | 62 | 16·78 | 10·42 | 0·0099 | *a* |
| | (AcOMe) | | 43 | 10·60 | 8·94 | 10·71 | *a* |
| | ,, | | 62 | 12·0 | 9·2 | 9·2 | *c* |
| Lactones | H | H | 43 | 12·0 | 10·4 | | 5 |
| | H | Me | 43 | 12·3 | 10·2 | | 5 |
| | | | | 12·0 | 10·0 | | *d* |
| | | | 62 | 13·2 | 10·8 | | *d* |
| | Me | Me | 43 | 11·4 | 9·07 | | 5 |
| | Me | Ph | 43 | 10·7 | 8·86 | 8·18 | *a* |
| | Me | Ph | 62 | 12·06 | 9·9 | 7·50 | *a* |

*Refs.*: *a*, This work. *b*, Tommila, Koivisto, Lyyra, Antell, and Heimo, *Ann. Acad. Sci. Fennicae*, 1952, **47**, *A*, 3. *c*, Raylander and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 3021. *d*, Tommila and Ilomaki, *Acta Chem. Scand.*, 1952, **6**, 1249.

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[13] Kenyon and Symons, *J.*, 1953, 2129.

[14] Kenyon and Symons, *J.*, 1953, 3580.

The results, together with those obtained by others, are summarised in the Table. Some selected results are displayed in the Figures, in order to summarise the important trends and differences for esters and $\gamma$-lactones.

*Racemisation of* (—)-*$\gamma$-Phenyl-$\gamma$-valerolactone.*—Solutions in acetic acid were stable at room temperature. Adding a trace of sulphuric acid caused rapid racemisation according to a first-order rate law. In more acidic solutions, racemisation was too fast to be followed kinetically, so no attempt was made to measure rate as a function of acidity. Several hours after racemisation was complete a pink colour was detected in these solutions, and spectral analysis revealed a weak band at 520 m$\mu$. The final intensity of this band increased with increasing acidity, reaching a maximum in the 30% sulphuric acid region. At all acidities the rate of growth was far less than the rate of racemisation. In 100% sulphuric acid no band at 520 m$\mu$ could be detected, but there was an intense band at 360 m$\mu$ ($\varepsilon_{\text{max.}} \approx 10^4$). At intermediate acidities both bands were found.

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